COMPARISON OF LOW DOSE MAGNESIUM SULPHATE TO STANDARD PRITCHARD REGIME FOR TREATMENT OF ECLAMPSIA

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ABSTRACT

Objective: To compare the effect of magnesium sulphate in eclamptic patients receiving standard Pritchard regimen with those on low dose Magnesium sulphate**.**

Study Design: Randomized control trial. Setting: This study is conducted at Gynecology & Obstetrics department of Lahore General Hospital for the six months duration of study from 4th January 2018 to 3rd July 2018.

Subject and method: Through Consecutive non-probability purposive sampling, Total admitted 100 cases (50 in each group) of eclampsia after fulfilling the inclusion and exclusion criteria were included in this study. After taking informed consent, they were divided into 2 groups group A & B by random allocation based on table of random numbers. All patients in group A received standard Pritchard regimen, while those in Group B were given low dose Magnesium sulphate. Both groups received same antihypertensive medications (methyl dopa & nefidipine). Patient was observed for absence or presence of knee jerk, oliguria and seizure recurrence.

Results; In our study, only 14% of individuals who received low dose magnesium sulphate developed oliguria compared to 18% of standard Pritchard regimen (p-value = 0.585) .Similarly only 12% individuals among low dose group developed absent knee reflex compared to 14% of individuals who received Pritchard dose (p-value = 0.766). However, seizure recurrence was slightly increased among low dose group i.e., 10% compared to 8% of those who received standard Pritchard regimen (p-value = 0.727). Statistically low dose magnesium sulphate has been equally comparable for the treatment of eclampsia**.**

Conclusion; There is no statistical difference among the low dose group compared to Pritchard regimen, so low dose magnesium sulphate can be instituted in resource restricted areas of population where getting serum magnesium levels is not possible.

Keywords: Eclampsia, Magnesium Sulphate, Low Dose, Pritchard regimen.

INTRODUCTION

Eclampsia is defined as new-onset seizures which may be tonic-clonic or generalized in a pregnant woman with preeclampsia which may even lead to Coma and death. It is a serious life threatening manifestation of preeclampsia refers to any subsets of conditions in the last half of the pregnancy such as new onset central nervous system dysfunction, hepatic dysfunction, severely elevated blood pressure, thrombocytopenia, progressive renal insufficiency and pulmonary edema**[1]**

Incidence of eclampsia varies from 0.00016% to 0.0001 % in developed countries. However, in developing countries it increases to 0.0006% to 0.0157% of deliveries. Recurrent seizures occur in 10 % of eclamptic patients[2,3].

Magnesium sulphate ($MgSO_4$) stays the main therapy for prevention of seizures in eclampsia, According to Pritchard regimen[5] loading dose of 4gm $MgSO_4$ intravenously(i/v) followed by 10gm intramuscularly(i/m) and maintenance dose of 5gm i/m injection 4 hourly till 24 hours after delivery or last convulsion. As the margin of safety between therapeutic and toxic levels of magnesium sulphate is narrow, monitoring of the serum magnesium levels to assess the severity of situation is a difficult task as its toxicity can lead to development of muscular paralysis, respiratory and cardiac arrest. This has led to development of role of low dose $MgSO_4$ in many studies. It is now being advocated that in low-dose $MgSO_4$ loading dose of 4 gms, is given i/v followed by maintenance dose of 2 gms of magnesium sulfate i/m three hourly. If convulsions occurred with in 30 minutes after the loading dose, it is called recurrence of convulsions and in those cases an additional dose of 2 gm i/m. will be given. However, studies in this regard are few and more data is needed to confirm that this low dose $MgSO_4$ will lead to fewer side effects [2,3]. After this study if this low dose is equally effective as standard regimen in controlling seizures it will be used in the future for management of convulsions in eclampsia[2].

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Pharmacodynamics/Kinetics of MgSO4; Onset of action as an anticonvulsant by I/M route is 1 hour and by I/V route Immediately. Duration of anticonvulsant activity for I/M route is 3-4 hours and for I/V route for 30 minutes. It distributes up to 50% to 60% in bone. While remains in extracellular fluid up to 1% to 2%. Protein binding almost 30% of the magnesium is found to be bound to albumin. It is excreted in urine as magnesium. While in feces it is excreted in the form of unabsorbed drug if ingested orally.

