Low Dose Magnesium Sulfate in Eclampsia

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ABSTRACT

In this prospective study we tried to assess the safety and efficacy of intravenous low dose magnesium sulfate for the management of eclampsia. A total of 100 women with eclampsia were divided into a study group and a control group, 50 women in each. The study group received 4 grams intravenous loading of magnesium sulfate and maintenance dose of 2 grams intravenous Magnesium Sulfate every 3 hours, up to 24 hours since the last fit or delivery, whichever was last and the control group was given the standard intramuscular regimen as advocated by Pritchard. The primary outcome was recurrence rate of seizures. The secondary outcome measures were development of magnesium toxicity if any, maternal and perinatal outcomes. The difference in the incidence of fit recurrence was not significant (p=0.31). Low dose magnesium sulfate regimen was as effective as standard intramuscular regimen in controlling the seizure of eclamptic women while maintaining high safety margin.

Keywords: Eclampsia, magnesium sulfate, low dose, Pritchard regimen, recurrent convulsion

INTRODUCTION

Hypertensive disorder of pregnancy is one of the major causes of maternal and fetal morbidity and mortality.[1] Eclampsia is a multisystem disorder with complex pathogenesis, not completely understood. Precipitation of convulsion due to cerebral involvement can kill the mother and fetus unless expertly managed.[2]

Globally it accounts for 10 to 12 % of maternal deaths of which 97% occur in the developing countries.[3] The major burden of maternal death is in Sub-Saharan Africa and South Asia, where the risk of death is nearly 200 times greater as compared to developed countries.[4] In India eclampsia accounts for 8% of maternal mortality as compared to 21% in Nepal.[5,6]

The superiority of magnesium sulfate over diazepam and other anticonvulsants in the management of eclampsia has been universally accepted.[7,8] The drug is considered as an affordable, safe and effective medical intervention in reduction of maternal mortality.[8] It halves the risk of eclampsia.[7,8,9]

The patient on magnesium sulfate needs to be monitored regularly for urine output, respiratory rate and tendon reflexes.[7,10] There is a risk of toxicity with higher doses of magnesium sulfate. Potential hazards include maternal hypotension, respiratory depression, respiratory arrest and even cardiac arrest.[10]

Due to apprehension regarding these hazards, limited use of this drug in many low income countries has been noted.[11] Reducing magnesium toxicity without compromising its efficacy in controlling seizures and lowering the mortality rate is still a challenge.[12] These problems have spurred researchers to conduct trials to identify a lower and a shorter dose regimen that controls the convulsion without any undue complications.[11,12] This study aims at assessing the safety and efficacy of intravenous low dose magnesium sulfate for the management of eclampsia.

MATERIALS AND METHODS

This is a randomized comparative interventional study over a period of one year from February 2011 to March 2012 in the Department of Obstetrics and Gynecology of Universal College of Medical Sciences and Teaching Hospital, Bhairahawa.

One hundred consecutive cases of antepartum, intrapartum and postpartum cases were selected for the study. Sample size was estimated using the formulae for estimation of sample size.[27] Patients with severe preeclampsia, cases of convulsion due to other causes and those with known systemic diseases and those who did not give consent were excluded from the study. Patients were matched for age and parity. Those who fulfilled the inclusion criteria were selected and allocated to receive either the standard regimen (control group) or low dose regimen (study group). The protocol for low dose regimen was a loading dose of 4 gms of magnesium sulfate in 20 ml of distilled water slow intravenously over 10 to 15 minutes, and 2 gms of magnesium sulfate in 10ml of distilled water intravenously slowly every 3 hours till 24 hrs after the last fit or delivery, whichever was later as maintenance dose. Standard regimen referred to: 4gms of Magnesium sulfate slowly intravenously over 5 mins followed by 5 gms of magnesium sulfate intramuscularly in the gluteal region. Then 5 gms of magnesium sulfate intramuscularly every 4 hrs till 24 hrs of the last fit or delivery whichever was last. If convulsion recurred within 30 mins after the loading dose,

an additional 2 gms of magnesium sulfate was administered in both the regimen.

