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Research Article

EVALUATION OF EFFECTS OF PATIENT CHARACTERISTICS ON SHORTER REGIMENS OF MAGNESIUM SULPHATE ADMINISTRATION IN PATIENTS WITH SEVERE PREECLAMPSIA – A RANDOMISED CLINICAL TRIAL

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A B S T R A C T

In developing nations like India, pre-eclamspia and eclampsia contribute significantly to maternal mortality. Magnesium Sulphate is the drug of choice to control seizures in eclampsia, and prevent convulsions in severe preeclampsia. Pritchard regimen, which involves administration of $MgSO_4$ for twenty-four hours till after delivery (or last fit), is the preferred regimen in low resource settings, though the side effects and concerns about toxicity of Magnesium Sulphate makes it advantageous to explore shorter regimens. We conducted a randomised prospective clinical trial study on 100 patients with either severe PET, signs of impending eclampsia, or HELLP syndrome. Patients were grouped into three groups of single dose post-partum (Group I), dosage for 12 hour post-partum (Group II), and dosage for 24 hours post-partum (Group III). The clinical outcomes such as time to return to ambulation, duration of indwelling catheter, time until contact with new born, and whether the mother breastfed within one hour were compared based on patient BMI, the mode of delivery, and whether the delivery was preterm. Only patients in Group II and III showed signs of $MgSO_4$ toxicity. Patients who had pre-term deliveries and patients who underwent caesarean section showed higher rate of adverse effects, higher time to return to ambulation, longer duration of indwelling catheter.

INTRODUCTION

Hypertension accounts for 14% of all maternal deaths, and it ranks as the second largest cause of maternal mortality in the world[1], especially in developing countries, where it can account upto 10-25% of maternal deaths, with the primary cause being eclamptic seizure[2]. Both Pre-eclampsia and eclampsia contribute to maternal and perinatal mortality[3]. In India, incidence rate of pre-eclampsia and eclampsia are 1.97% and 0.43%, respectively[4].

The prevention of seizures and control of blood pressure are the two important considerations during management of preeclampsia[5]. To prevent eclamptic convulsions in severe preeclampsia, and to control seizures in eclampsia, anticonvulsants are used.

Magnesium sulphate ($MgSO_4$) is used worldwide to control seizures and reduce maternal mortality[6]. Two primary regimens are available for administration of $MgSO_4$ – Pritchard Regimen and Zuspan Regimen. Zuspan regimen is more commonly used worldwide[7], but limited resources in developing countries makes it less utilised, and Pritchard regime is preferred in such settings[8].

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over 5-10 min, followed by 5gm (50%) in each buttock given intramuscularly. Thereafter, 5 gm (50%) is given intramuscularly into alternate buttocks every 4 hr[9]. The drug should be administered till 24 hours after delivery or after the last fit (whichever comes last)[10,11,12].

Since $MgSO_4$ can present side effects in patients, its advantages must be weighed along with the adverse effects[13]. The side effects also increase the amount of monitoring required, which in low resource settings can be a hurdle. In some cases, withholding $MgSO_4$ after a few doses due to toxicity saw no episode of repeated seizure[14].

The adequate dosage regimen of MgSO4 has been a subject of studies and debate[6]. The reduction of duration $MgSO_4$ therapy can offer advantage in terms of reduction of resources spent on monitoring the patient, and improve the possibility of early ambulation in the patient. A reduced regimen can also offer quick contact with the new born, and preclude such recommended practice as kangaroo care. It can also help reduce burden on healthcare system in low-resource settings and peripheral healthcare centres.

Few trials have been performed to evaluate the efficacy of shorter regimen of $MgSO_4$ administration in patients of severe preeclampsia, especially in developing nations.

AIMS AND OBJECTIVES

We conducted a study to compare outcomes of $MgSO_4$ administration in three regimens: as a single dose, and 12 hours postpartum regimen, and the conventional 24 hours postpartum in the cases of severe preeclampsia.

In this paper, we present the results of evaluation of the effects of the three regimen based on the following characteristics of the patients: BMI, mode of delivery, and period of gestation (whether the delivery was preterm or term).

The clinical outcomes evaluated were: Time to return to ambulation, Duration of indwelling catheter, time until contact with the newborn, breast feeding within one hour, adverse effects observed, and severe cases of $MgSO_4$ Toxicity.

