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A COMPARATIVE STUDY OF LOW DOSE MAGNESIUM SULPHATE REGIME VERSUS ZUSPAN'S REGIME IN SEVERE PRE-ECLAMPSIA AND ECLAMPSIA

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ABSTRACT: BACKGROUND: Pre-eclampsia and eclampsia are the major health problem in developing countries. MgSO₄ is the standard drug in the control of eclamptic convulsions. **OBJECTIVE:** The aim of the study is to compare the efficacy of low dose MgSO₄ regime versus Zuspan's regime in control and prevention of convulsions and to compare the therapeutic levels, maternal outcome and fetal outcome. **STUDY DESIGN:** It was a randomized prospective study conducted at Kempegowda Institute of Medical Sciences and Hospital, Tertiary level referral hospital from January 2009 to June 2010. This Study included 60 patients who were admitted with eclampsia and severe pre-eclampsia. A Study group of 30 patients were randomized to receive low dose Magnesium Sulphate and a Control group of 30 patients received Zuspan's regime. Type of convulsions, no. of convulsions, therapeutic drug level, maternal complications and perinatal outcome are compared between study and control groups. **RESULTS:** Both the groups are comparable in terms of type of convulsion, No. of convulsion, therapeutic drug level, maternal complications and perinatal outcome. **CONCLUSIONS:** Low dose MgSO₄ can be used as preventive and therapeutic measure in severe pre-eclampsia and eclampsia with equal effectiveness as Zuspan's regime.

KEYWORDS: Pre-eclampsia, Eclampsia, Convulsions, MgSO₄, Serum Magnesium Level.

INTRODUCTION: Pregnancy can induce hypertension in normotensive women or aggravate already existing hypertension. Eclampsia is occurrence of convulsions in patients with pre-eclampsia. It causes significant mortality and morbidity in the mother, fetus and newborn.

Major breakthrough in the management of eclampsia came when Dr. J. A. Pritchard published his standardized treatment regime in 1984. Pritchard regime include loading dose of MgSO₄ 4gm IV and 5gm IM Inj in each buttock. This is followed by the maintenance dose of 5gm IM 4th hourly to alternate buttocks.

Collaborative eclampsia trial in 27 centers in 9 developing countries found MgSO₄ to be better anticonvulsant.

Currently the most common used regimens are standard IM regime of Pritchard and intra venous regime of Zuspan and Sibai. Pritchard suggested that the dose of MgSO₄ should be limited in women who are small built. Indian women are of smaller built especially from lower socio economic group weigh less than their counter parts in western world. Hence the study was aimed at lower dose regimes may be equally effective in the control and preventions of seizures with a simultaneous reduction in the toxicity of the drug.

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MATERIALS AND METHODS: This was a prospective randomized control study conducted in patients admitted to the department of OBG, KIMS Hospital, and Bangalore between Jan. 2009 to June 2010. Sample size 60.

INCLUSION CRITERIA: Patients with imminent eclampsia (Hypertension with frontal headache and vomiting, blurring of vision, epigastric pain) and eclampsia after taking informed consent from the patient attendant.

EXCLUSION CRITERIA: Patient with cardiac disease, renal failure and chronic lung disease, patient with hypersensitivity to MgSO_4 .

PROCEDURE: A total number of 60 patients of eclampsia and severe pre-eclampsia are included in the study. Study group includes 30 pregnant women who received low dose Magnesium Sulphate with a loading dose of 4gm MgSO_4 I. V and maintenance dose of 2gm/4hr I. V. infusion. Recurrent convulsions were treated with an additional dose of 2gm I. V and changed over to Zuspan's regime. Control group includes 30 pregnant women who received Zuspan's regime with a loading dose of 4gm of MgSO_4 IV and maintenance dose of 2 gm /hr I. V. infusion. Recurrent convulsions were treated with an additional dose of 2gm I. V. Patients are monitored with respiratory rate, knee jerk and urine output. If any signs of toxicity Inj. Calcium Gluconate 1amp slow I. V was given. Blood samples were taken at first, sixth hour and twelfth hour after loading dose of MgSO_4 . Serum Mg level was determined by Calmagite method.

STATISTICAL ANALYSIS: Student's t-test is used for numerical data to determine whether an observed difference between the means of two groups can be considered statistically significant. Chi-square test is used to find out whether observed differences between proportions of events in two groups may be considered statistically significant.

RESULTS: A comparative study between Study group consisting of 30 pregnant women with severe pre-eclampsia and eclampsia treated with low dose MgSO_4 (loading dose 4gm I. V, maintenance dose 2gm/4hr I. V. infusion) and Control group consisting of 30 pregnant women with severe pre-eclampsia and eclampsia treated with Zuspan's regime (loading dose 4gm I. V, maintenance dose of 2gm/hr I. V. infusion) was undertaken at Kempegowda Institute of Medical Sciences and Research Centre. The aim of the study was to assess the effectiveness of low dose MgSO_4 regime for the prevention of convulsion in severe pre-eclampsia and eclampsia and to compare the therapeutic levels, maternal complications and fetal outcome in low dose regime and Zuspan's regime.