Follow up was done until the patient was discharged from the hospital. Approval for the study was taken from the ethical committee of the hospital.

The patients were monitored with particular attention to respiratory rate, urine output and patellar reflex. In case of signs of magnesium sulfate overdose, administration of magnesium sulfate was stopped and 10 ml of 10% Calcium gluconate over 10 mins was administrated intravenously. A sublingual Nifedipine capsule or oral Nifedipine was used to control blood pressure depending on the level of consciousness. Obstetric management was carried out after stabilizing the patient.

We observed the recurrence of seizures, maternal & perinatal outcome and development of magnesium toxicity, if any. Perinatal outcome was recorded in terms of live and still birth. Any complication in terms of (PPH) post partum haemorrhage and pulmonary edema were noted.

Data analysis was done using SPSS 17 and PHSTAT 2; z-test and chi square test was used to test for levels of association between the variables; p-value was calculated under predetermined level of significance of 0.05.

RESULTS

A total of 100 women (50 in each group) were evaluated during the study period. The mean age of whole study group was 22.04± 5.25 SD. The mean age of the study group was 22.62±5.70SD and that of control group was 21.46±4.76 SD. Majority of the women with eclampsia were between the age group of 20-30 years in both the groups.The difference was not statistically significant. (p value=0.26). The youngest woman with eclampsia in the low dose group was 17 years and that in the Pritchard group was 16 years. The oldest age being 40 years in both the groups. (Table 1)

Table 1: Clinical Details

S.N.	Patient Characteristics		Standard regimen	Low dose regimen
1	Age in years	<20	19	12
		20--30	29	34
		>30	2	4
2.	Parity	1	42	36
		2 -- 4	6	10
		>4	2	4
3.	Type of Eclampisa	Antepartum	47	48
		Intrapartum	1	0
		Postpartum	2	2
4.	Gestational age at delivery	>36	38	42
		<36	12	8
5.	Mode of delivery	C- section		
		SVD		
6.	Antenatal care	No		
		Yes		

Majority of the women in both the groups were primigravida. (78%) ; 36 women (72%) in the low dose regimen and 42 women (84%) in the control group were primigravida. The difference between these two groups are not statistically significant (p=0.34) ; 10 women (20%) and 6 women (12%) were multigravida in the study group and the control group respectively. Four (8%) and 2 (4%) of the patients were grandmultipara in the study group and control group respectively. (Table 1)

Most of the patient were in the gestational age group of 36-42 weeks in both the groups. Forty- two (84%) in the study group and 38 (76%) in the control group. The difference was not statistically significant (p= 0.31). Eight (16%) in the low dose and 12 (24%) in the Pritchard regimen were in the gestational age less than 36 weeks. (Table 1).

For women who entered the trial before delivery, there was no significant difference between the caesarean rate 25 (25/50; 50%) in the low dose and 23 (23/ 50; 46%) in the Pritchard regimen (p=0.68). Rest of the patients delivered vaginally. (Table 1) The difference in the incidence of fit recurrence after the initiation of treatment with the magnesium sulfate was not statistically significant when both the groups were compared (p= 0.31). Only one patient had recurrence of fit making an incidence of 2% in the study group. The recurrence which she had was after the initial loading dose. Two grams (4ml of 50% magnesium sulfate) was given intravenously slowly and this was adequate to control the convulsion in the patient. There was no recurrence in the control group. (Table 2)

Table 2: Recurrence rate

Recurrence	Standard regimen	Low dose regimen
Yes	0	1
No	50	49
Total	50	50

There were no maternal deaths in either group. There was no significant difference between the serious maternal morbidity. In the study group and control group, 3 patients (6%) and 4 (8%) had postpartum hemorrhage (PPH) respectively. The difference between the two groups were not statistically significant (p=0.69). In study group, 8% of the patient and in the control group, 4 % developed pulmonary edema. This observation was not statistically significant (p=0.39). (Table 3).Magnesium sulfate toxicity was not observed in either of the regimens. Among the babies in the antepartum and intrapartum eclampsia 8% in both the regimens were still born. (p=1) (table 4)

Table 3: Maternal Complications.