MATERIAL AND METHODS

We carried out a randomised prospective clinical trial at Dr. RPGMC, Tanda, Himachal Pradesh on pregnant women who presented with severe preeclampsia. ACOG guidelines were used to define "severe preeclampsia" as systolic BP greater than 160mm Hg, or diastolic BP of greater than 110mm Hg on bed rest on two occasions at least four hours apart. Patients included in the study had at either severe PET, signs of impending eclampsia, or HELLP syndrome. Patients excluded were:

1. Those who had seizures
2. Those who had been put on $MgSO_4$ before the commencement of study
3. Those who had conditions like diabetes or renal disease
4. Those who had urine output less than 25ml/hr

Patients were grouped randomly into three groups of $MgSO_4$ doses, namely Group I (those who were given a single dose), Group II (those given doses upto 12 hours postpartum), and Group III (those who were given doses for 24 hours postpartum). A total of 100 patients were selected to be the part of the study. Out of these, 33 each were ascribed to Group I and II, and 34 patients were in Group III.

Detailed patient history was taken and general physical examination, including detailed obstetric examination was carried out. The route of administration of doses of $MgSO_4$ was similar in all three groups. All doses were administered as per Pritchard regimen.

Patients were defined to be suffering from adverse effects if they reported experiencing nausea, vomiting, flushing, hypersensitivity, light-headedness, or pain at the injection site. The signs of $MgSO_4$ toxicity recorded were loss of deep tendon reflexes, oliguria, and respiratory depression.

The results were analysed based on the patient BMI, mode of delivery, and whether the delivery was preterm or not. The time the patient took to return to ambulation was recorded, and so was the duration of indwelling catheter, and time until contact with the newborn. Additionally, whether the patient could engage in breast feeding within one hour was evaluated as a clinical outcome,

The data was meticulously recorded and analysed using python scripts and SPSS software.

OBSERVATIONS

Majority of patients in all Groups were in the normal BMI range – 90.9% in Group I, 81.81% in Group II, and 88.2% in Group III.

The mean period of gestation in Group I was 35.93±2.87 weeks, in Group II was 36.7±6.2 weeks, and in Group III was 36.57±2.72 weeks.

Of all the 100 cases, 49 cases showed adverse effects, and their distributions by the three different group are shown in Table 1. The maximum number of patients (13) reported pain at injection site as their primary complaint, 11 patients experienced nausea and flushing. Four patients experienced vomiting, 1 complained of light-headedness, and nine experienced induration at injection site.

Table 1 Adverse cases by Groups

	Cases with Adverse Effects
Group I (n=33)	5 (10.2%)
Group II (n-33)	18 (36.73%)
Group III (n=34)	26 (53.06%)

Table 2 Distribution of BMI by Groups

	Group I (n=33)	**Group II (n=33)**	**Group III (n=34)**
Underweight	0	2 (6.06%)	0
Normal	30 (90.91%)	27 (81.82%)	30 (88.24%)
Overweight	2 (6.06%)	4 (12.12%)	4 (11.76%)
Obese	1 (3.03%)	0	0

A total of 5 cases of $MgSO_4$ toxicity were observed, with 2 cases of loss of patellar reflexes, 2 cases of Oliguria. Four cases of toxicity were observed in Group III. One case of loss of patellar reflexes was observed in Group II.

Group III showed the longest time to ambulation, with an average value of 17.12±8.157 hrs, whereas Group I showed the lowest average value of 10.94±6.851 hrs. The patients in Group II showed an average value of 13.12±6.153 hrs.

Group III showed the highest average duration of indwelling catheter (24.35±1.04 hrs), followed by Group II (14.64±3.16 hrs), followed by Group I, which showed the lowest value (7.91±4.38 hrs).

Patients in Group I were observed to take the lowest average time until contact with newborn at 1.08±0.50 hrs, followed by Group II (1.14±0.53 hr), and finally by Group III (1.28±0.62 hrs).

Most of the patients (69.70%) in Group I started breastfeeding within one hour. Patients in Group III showed the lowest percentage (58.82%), as compared to 63.64% in group II.

One case was required to be changed to Group III, to a regimen for 24 hours, due to persistently high BP and signs of impending eclampsia. The patient belonged to Group II, had normal BMI, showed no effects of $MgSO_4$ toxicity and no adverse effects were observed. The patient had a term delivery.

Table 3 Total number of cases with adverse effects, cases that showed $MgSO_4$ toxicity, and breast feeding within 1 hour by BMI

	Cases with adverse effects (Cases with adverse effects/Total Patients in BMI Category)			Cases that Showed $MgSO_4$ toxicity (Cases that showed $MgSO_4$ toxicity/Total Patients in BMI Category)			Number of Patients who Breast Fed within 1 hour		
	Group I	**Group II**	**Group III**	**Group I**	**Group II**	**Group III**	**Group I**	**Group II**	**Group III**
Underweight	-	2/2 (100%)	-	-	0/2	-	-	2 (100%)	-
Normal	4/30 (13.33%)	16/27 (59.26%)	22/30 (73.33%)	0/30	0/27	2/30 (6.67%)	19 (63.33%)	12 (44.44%)	14 (46.66%)
Overweight	1/2 (50%)	0/4	3/4 (75%)	0/2	1/4 (25%)	2/4 (50%)	1(50%)	2 (50%)	2 (50%)
Obese	0/1	-	-	0/1	-	-	0	-	-