MATERIAL & METHODS

The study was done in department of Gynaecology and obstetrics Lahore General hospital for period of 6 month from 03-01-2018 to 04-06-2018 by randomized controlled trial Sampling technique. By non-probability consecutive technique, a sample size of 100 patients was calculated (50 in each group) taking 5% level of significance and 80% power of test.

Inclusion criteria; Patients between age 18-45 years, raised blood pressure (systolic BP ≥140mmHg and/or diastolic BP ≥ 90mmHg), history of new onset convulsions after 20 weeks of gestation but no more than 4 weeks postnatally. Exclusion criteria; the patients before 20 weeks of gestation, suffering from seizures, renal insufficiency, hypertension or proteinuria, previously taking anti-epileptic, anti-psychotic, suffering from other causes of loss of consciousness or altered mental status secondary to hypoglycemia, cerebrovascular accidents, Hypoglycemia, meningitis and encephalitis determined through history and examination.

This study was performed after approval from the Hospital ethical committee. After taking informed consent, 100 patients (50 patients in each group) admitted with eclampsia were divided into 2 groups A & B by random allocation.

In group A received standard Pritchard regimen (loading dose of 4gm MgSO4 diluted in 20ml normal saline given slowly i/v over a period of 5 minutes followed by 10gm i/m injection and maintenance dose of 5gm i/m injection 4 hourly on alternate buttocks till 24 hours after delivery or after last convulsion whichever was later.

In group-B the low-dose regime was used that was 4gms of $MgSO_4$ as loading dose, given i/v followed by maintenance dose of 2 gms i/m three hourly. If convulsions occurred with in 30 minutes after the loading dose, in those cases an additional dose of 2 gm i/m. was given. Patients were observed in high dependency area & managed additionally for delivery control. Both groups received same antihypertensive medications (methyl dopa & nefidipine). The outcomes were presence or absence of normal knee reflex,<30ml/hour urine output(oliguria) and recurrence of seizers in both groups.

The data was entered on the pre-formed Performa for analysis. All data was be entered and analyzed using SPSS version 22. Qualitative data like loss of knee tendon reflex and oliguria was presented in form of frequency (%). The quantitative data like age, BMI was presented in form of mean ± S.D. Chi-square test was used to compare loss of knee reflex and oliguria in both study groups. P-value ≤ 0.05 was considered as significant. Data was stratified for age, gestational age and BMI. Chi-square test was used post stratification with p-value less than 0.05 considered as significant.

RESULTS

In this study the mean age of the patients was 28.56 with standard deviation(S.D) of 5.575 with minimum age of 18 years and maximum of 39 years and mean weight of patients was 82.21kg (S.D 15.877) with minimum weight of 45kg and maximum of 128kg.The mean height of patients was 1.69m(S.D 0.068) with minimum height of 1.45m and maximum of 1.82m.The mean BMI of patients was 28.58(S.D 6.665) with minimum BMI of 15 and maximum of 46.

In this study among the low dose group mean age was 27.64years, mean weight was 80.5kg, mean height was 1.6934, mean BMI was 28.4015, 16.986, 0.7430, 7.37794, and 0.93044 respectively. However, those in Pritchard group had mean age was 29.48 years, mean weight was 81.92kg, mean height was 1.6932, mean BMI was 28.7680 and S.D of 5.575, 15.87724, 0.06785, 6.66474, and 0.87496 respectively (Table#1).

In this study patient developed Oliguria among the low dose group and Pritchard group showed only 14% developed oliguria in low dose group vs 18% of those on Pritchard regimen respectively with p-value of 0.585. (P-value = 0.585) as shown in Table#2. None of the patients in underweight and morbidly obese category developed any oliguria. (P value = 0.753, non-significant).

