Feasibility of low dose magnesium sulphate for eclampsia – a randomized study

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Abstract

Introduction: Eclampsia is a preventable malady, yet remains a leading cause of maternal mortality and morbidity worldwide. Magnesium sulphate despite being the anticonvulsant of choice largely remains underutilized in low resource settings due to various constraints. Tailoring the dose as per local needs has given the scope to adopt a lower dose in these countries. We aimed to compare the efficacy of low dose regimen of magnesium sulphate ($MgSO_4$) with Pritchard's regimen in patients of eclampsia.

Method: A prospective cross sectional study was carried out in the department of Obstetrics and Gynecology at Himalayan Institute of Medical Sciences, Dehradun, India over a period of one year which included a total of 60 patients of eclampsia divided into two groups by randomization. Group A received low dose magnesium sulphate (Dhaka regimen) and Group B patients were managed with Pritchard's regimen of $MgSO_4$. The recurrence of fits, toxicity profile and feto-maternal outcome was studied. Data generated was analyzed using SPSS version 20.

Results: Majority of the patients were primigravida (66.67%) and unbooked (73%). Low dose regimen was equally effective in controlling the seizures and only two patients (6.6%) had recurrent seizures (p=1.00).Incidence of loss of deep tendon reflex was 10% with low dose $Mgso_4$ and 13.3% with standard dose (p=0.69). Mean values of serum magnesium in both the groups was comparable. There was one maternal death in our study.

Conclusion: With an efficacy comparable to Pritchard's regimen in controlling eclampsia, low dose $Mgso_4$ is a viable alternative especially at primary and secondary health care levels.

Keywords: Dhaka regimen, eclampsia, low dose magnesium sulphate, Pritchard's regimen, recurrent convulsion

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Introduction

Eclampsia remains an important cause of maternal and perinatal morbidity and mortality in under privileged population. An estimated 50,000 women die each year globally.[1] Magnesium sulphate ($MgSO_4$) is the anticonvulsant of choice which prevents and controls eclamptic fits and also reduces maternal and neonatal morbidity.[2] Despite its proven benefits, the acceptance of $MgSO_4$ in many low and middle income countries remains low, especially at primary and secondary care levels. Apprehension regarding its dose related toxicity remains the main limiting factor particularly in clinical environments where the capacity for patient monitoring is limited.[3,4]

Ever since the introduction of Pritchard regime, appropriate dose of magnesium sulphate and therapeutic serum magnesium levels have always been a matter of debate.[5] Witlin recommended an adjustment of dose according to patient's body mass index.[6] Therefore, it appears logical to modify the dose of magnesium sulphate especially in Asian women with lower BMI. Various studies have been carried out to determine the lowest effective dose and these modifications have shown promise in terms of decreased side effects and comparable efficacy but available data are too limited to draw a reliable conclusion.[4,7,8] The present study was therefore conducted to compare the efficacy and safety of low dose regimen of $MgSO_4$ as proposed by Mosammat Rashida Begum with standard Pritchard's regimen in Uttarakhand state of northern India which lacks any such study.[3,5]

Material and Methods

This prospective cross sectional study was carried out in the department of Obstetrics and Gynecology, Himalayan Institute of Medical Sciences, Dehradun from January 2013 to January 2014 after taking approval from the institutional ethical committee. This is a tertiary care teaching hospital located in the periphery of Dehradun city attending referred patients from Garhwal region of Uttarakhand and western Uttar Pradesh states of India. All cases of impending eclampsia, antepartum and postpartum eclampsia presenting in obstetric emergency were included in the study. The patients who had already received either magnesium sulphate or any other anticonvulsant before coming to this Institute were excluded from the study. An informed consent was obtained from the patient or if she was not conscious, from the patient's spouse or the nearest relative. A detailed history and thorough

clinical examination was carried out in all the patients along with relevant investigations which included blood group and Rh type, complete hemogram, platelet count, liver function tests, kidney function tests, coagulation profile, urine analysis for proteinuria and fundoscopy.