Table 4 Average duration of indwelling catheter, duration of indwelling catheter, and time until contact with the newborn grouped by BMI

	Average Time to Ambulation (Average Time (hrs))			Average duration of indwelling catheter (Average Time (hrs))			Time until contact with new born (Average Time (hrs)		
	Group I	**Group II**	**Group III**	**Group I**	**Group II**	**Group III**	**Group I**	**Group II**	**Group III**
Underweight	-	15	-	-	14±2	-	-	0.79±0.21	-
Normal	10.97	12.78	16.67	7.9 ±4.43	14.63±3.14	24.33±1.04	1.07±0.47	1.14±0.54	1.27±0.63
Overweight	14	14.5	20.5	9±2	15±3.32	24.5±0.87	1.5±0.5	1.31±0.48	1.31±0.55
Obese	4	-	-	6	-	-	0.5	-	-

The distribution by BMI in different groups are shown in Table 2. The results for clinical outcomes grouped by BMI, particularly cases with adverse effects, cases that showed $MgSO_4$ toxicity, and whether the mother breastfed within one hour are shown in Table 3. Clinical measures like time to return to ambulation, duration of indwelling catheter, and time until contact with the newborn are shown in Table 4.

Table 5 Number of Preterm deliveries by Group

	Preterm Deliveries
Group I (n=33)	20 (60.61%)
Group II (n=33)	16 (48.48%)
Group III (n=34)	20 (58.82%)

shown in Table 5. The total number of cases that showed adverse effects, cases that showed $MgSO_4$ toxicity, and whether the mother breastfed within one hour, grouped by term of delivery are shown in Table 6. Clinical measures like time to return to ambulation, duration of indwelling catheter, and time until contact with the newborn are shown in Table 7.

The number of cases with different mode of delivery by regimen group are shown in Table 8. The total number of cases that showed adverse effects, cases that showed $MgSO_4$ toxicity, and whether the mother breastfed within one hour, grouped by mode of delivery are shown in Table 9.

Table 6 Total number of cases with adverse effects for preterm pregnancies

	Total No. of Cases with Adverse Effects		Cases that Showed $MgSO_4$ toxicity		Number of Patients who Breast Fed within 1 hour	
	Pre-term Delivery	**Term Delivery**	**Pre-term Delivery**	**Term Delivery**	**Pre-term Delivery**	**Term Delivery**
Group I	2/20 (10%)	3/13 (23.08%)	0/20	0/13	11/20 (55%)	9/13 (69.23%)
Group II	6/16 (37.5%)	12/17 (70.59%)	1/16 (6.25%)	0/17	8/16 (50%)	8/17 (47.06%)
Group III	15/20 (75%)	11/14 (78.57%)	1/20 (5%)	3/14 (21.43%)	7/20 (35%)	9/14 (64.28%)

Table 7 Time to return to ambulation, Average duration of indwelling catheter, and time until contact with the newborn for preterm and term pregnancies

	Time to Ambulation		Average duration of indwelling catheter		Time until contact with new born (Average Time (hrs)	
	Pre-term Delivery (hrs)	**Term Delivery (hrs)**	**Pre-term Delivery (hrs)**	**Term Delivery (hrs)**	**Pre-term Delivery (hrs)**	**Term Delivery (hrs)**
Group I	11.6±0.12	9.92±0.01	7.85±4.71	8±3.59	1.19±0.53	0.91±0.35
Group II	13.56±0.11	12.70±0.09	15.25±2.90	14.06±3.19	1.11±0.45	1.17±0.59
Group III	16.75±0.14	17.64±0.13	24.2±0.87	24.57±1.18	1.32±0.55	1.21±0.68

Table 8 Number of patients grouped by mode of deliveries and Regimen Group

	Group I	Group II	Group III
Vaginal Delivery	18/33 (54.54%)	15/33 (45.45%)	15/34 (44.12%)
Caesarean Section	13/33 (39.39%)	17/33 (51.51%)	18/34 (52.94%)
Operative Delivery	2/33 (6.06%)	1/33 (3.03%)	1/34 (2.94%)

Table 9 Total number of cases with adverse effects, cases that showed $MgSO_4$ toxicity, and breast feeding within 1 hour grouped by Mode of Delivery