In our study13 out of 100 individuals developed loss of ankle reflex. There were only 12% patients in low dose group vs 14% of those on Pritchard regimen respectively with p-value of 0.766 as shown in Table #3. None of the patient was underweight and morbidly obese category developed absent knee reflex. (P value = 0.700, non-significant).

In our study recurrence of seizures within seven days of institution of last dose of magnesium sulphate developed in 9 out of 100 patients out of these 9 patients 5 were among the low dose group while 4 received Pritchard regimen with p value of 0.727 as

shown in Table#4. Odds ratio of seizure recurrence with low dose is 0.783 times as compared to Pritchard regimen. Relative risk for outcome to be have seizures in low dose group is 1.25.

Table # 1: Distribution of variable in Study groups

Study Group		Age	Weight (kg)	Height (m)	BMI	Gestational Age (weeks)
Low Dose	Mean	27.64	80.5000	1.6934	28.4015	3.10
	N	50	50	50	50	50
	Std. Deviation	5.813	16.98649	.07430	7.37794	1.129
Pritchard Dose	Mean	29.48	81.9200	1.6932	28.7680	3.14
	N	50	50	50	50	50
	Std. Deviation	5.223	14.82392	.06149	5.93646	1.088
Total	Mean	28.56	81.2100	1.6933	28.5848	3.12
	N	100	100	100	100	100
	Std. Deviation	5.575	15.87724	.06785	6.66474	1.104

Table # 2: Incidence of Oliguria across study group

			Study Group		Total
			Low Dose	Pritchard Dose	
Oliguria	No Oliguria	Count	43	41	84
		% within oliguria	51.2%	48.8%	100.0%
		% within Study Group	86.0%	82.0%	84.0%
	Oliguria	Count	7	9	16
		% within oliguria	43.8%	56.3%	100.0%
		% within Study Group	14.0%	18%	16.0%

Table # 3: Incidence of Absence of Knee Reflex across study groups

			Study Group		Total
			Low Dose	Pritchard Dose	
Absent Knee Reflex	No	Count	44	43	87
		% within Absent Knee Reflex	50.6%	49.4%	100.0%
		% within Study Group	88.0%	86.0%	87.0%
	Yes	Count	6	7	13
		% within Absent Knee Reflex	46.2%	53.8%	100.0%
		% within Study Group	12.0%	14.0%	13.0%

Table # 4: Incidence of seizure recurrence across study groups

			Study Group		Total
			Low Dose	Pritchard Dose	
Seizure Recurrence within 7 days of institution of dose of Magnesium sulphate	No	Count	45	46	91
		% within seizure recurrence within 7 days of institution of dose of Magnesium sulphate	49.5%	50.5%	100.0%
		% within Study Dose	90.0%	92.0%	91.0%
	Yes	Count	5	4	9
		% within seizure recurrence within 7 days of institution of dose of Magnesium sulphate	55.6%	44.4%	100.0%
		% within Study Group	10.0%	8.0%	9.0%

DISCUSSION

Magnesium sulphate is the main drug for seizures treatment in eclamptic patients.[3,4]. Monitoring serum magnesium levels is a cumbersome method in resource restricted setup of developing countries like Pakistan and without monitoring serum levels, risk of magnesium toxicity increases which present in form of oliguria and absent deep reflexes initially. However, with institution low dose magnesium sulphate these risks can be decreased. In our study, only 14% of individuals who received low dose magnesium sulphate developed oliguria compared to 18% of standard Pritchard regimen (p-value =0585, nonsignificant). Similarly, only 12% individuals among low dose group developed absent ankle reflex compared to 14% of individuals who received Pritchard dose (p-value = 0.766, nonsignificant). However seizure recurrence was slightly increased among low dose group i.e, 10% compared to 8% of those who received standard Pritchard regimen (p-value =0.727.nonsignificant). There were 5 patients in low dose group compared to 4 in Pritchard dose group who developed recurrent seizures who were then shifted to Pritchard standard dose magnesium sulphate dosage to prevent further seizures. Statistically low dose magnesium sulphate has been equally effective in treatment of eclampsia while lowering the risk for development of magnesium toxicity [3,4]. Some of the studies are discussed below which compare the low-dose magnesium sulphate to standard Pritchard regimen: According to study by Latika Sahu and et all, incidence of loss of deep tendon reflexes is 16% vs 44% in low dose vs Pritchard regimen, while for that of oliguria is 4% vs 20% respectively[5,6,7,8].