	Standard regimen		Low dose regimen
Type of complication	Pul. edema	2	4
	PPH	4	3

Table 4: Perinatal outcome

Perinatal outcome	Pritchard regimen	Low dose regimen
Live Birth	46 (92%)	46 (92%)
Still Birth	4 (8%)	4 (8%)

DISCUSSION

"She who is living between life and death is the exact translation that describes a pregnant woman especially in developing countries illustrating the risk a woman faces when she becomes pregnant."[13] Eclampsia was recognized centuries ago as a seizure occurring uniquely in the context of pregnancy, as they resolved with delivery.[9] Eclampsia is a multisystem disorder with complex pathogenesis, cerebral involvement causing convulsion, which can kill the mother and fetus unless timely and expertly managed.[9]

A hundred eclamptic patients were encountered out of 3463 deliveries in the study period of one year. The incidence of eclampsia in our study was 2.8% which is comparatively higher than the developed countries, 0.04% in USA ,0.03% in UK& 0,06% in Netherlands.[14-16] But the incidence in our study is slightly higher compared to the observation of 1.28% by Chowdhury, 1.7% by Seth from India and 1.2% of Regmifrom eastern Nepal.[17-19] It reflects the lack of awareness, illiteracy, social constraints and poor or no antenatal care in this part of the country.

Studies in India and Bangladesh have revealed that early age at marriage and young age pregnancy are the social practices in these parts of the world [2,17]. From our study we observed that Nepal is not an exception.

Regmi *et al* observed incidence of eclampsia was up to 86% in primigravida, similar incidence was observed in our study.[19] Similar observations were also noted by Indian and Bangladeshistudies.[2,11,17,20] Antepartum eclampsia was observed in 95% of women in our study. Chowdhury *et al* from India and Regmi *et al* also reported the same.[17,19]

The eclampsia Trial Collaborative group concluded that magnesium sulfate is the drug of choice for the management of eclampsia.[7] Yet there is a great deal of controversy regarding its mechanism of action.[21] Some authors suggest that it has a peripheral anticonvulsant action while others argue that the anticonvulsant action is mediated through central action.[21] Another group of investigators explained that the ionized magnesium that exists after administration prevents eclampsia by selectively dilating the central vasculature and relieving vasospasm associated with preeclampsia.[21]

But, a potential concern for the magnesium sulfate therapy is its narrow therapeutic index and the risk of side effects which would increase with higher doses.[10] The low dose regimens are based on the concept that the average women in the Indian subcontinent has a low BMI as compared with women in several other parts of world.[20] The advantage of intravenous low dose regimen is that the patient need not take repeated painful intramuscular injections as well.[20]

Although magnesium sulfate is a potent anticonvulsant drug, at times convulsions recur. In the 2 controlled trails, they observed 13.2% and 5.7% recurrence.[7] Chowdhury *et al*observed recurrence rate of 1.57% and 3.3% in the low dose intravenous and standard regimen respectively[17]. In a comparative interventional study done by Bhattarchjee *et al* observed incidence of 7.46% in the intravenous and 8.57% in the intramuscular regimen.[20]

Serdesai *et al* evaluated the efficacy of low dose regimen of magnesium sulfate and observed that 86% of the eclamptic patient were controlled by the loading dose only.[12] Seth *et al* observed a recurrence rate of 7.6% in Pritchard regimen and 5% in low dose regimen and 15% in loading dose only.[18] The Nigerian study reported recurrence of 4.2% in low dose regimen.[22]The recurrence rate in our study was 2% in low dose regimen and none in the standard regimen. The result obtained is comparable with the above studies. Only one patient had recurrence which was controlled by an additional dose of intravenous 2 gms of magnesium sulfate.