In the present study most of the patients were between 21 and 25 years (40% in Study group and 57% in Control group) and mean age being 25.13 ± 4.87 in Study group and 24.43 ± 4.75 in Control group. The mean Gestational Age in Study group was 31.96 ± 4.39 and in Control group was 34.13 ± 4.02 . Severe pre-eclampsia and eclampsia are more common in primi gravida (47% in Study group and 70% in Control group). Almost half of the patients had BMI between 18.5 and 24.9 (40% in Study group and 43% in Control group) with a mean of 25.18 ± 3.47 in Study group and 24.65 ± 2.98 in Control group. Most patients had impending eclampsia (90% in Study group and 83% in Control group).

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Significant difference in serum Mg levels at 1st hr, 6th hr and 12th hr was noted between the two groups as shown in Table 5. Therapeutic serum Mg level was achieved in 90% patients in 1st hr and 6th hr in both the groups, 80% in Study group and 90% in Control group at 12th hr. Treatment related complications were rare in the study. There was no recurrence of convulsions in Study group. There was a case of recurrent convulsion in Control group – 12. 5%.

Sl. No.	Characteristic	Study group n=30 Mean $\pm$ SD	Control group n=30 Mean $\pm$ SD	P Value
1	Mean Maternal Age	25. 13 $\pm$ 4. 87	24. 43 $\pm$ 4. 75	P=0. 618 P=>0. 05
2	Mean Gestational Age	31. 96 $\pm$ 4. 39	34. 13 $\pm$ 4. 02	P=0. 059 P=>0. 05
3	Mean BMI	25. 18 $\pm$ 3. 47	24. 65 $\pm$ 2. 98	P=0. 567 P=>0. 05
4	Mean BP	163 $\pm$ 15. 0819/104 $\pm$ 13. 5	164. 33 $\pm$ 12. 57/104. 2 $\pm$ 9. 6	P=0. 939 P=0. 05

Table 1: Comparison of baseline characteristics of the patient

No statistically significant association is observed between two groups in base line characteristics.

Type	Study group No. (%)	Control group No. %	P Value
Impending eclampsia	27 (90)	25 (83)	P=0. 689 P=>0. 05
Antepartum eclampsia	02 (07)	04 (14)	
Postpartum eclampsia	01 (03)	01 (03)	

Table 2: Severity of disorder at recruitment

No statistically significant association is observed between the two groups and type of eclampsia.

No. of Convulsions	Study group No. (%)	Control group No. (%)	P Value
1	01 (33)	00 (0)	P=0. 410 P=>0. 05
2	02 (67)	03 (60)	
3	0 (00)	01 (20)	
5	0 (00)	01 (20)	

Table 3: No. of convulsions before initiation of treatment

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Anti Hypertensives	Study group No.	Control group No.	P Value
Nifedipine	15	09	P=0. 306 P=>0. 05
α dopa	01	04	
Nifedipine + α dopa	12	16	
Nifedipine + Labetalol	01	01	
Nifedipine + NTG	01	00	
Table 4: Use of anti hypertensives in patients			

α dopa = alpha methyl dopa, NTG = Nitroglycerine.

Time in Hours	Study group Serum Mg/dl	Control group Serum Mg/dl	P Value
1 st	5. 69 $\pm$ 1. 07	7. 33 $\pm$ 0. 68	P<0. 01
6 th	5. 05 $\pm$ 0. 63	6. 97 $\pm$ 0. 71	P<0. 01
12 th	4. 79 $\pm$ 0. 61	6. 37 $\pm$ 0. 69	P<0. 01
Table 5: Serum Mg at 1 st , 6 th , and 12 th hour			

There is statistical significant association between serum Mg at 1st Hr and Groups, 6th Hour and Groups and 12th Hour and Groups.

Out come	Study group	Control group	P- Value
Recurrent convulsions	0	01	P=0. 388 P>0. 05
Placental abruptions	01	01	
Atonic PPH	00	02	
Partial HELLP	02	01	
Table 6: Maternal outcome			

Sl. No.	Out come	Study group No. (%)	Control group No. (%)	P Value
1	Still birth	7 (26)	7 (22)	P=0. 622 P>0. 05
2	Live birth	20 (74)	24 (75)	
	Preterm	14 (52)	16 (50)	
	Term	06 (22)	08 (25)	
3	Neo Natal Death	00 (00)	01 (03)	P=0. 095 P>0. 05
4	Mean birth weight	1505± 752. 7	1862 ± 763. 5	
Table 7: Perinatal outcome				

No statistical significant association is observed between perinatal outcome and the groups.

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There was no cases of maternal mortality. Most babies had good Apgar > 7 at 1st minute and 5th minute. Most babies had birth weight of < 1500 gms (48% in Study group and 40% in Control group). Most of the babies were preterm. Corrected perinatal mortality rate (corrected for extreme prematurity) in Study and Control groups were 25.92% and 25.80% respectively.