Sahu showed that there was 16% loss of knee jerk in low dose magnesium sulphate group compared to 44% in standard dose magnesium sulphate group. However, in our study this has come down to only 12% vs 14% respectively (p-value = 0.766). while Sahu observed oliguria to be 4% vs 20% in low dose vs standard dose magnesium sulphate group respectively, in our study this has come to10% compared to 8% (p-value = 0.585). This could be due to the larger sample size of our study. Moreover one patient developed oliguria while being on low dose magnesium sulphate and didn't develop any loss of knee reflex study by Saha Pk on 42 patients compared low dose Dhaka regimen with standard dose Zuspan regimen and found that there was no significant differences in seizure recurrence, however dose had to be defferd in Zuspan regimen due to increased incidence of loss of knee jerk in group that received low dose Dhaka regimen, which is consistent with our study [7,8] . In our study there was also seizure recurrence of 0% (low dose group) vs 8% (standard dose group) with p-value of 0.00 which is significant. Bhattacharjee et all75 observed that in 144 patients that incidence of fit recurrence in low dose magnesium sulphate was statistically insignificant when compared to standard dose magnesium sulphate (7.46% vs 8.57%, p= 0.939), however in that study there was no statistical difference in development of magnesium toxicity among both the groups as none of the patients in either group developed toxicity in their study. In our study 12% patients in low dose group vs 14% of those on Pritchard regimen respectively with p-value of 0.00 developed loss of knee jerk.

. While this incidence was 14% vs 18% in terms of oliguria when comparing low dose magnesium sulphate to standard Pritchard regimen respectively. Mahajan NN showed that loss of knee jerk was present in 41% of the individuals in low dose magnesium sulphate group[10]. Which was too high compared to our study group that was only 12% patients developed absent knee jerk. Which is quite low but in the study of Mahajan NN these 41% patients had received either diazepam or Phenergan for treatment of recurrent fits. An integrative review by Jeffry et all showed the overall rate of absent deep tendon reflex among all 9556 aggregated women was 1.6%, with a range of 0-57%.[11]. Patients in our study has loss of deep tendon reflex (knee reflex) in 12% with low dose magnesium sulphate vs 14% in standard dose magnesium sulphate respectively which is compatible with the above stated review. Increased weight and obesity have been implicated with increased incidence of eclampsia in general population as well in other studies[9,10,11].

A systemic review of 753 publications evaluated magnesium sulphate for treatment of eclampsia revealed that when low dose regimen was compared to Pritchard regimen there was no difference in eclampsia recurrence, which is consistent with our study where 10% in low dose suffered seizure recurrence vs 8% in standard Pritchard regimen,[11,12]. However sample size of our study was small to conclude it is definitively. Magnesium toxicity stays as a concern when it comes to eclampsia prophylaxis in patients, there has been other studies like one by Keepanasseril which compared single loading dose of Magnesium sulphate with low dose Dhaka regimen for seizure prophylaxis in severe preeclampsia using a randomized controlled trial in 402 women.[13]. In the low-dose Dhaka regime, injection site abscess and respiratory depression occurred in one woman each group which implies that drug toxicity can

occur even when only a single loading dose is given to the patient[12,13].

CONCLUSION

Low dose magnesium is not inferior to standard dose Pritchard regimen for management of eclampsia. There is no statistical difference among the low dose group compared to Pritchard regimen, so low dose magnesium sulphate can be instituted in resource restricted areas of population where getting serum magnesium levels is not possible. The low dose will be cost effective and will make easier to monitor patients in heavy overburden hospitals. Adoption of low dose treatment can cope with fear of toxicity of drug which is linked to high serum magnesium levels and can be life saving for mother with low dose of magnesium sulphate.

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