A computer generated software (star trek) was used to assign patients into two groups by randomization. Group A received low dose $MgSO_4$ -Dhaka regimen. This comprised of a loading dose of 4 grams of $MgSO_4$ intravenous in dilution and 3 grams intramuscular (i.m) in each buttock (10 grams). A maintenance dose of 2.5 grams (i.m) was given 4 hourly in alternate buttock. Cases in group B received $MgSO_4$ as per Pritchard's regimen. This included a loading dose of 4 grams intravenously in dilution and 5 grams of magnesium sulphate deep intramuscularly in each buttock (14 grams). Subsequently 5 grams of $MgSO_4$ were given i.m every 4 hourly in alternate buttock. In both the groups, drug was continued for 24 hours after the delivery or last seizure, whichever was later. Patients were monitored for oxygen saturation, blood pressure and pulse rate.

Evidence of magnesium toxicity was detected by observing respiratory rate, patellar reflexes and urinary output four hourly. Maintenance dose was skipped if deep tendon reflexes were absent, respiratory rate was <16 per minute or urinary output less than 30 ml per hour. If seizures reappeared or were not controlled after Dhaka regimen, it was considered as failure of the regime and then standard dose of $Mgso_4$ was given. Labetalol injection was given as antihypertensive when the diastolic blood pressure was more than 110 mm Hg, in the initial dose of 10 mg intravenously. It was then increased to 20 mg after 10 minutes or further to 40 mg if needed. The aim was to bring the diastolic blood pressure to ≤ 100 mm Hg. When the patient was stabilized, obstetric management was carried out according to Bishop's Score, gestation age and viability of the fetus.

Blood samples for serum magnesium were drawn 4 hours after the loading dose in both the groups (before giving maintenance dose), before the last dose of $MgSO_4$ and when clinical signs of toxicity appeared.Calmagite method was used to estimate serum magnesium levels. The height and weight of the patients were recorded in the immediate postpartum period when the patient was ambulatory (3^{rd} or 4^{th} postpartum day). The primary objective of the study was to determine the efficacy of low dose regimen in managing eclampsia by studying the recurrent convulsion rate. Maternal complications, birth weight of the baby, Apgar score and neonatal outcome were evaluated in low dose and standard dose groups as a secondary objective. Data was analyzed using SPSS version 20. The chi square test was used to determine statistical significance for categorical variables and a p value ≤ 0.05 was taken as significant.

Results

There were a total of 1872 deliveries in the institute during the study period. Out of these, 60 cases of eclampsia satisfying the inclusion and exclusion criteria were studied. The incidence of eclampsia was 3.2%. The mean age of the patients was 25.5 years. Majority of patients were primigravida (66.67% and 76.67% in groups A and B respectively) and received no prenatal care as shown in Table 1. The distribution of cases according to gestation age in both the groups is also depicted. Most of the patients were of antepartum eclampsia (73.3% and 80%) in both the groups, followed by impending eclampsia (20% and 16.6% respectively). In this study, the patients of antepartum eclampsia were weighed on third or fourth day of delivery when the patient was ambulatory. 6.1% patients weighed ≤ 40 kg, majority (84.2%) weighed between 40–50 kg, 7.4% were between 50–60 kg and 2.3% cases were more than 60 kg.

The hematological and biochemical parameters were found to be comparable in both the groups. As shown in Table 2 there was no significant difference in maternal complications in both the groups. One patient died in Group B due to disseminated intravascular coagulopathy (DIC). 57% patients in group A and 63% in group B delivered vaginally and lower segment caesarean section (LSCS) was carried out mainly for fetal distress and non progress of labour.

Neonatal outcome is summarized in Table 3. Apgar score, stillbirth rate and neonatal death rate were comparable in both the groups. There were 53% low birth weight babies in group A and 46.6% in group B. Neonatal deaths were mainly due to birth asphyxia, respiratory distress syndrome and septicemia.