	Cases with adverse effects			Cases that Showed $MgSO_4$ toxicity			Number of Patients who Breast Fed within 1 hour		
	Group I	Group II	Group III	Group I	Group II	Group III	Group I	Group II	Group III
Vaginal Delivery	2/18 (11.11%)	7/15 (46.67%)	11/15 (73.33%)	0/18	1/15 (6.67%)	2/15 (13.33%)	16/18 (88.89%)	11/15 (73.33%)	12/15 (80%)
Caesarean Section	3/13 (23.08%)	10/17 (58.82%)	14/18 (77.78%)	0/13	0/17	2/18 (11.11%)	3/13 (23.08%)	5/17 (29.41%)	3/18 (16.67%)
Operative Delivery	0/2 (0%)	1/1 (100%)	1/1 (100%)	0/2	0/1	0	1/2 (50%)	0/1	1/1 (100%)

Table 10 Time to return to ambulation, average duration of indwelling catheter, and time until contact with the newborn for different mode of deliveries

	Time to Return to Ambulation (hrs)			Average duration of indwelling catheter			Time until contact with new born (Average Time (hrs)		
	Group I	Group II	Group III	Group I	Group II	Group III	Group I	Group II	Group III
Vaginal Delivery	5.94±1.39	8.8±4.37	11.8±7.64	5.72±1.94	12.8±1.6	24.13±0.5	0.77±0.18	0.85±0.40	0.95±0.57
Caesarean Section	18.62±3.95	16.35±4.66	21.5±5.52	11.38±4.67	16.41±3.16	24.56±1.30	1.58±0.38	1.37±0.52	1.58±0.48
Operative Delivery	6	23	18	5±1.0	12.0	24.0	0.63±0.04	1.5	0.67

Clinical measures time like to return to ambulation, duration of indwelling catheter, and time until contact with the newborn are shown in Table 10.

DISCUSSION

BMI distribution across all three groups was similar to study by Dasgupta S *et al*[8]. The mean period of gestation in the present study was similar to studies by El-Khayat W *et al*[15] and Kashanian M *et al*[13], whereas in a study by Ranganna H *et al*[5] the mean period of gestation was slightly higher. The percentage of patients who had vaginal deliveries was similar to the study by El-Khayat W *et al*[15], and the significantly higher rate of caesarean deliveries was also observed in other studies like Nagaria T *et al*[3], Rimal SP *et al*[16], and Dasgupta S *et al*[8].

Group I showed the lowest percent of cases with adverse effects, suggesting that the regimen can improve patient satisfaction, while delivering similar results to a 24 hour regimen.

Only 2 patients were underweight, and both patients showed adverse effects. Group III showed the highest percent of cases with adverse effects, across all BMI categories. High percentage of patients in the overweight category showed adverse effects in Both Group I and III regimens. In Group III, 57.69% of cases that showed any adverse effects were pre-term delivery. This ratio was lowest (33.33%) for Group II.

Patients who underwent Caesarean section showed the highest number of adverse effects across all groups, and Group III showed the highest percentage of cases with adverse effects among them. The lowest percentage of adverse effects were observed for patients in Group I who had vaginal delivery, further suggesting Group I to be the preferable regimen for women having either vaginal or caesarean section.

No case of $MgSO_4$ toxicity was observed in Group I, suggesting the regimen as safer of the three. No case of toxicity was observed in underweight patients, and all cases were observed in the patients with normal BMI or overweight patients. Of all the four cases of $MgSO_4$ toxicity in Group III, two each were observed in women with vaginal delivery and caesarean section. In Group II, the only observed case of $MgSO_4$ toxicity was in the patient who had vaginal delivery.

For Group I and II, time to return to ambulation was higher for women who had pre-term delivery. On the contrary, for Group III, women with full term delivery showed higher time to return to ambulation. Generally speaking, Group I and II regimen offer better results for pre-term and full term deliveries. Patients who gave birth via vaginal delivery showed the lowest time to return to ambulation across all groups, and the difference between patients undergoing vaginal delivery and caesarean section was significant.

All underweight patients started breastfeeding within one hour. Lower percentage of patients who had pre-term deliveries commenced breastfeeding in Group I and III, and the

difference was insignificant in Group II. High fraction of patients who had vaginal deliveries started breastfeeding in an hour.

CONCLUSION

The present study indicates a single dose of $MgSO_4$ can offer similar results to a 24 hour regimen, while improving the quality of patient care, and minimising the adverse effects. When it comes to BMI, since most patients were in the normal range, Group I offered the best result, and making other conclusions is difficult, owing to small sample size.

Patients who have pre-term deliveries showed the highest number of cases with adverse effects, lower percentage of commencement of breastfeeding in an hour, higher time to return to ambulation, higher duration of indwelling catheter, and higher average time of contact with newborn across all groups. This indicates such patients must be carefully monitored, while on $MgSO_4$, and Group I (single dose) should be preferred for them.

Patients delivering via caesarean section showed similar results, indicating that a single dose can be used to improve patient experience in them.

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