Begum *et al* reported the recurrence rate of 4% in loading dose.[2] A randomized study was conducted by Regmi *et al* and observed recurrence of 4.6%.[19] The ultrashort regimen of 14 gms used by Elke BA *et al* from Nigeria reported recurrence of 7.4%, which are much higher as compared to our study.[23]

In a study done by Bangal *et al*, the use of low dose Magnesium sulfate reported convulsions were controlled in 94% of cases with a total dose of less than 20 gms, which is 54.5% less than that used in the Pritchard regimen.[24]

Bhattarcharjee *et al* in their study showed that the efficacy of low dose intravenous regimen was comparable with standard regimen in respect to recurrence rate

of convulsions, chance of toxicity and maternal and perinatal outcomes whereas the total dose was lowered significantly (26.88 gms SD 3.48 and 51.65 gms SD 5.1 respectively; $p < 0.0001$).[20]

During the study period, attempts were made so that all the antepartum women with eclampsia would deliver within 24 hrs of admission either by induction or augmentation of labor. Caesarean section was performed mainly for obstetric indications.

The incidence of Caesarean section was 50% in low dose and 46% in the standard regimen. The high incidence is mainly due to the fact that our institute follows the principle of early termination of pregnancy in cases of eclampsia reducing complications to a greater extent.

Begum *et al* observed 68.42% in loading dose and 67.05% in standard dose.[2] Similar result was observed by Regmi *et al* from Dharan.[19] Placental abruption, delay in seeking health facility and prematurity were common cause of still birth. The overall still birth rate was 8% in both groups. Similar result was obtained by the research done in India.[20]

Pulmonary edema results due to endothelial dysfunction and leakage of the plasma into the interstitial space as a result of the increased permeability, attempts to expand the intravascular volume and vigorous fluid therapy. We had 8% patients of pulmonary edema in low dose and 4% in Pritchard regimen. Chowdhury also reported similar results.[17]

Post Partum Haemorrhage was seen in 6% and 8% of patient in the low dose and Pritchard regimen respectively which was comparable to that observed by Chowdhury *et al*and Seth *et al*.[17,18]

The maternal mortality varies depending on the condition of the women on admission and hospital facilities available. Serdesai *et al* had reported 2.6% maternal mortality in her study. Begum *et al* reported 4.5% and 5% mortality in loading and standard regimen respectively.[12] In the study done by Chowdhury JR, they observed mortality of 3.3% and 5%.[17] Similarly, Bhattarchjee reported 1.49% and 4.29% in intravenous and standard regimen respectively.[20] Regmi *et al* observed mortality of 2.3%.[19]

The Collaborative Eclampsia Trial reported mortality rate of 2.6% -- 3.8%.[7] Elke BA *et al* reported the maternal mortality as high as 9.9%.[23] We did not encount mortality during our study period. Close personal monitoring of the eclamptic mother is the key to minimize the maternal mortality.

Current protocols for the use of magnesium sulfate are mainly based on the pioneering report of Pritchard *et al* which included 245 cases of eclampsia.[25] Efficacy of magnesium sulfate in prevention and treatment of eclampsia is time tested and supported by a variety of studies.[7-9] However, the dose and protocols are not evidence based and narrow therapeutic index and toxicity is still a major concern in clinical use.[17,19,20]

The low dose intravenous regimens have a benefit of control of convulsion in much lower dose with no need of repeated painful intramuscular injections.[20] Begum *et al* in 2001 concluded that half of the one standard regimen appeared to be sufficient to control convulsions efficiently and level of magnesium remained at the lower level.[11]

Bhattarcharjee *et al* has used considerably lower maintenance dose of 0.75 gm/ hr to increase the safety margin without compromising effectiveness.[20] Regmi *et al* suggested that loading dose is as effective as standard regimen in controlling seizure.[19]

Serdesai *et al* found low dose very effective to control and prevent eclampsia and imminent eclampsia without any drug toxicity.[12] Malapaka *et al* found low dose to be as effective as Pritchard regimen and significantly less toxic ($p=0.014$).[26] Dose required for the control of convulsion with the lower dose was less than half of the standard regimen. There was no magnesium related toxicity and the fits were controlled. We observed that low dose of magnesium sulfate is equally effective in treating convulsions among women with eclampsia without magnesium toxicity. The low dose of magnesium sulfate in eclampsia can be used effectively in the management of eclampsia with an advantage of high safety margin. Low dose Magnesium sulfate protocol is associated with similar efficacy in controlling fits and has potentially less chance of toxicity and complication rates, hence, it is a viable alternate to standard regimen.

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