Incidence of LSCS was 20% in Study group and 28% in Control group. Most common indications for emergency LSCS in our study were impending eclampsia and fetal distress noticed before the initiation of Magnesium Sulphate treatment.

DISCUSSION: Pre-eclampsia complicates 2 to 8% of pregnancy and a major cause of morbidity and mortality for women and her child. MgSO₄ is the drug of choice for women with eclampsia and severe pre-eclampsia and better than diazepam, phenytoin.

As the body excretes magnesium via the Kidneys, urine output must be sufficient to process the continuous infusion (ie., $\geq 30\text{ml/hr}$). When output drops below this level, the patient can rapidly develop toxicity. But as long as deep tendon reflexes, respiratory rate, and urinary output are normal, practitioners are reassured of attaining therapeutic levels. Patients diagnosed with Pre-eclampsia may have renal impairment as a result of the disease process and are, therefore, at particular risk for developing hypermagnesemia. Magnesium Sulphate is not an innocuous drug (Fernando Arias) and it would be ideal to monitor serum Magnesium Sulphate which is not feasible in developing countries. Therapeutic serum magnesium levels are 4.9- 7.3 mg/dl and the loss of deep tendon reflexes¹ and respiratory depression¹ occurs when serum magnesium levels are 7.0 – 10.0 mg/dl and 10.0 – 13.0mg/dl. So the safety margin between the therapeutic and toxic levels is very less.

Since the introduction of Pritchard² regime there has been constant discussion regarding the dose of MgSO₄ and therapeutic serum levels. Pritchard thought that MgSO₄ dosing should vary according to patient's weight or BMI. Based on these observations various low dose regime have been introduced in Asian countries.

Present study was done to compare the efficacy of Zuspan's regime and low dose regime in control of convulsions in patients of impending eclampsia and eclampsia. The range of serum Mg levels was 3.6 – 8.8 mg/dl with mean values of 4.89 ± 1.68 mg/dl in the Study group [low dose]. This is comparable with the study by Dr. Suman. P. Sardesai³ where serum Mg level were in therapeutic range of 3.14 – 6.74mg/dl (mean 4.89 ± 1.75 mg/dl) in the low dose group and eclamptic convulsions were controlled in 92% of the cases. They concluded that low dose MgSO₄ regime is as effective as Pritchard regime. Dr. Niraj N Mahajan⁴ in 'Padhar regime' advocates 6gm I. V loading dose of MgSO₄ and 4gm I. V maintenance dose every 4 hr. Out of 95 eclamptic patients in their study only one woman had recurrent convulsion and concluded that the low dose regime appears to control and prevent convulsions effectively in Indian Woman.

Study by Begum et al⁵ from Dhaka with low dose magnesium regime reported the range of serum Mg levels as 1.74 – 6mg/dl with a mean value of 3.87 ± 0.78 Mg/dl. Out of 65 patients only one developed recurrent convulsions. They concluded that half of the standard dose of Magnesium Sulphate appeared to be sufficient to control convulsions effectively and serum levels of magnesium remained lower than levels which produce toxicity.

Recurrent convulsion in Dr. Suman P Sardesai³ study was 8% and that in Begum et al⁵ study was 3.9%. There were no recurrent convulsions in our low dose Study group.

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In our present study serum Mg level of 6.89mg/dl $\pm$ 0.69 were seen in Control group with recurrent convulsion rate of 12.5%. Study by Sibai et al⁶ using a loading dose of 4gm I. V followed by a maintenance of 2gm/hr infusion serum Mg level in random sample was 4.37mg/dl $\pm$ 0.77, with recurrent convulsion rate of 15.2%.

Pritchard study have reported in a study between 1975 – 1983 recurrence rate of 12. 1%.

Though there is a significant difference in serum Mg levels, there is no statistical difference in the control of convulsions between the Study and Control groups in our present study. The corrected perinatal mortality rate (Corrected for extreme prematurity) in Study and Control groups was 25. 92% & 25.80% respectively which is comparable with Sardesai study.

There was no maternal mortality in our study. Sardesai et al reported 2.6% maternal mortality in low dose regimen, Begum Et al reported maternal mortality of 4.5% & 5% in low dose and Pritchard regime.

CONCLUSION: Low dose MgSO₄ is equally effective as Zuspan's regime in controlling and preventing recurrent convulsions in eclampsia and impending eclampsia. Therapeutic serum Mg level were achieved with low dose MgSO₄ even in patients with high BMI. Though there is a significant difference in serum Mg levels, there is no statistical difference in the control of convulsions between the two groups. MgSO₄ both Zuspan and low dose are not associated with any Mg toxicity. Both regimes are equally safe for both the mother and fetus and do not affects the Obstetric outcome. A continued study with low dose MgSO₄ regime in a large number of patient is required to further assess whether it can replace the standard high dose regime in Indian population for control of convulsion in severe pre-eclampsia and eclampsia.

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