No patient in the standard dose group and two patients in lower dose group had recurrence of seizures during maintenance dose of Dhaka regimen and required to be shifted to Pritchard regimen for seizure management. An improved outcome was observed with low dose regimen. Four (13%) patients in group B compared to three patients (10%) in group A experienced loss of deep tendon reflexes. Six (20%) patients developed oliguria in standard dose group compared to two (6.6%) patients on low dose regimen of $MgSO_4$.Therefore maintenance dose of $Mgso_4$ was skipped in these patients. Mean serum magnesium level on absence of knee jerk in group A was 3.43±0.05mg/dl and3.87±0.32mg/dl in group B. The values of mean serum magnesium at the time of oliguria in groups A and B were 4.5±0.14 mg/dl and 4.76 ±0.31 mg/dl respectively. However, mean serum magnesium levels in group A and group B were comparable.

Table 1: Patient characteristics in the two groups

Age Group (years)	Group A (n=30)	Group B (n=30)
20 – 25	18(60%)	16(53.33%)
26 – 30	9(30%)	10(33.33%)
31 – 35	3(10%)	4(13.33%)
Mean age	25.5±4.14	25.96±4.67
Booked/unbooked		
Booked	8(26.67%)	13(43.33%)
Unbooked	22(73.33%)	17(56.67%)
Parity		
Primigravida	20(66.67%)	23(76.67%)
Multigravida	10(33.33%)	7(23.33%)
Gestational age		
< 28 weeks	5(16.67%)	1(3.33%)
28 – 31.6 weeks	3(10%)	7(23.33%)
32 – 35.6 weeks	15(50%)	9(30%)
≥ 36 weeks	7(23.33%)	13(43.33%)

Table 2: Maternal morbidity and mortality in the two groups

Maternal Complications	Group A (n=30)	Group B (n=30)	Chi square	p value
Abruptio placentae	4(13.33%)	2(6.67%)	0.73	0.670
Oligohydramnios with IUGR	8(26.67%)	8(26.67%)	0	1.00
Abnormal coagulation profile	11(36.67%)	11(36.67%)	0	1.00
Oliguria	4(13.33%)	3(10%)	0.16	0.690
Preterm labour	10(33.33%)	8(26.67%)	0.02	0.884
Postpartum haemorrhage	3(10%)	3(10%)	0	1.00
Acute renal failure	3(10%)	2(6.67%)	0.21	0.643
DIC	2(6.67%)	2(6.67%)	0	1.00
Mortality	0(0.00%)	1(3.33%)	1.00	0.317

Table 3: Neonatal outcome in the two groups

Outcome	Group A (n=30)	Group B (n=30)	Chi square	P value
Live Births	19(63.33%)	22(73.33%)	0.68	0.409
Still births	11(36.67%)	8(26.67%)		
Intrapartum deaths	0(0.00%)	2(6.67%)		
Intrauterine deaths	11(36.67%)	6(20%)		
	n=19	**n=22**		
Mean birth weight	1.80±0.67	1.93±0.62	t= 0.645	0.522
Apgar Score				
8 – 10(normal)	9(47.37%)	12(54.54%)		
6 – 7(mild asphyxia)	3(15.79%)	6(27.27%)		
4 – 5 (moderate asphyxia)	6(31.58%)	4(18.18%)		
0 – 3 (severe asphyxia)	1(5.26%)	0(0.00%)		
NICU Admission	15(78.95%)	17(77.27%)	0.26	0.607
Neonatal Mortality	4(21.05%)	4(18.18%)	0.00	1.00

Discussion

Magnesium sulphate has been recommended by World Health Organization (WHO) as the most effective and safe drug for prevention and control of seizures in eclampsia.[9] Begum and co-workers had reported that half of the standard dose of $MgSO_4$ appeared to be sufficient to control convulsions. Considering the effectiveness of their regimen in low resource settings, the present study was undertaken.

The incidence of eclampsia in India ranges from 0.5% to 1.8% but in our study it was 3.2%.[10] This is because this health facility being a tertiary care hospital receives such patients from near and far off places. A higher incidence of 9% and 5.2% of eclampsia was also found by Ekele et al and Begum et al respectively.[3,11] Majority of patients in our study were antepartum eclampsia that is also observed by Begum et al and Regmi et al.[3,12] Eclampsia is a disease of primigravida which was seen in this study as well. Jana et al reported 89.7% primigravida with eclampsia in their study.[13] Pritchard et al observed 75% of eclampsia cases in primigravida and similar observations were made by Begum et al and Bhattacharjee et al.[3,14] Most of our patients were unbooked and never received any antenatal checkup (ANC) which remains the corner stone for prevention of eclampsia. This was also observed by Ekele et al and Jana et al.[11,13] As eclampsia is a sequel to uncontrolled and elevated blood pressure, therefore, regular ANC, screening and treatment of preeclampsia remains the key factor to prevent such morbidity.[15] Previously the collaborative group had concluded that there was compelling evidence in favour of $MgSO_4$ for the treatment of eclampsia but it is seen that the health personnel are reluctant to administer it, instead prefer diazepam or phenytoin probably fearing potential toxicity due to standard dose of $MgSO_4$.[2] Timed management and transportation of these patients to hospital could prevent maternal and fetal catastrophe if only the drug is given at peripheral health centres in a lower dose without fear.

Magnesium has a narrow therapeutic index (4-7 meq/l). Therefore, for evaluating toxicity, all our patients were monitored clinically and by serum magnesium levels. A higher number of patients lost deep tendon reflexes with Pritchard's regimen. It was however seen that serum magnesium levels did not correlate with clinical parameters and remained within therapeutic range. Similar observations were also made by Shilva et al and Chinayon et al.[7,16] Ekele and Badung also found serum magnesium levels within the therapeutic range and discouraged routine estimation of serum magnesium during magnesium sulphate.[17] Therefore, for judging toxicity, clinical monitoring seems more feasible than serum magnesium levels and the former is always stringently required for Pritchard regimen thereby restricting its use in resource poor settings with inadequate manpower.

Seizures were well prevented and controlled in our study except in two patients (6.6%). Begum et al reported only one case of recurrent convulsion out of 65 in their study where as a recurrence rate of 10-20% was quoted by Pritchard et al and Sibai.[3,5,18] Recurrence rates varying from 4.6% - 8% were reported by some researchers with low dose $MgSO_4$ in their studies.[19,20,21] It therefore seems that a lower dose of $MgSO_4$ is equally effective in managing eclamptic convulsions.

The reported maternal mortality due to eclampsia ranges from 0.4% to 14% depending on the severity of the organ damage and delay in initiation of treatment.[6] In the present study there was no maternal mortality in group A and one patient expired in group B due to DIC and renal shut down. Begum et al and Shilva et al also reported nil maternal mortality.[3,7] A lower maternal mortality (2.7% versus 3.2%) compared to collaborative trial was observed by Jana et al in their series.[13] In our study a high incidence of still births was seen in both the groups (36.6% and 26.6%) respectively. This is due to the fact that patients present to this health facility quite late and majority of them had neglected antepartum period. Perinatal mortality of 32%, 48% and 38% was reported by Shilva et al, Ekele et al and Seth et al respectively and comparable data was also reported by Sardesai et al. [7,17,19,21]

Our study had certain limitations. This was a small study carried over a short duration. However, it can contribute to the literature regarding the efficacy and safety of low dose of magnesium sulphate as it has been a comparative study between two widely popular regimens. To increase confidence in the findings, a randomized, multicentric trial on a larger sample and for a longer duration is necessary.

Conclusion

Low dose regimen is a viable alternative to standard dose of $Mgso_4$ especially in developing countries. With favorable toxicity profile and efficacy comparable to Pritchard's regime, low dose $MgSO_4$ can be adopted at primary health centres (PHCs) and rural hospitals in India without involving much manpower.

Conflict of Interest: None

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