ORIGINAL ARTICLE

Low-dose Intravenous Magnesium Sulfate: Efficacy and Safety in Eclamptic Indian Women

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Abstract

Objective: The aim of our study was to evaluate the efficacy and safety of low dose intravenous magnesium sulfate against the conventional Pritchard's regimen in cases of eclampsia.

Materials and methods: A total of 60 eclamptic cases attending the labor room were randomly allocated to receive low dose intravenous magnesium sulfate, i.e., 4 g intravenous bolus dose followed by a 0.8 g per hour maintenance dose to be continued up to 24 hours after delivery or the last fit, whichever is later, or conventional Pritchard's regimen. The two groups were compared for efficacy and safety.

Results: Low-dose regimen was found to have a statistically significant lower incidence of side-effects and complications. Failure of therapy was seen in more number of cases with low dose because of the lower serum magnesium levels.

Conclusion: Low-dose regimen is a good option for lean Indian women especially at the peripheral centers where intensive serum magnesium level monitoring is not practically feasible because of reduced risk of toxicity.

Keywords: Eclampsia, Low-dose magnesium sulfate, Pritchard's regimen.

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Introduction

Pregnancy-induced hypertension is one disorder of pregnancy which continues to take a heavy toll of maternal and fetal lives, remaining one of the unsolved parts of the deadly triad of maternal deaths (hemorrhage, infection and pregnancy-induced hypertension). Incidence of eclampsia in India varies from 0.5 to 1.8% and is associated with a maternal mortality of 2%.[1]

Eclampsia refers to the occurrence of new-onset, generalized, tonic-clonic seizures or coma in a woman with preeclampsia. The incidence of eclampsia is approximately 1 in 1,600 pregnancies.[2]

Magnesium sulfate is considered to be the gold standard in the management of eclampsia. The dose of magnesium sulfate administered varies according to a variety of empirical regimens. There is also concern for the safety of magnesium sulfate because of its narrow therapeutic index. Low-dose magnesium sulfate will reduce magnesium sulfate toxicity and need for serum level monitoring may not be necessary in resource constrained environments which will ultimately translate to reduced cost of treatment.[3]

This study aimed at evaluating the efficacy of a low-dose intravenous magnesium sulfate regimen compared with Pritchard's intramuscular regimen being practised in our study center and assess fetomaternal outcome in both groups.

Materials and Methods

This study was carried out in the Department of Obstetrics and Gynaecology, SN Medical College, Agra. It was a prospective randomized controlled study. A total of 60 eclamptic women admitted in the labor room of the Department of Obstetrics and Gynaecology, SN Medical College, Agra, were included in the study. All cases of eclampsia i.e., antepartum, intrapartum, and postpartum were included in the study. Known case of epilepsy, magnesium sulfate sensitivity, women who already had established disseminated intravascular coagulopathy (DIC), intracranial hemorrhage, massive pulmonary edema, renal failure, coma and shock and those with contraindications to magnesium sulfate like myasthenia gravis were excluded.

After selection they were randomly allocated into two groups. The study group comprised of 30 cases of eclampsia who received a low dose of magnesium sulfate i.e., 4 g IV magnesium sulfate (4 g of 50% magnesium sulfate diluted in 20 cc of 5% dextrose) followed by a 0.8 g per hour maintenance dose. The control group comprised of 30 cases of eclampsia who received standard Pritchard's regimen i.e., 4 g magnesium sulfate (20 mL of 20%) IV over not less than 10–15 minutes immediately to be followed by 10 g (20 mL of 50%) IM 5 g in each buttock and following maintenance dose of 5 g magnesium sulfate (10 mL of 50%) was given every 4 hours at alternate buttocks. This treatment was continued till 24 hours after last eclamptic fit/24 hours post-delivery. It was terminated in cases of appearance of untoward effects like urine output <25 mL/hour, respiratory rate <12/minute or disappearance of deep tendon reflexes. The cases were treated with adequate anti-hypertensives, hydration and other required methods. Delivery was mandatory except in cases of postnatal eclampsia.

In the study group, cases with a recurrence of two or more episodes of convulsions 30 minutes after the initiation of low-dose

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magnesium sulfate were considered as failure of therapy and it was switched over to conventional IV therapy. A single episode of convulsion was treated with a 2 g intravenous stat dose.

Observations

Different regimens for the administration of magnesium sulfate have been tried and the most commonly recommended is the Pritchard's regimen, which is still in use. The dose of magnesium sulfate used in this regimen is based on the height and weight parameters of western women. Indian women have a lesser weight, height and BMI than their western counterparts. So these doses frequently cause toxicity in these women. Hence a need was felt to work on the administration of low dose intravenous regimens for the management of eclampsia.

The cases in the study and control groups were comparable with regard to age, parity, socioeconomic status, and literacy status. There were 25 (83.3%) cases in the study group who had antenatal eclampsia, while in the control group there were 26 (86.7%) cases with antenatal eclampsia. No case with intrapartum eclampsia was recorded in the present study. There were 5 (16.7%) cases in the study group and 4 (13.3%) cases in the control group who had postnatal eclampsia (Table 1).

Majority of cases in both the study group, i.e., 20 (80%) and the control group, i.e., 19 (73.1%) delivered vaginally. Only 5 (20%) cases in the study group and 6 (23.1%) cases in the control group delivered by cesarean section. No instrumental delivery was done in the study group and only 1 patient delivered by instrumental delivery in the control group. The difference between the two groups was not statistically significant (Table 2).

In our study, it was seen that during therapy, serum magnesium level was found to be <1.5 mEq/L in 1 patient (3.3%) in both the study group and the control group. It ranged from 1.5 to 2 mEq/L in 29 cases (96.7%) in study and 22 cases (73.3%) in the control group. The level was found to be >2 mEq/L in none of the cases in the study group and 7 cases (23.3%) in the control group. This value was found to be statistically significant (p value = 0.012). The mean serum magnesium level during treatment in the study group was 1.66 mEq/L and SD was 0.14 and in the control group mean was 1.9 mEq/L and SD was 0.21. The mean difference was 0.13 with CI 95%. The p value was 0.009. This difference was statistically significant (Table 3).

In the study group it was observed that 5 cases (16.7%) required a total dose of 23.2 g while 11 cases (44%) required 23.2–32.8 g. Ten cases (40%) required 32.8–42.4 g and 4 cases (13.3%) required >42.4 g of magnesium sulfate (Table 4). In the control group it was observed that 6 cases (20%) required a total dose of 44 g while 10 cases (33.3%) required 45–59 g. Ten cases (33.3%) required 60–74 g and 4 cases (13.3%) required >74 g of magnesium sulfate (Table 4).

The mean dose required to control fit in the study group was 25.2 g while in the control group it was 60.2 g. The p value came out to be 0.02, which was statistically significant.

Failure of therapy was observed with recurrence of 2 or more fits after 30 minutes of administration of magnesium sulfate. In the study group it was seen in 4 cases, out of which 3 cases (10%) were switched over to conventional IV dose and repeated dose of 2 g IV was given in 1 patient (3.3%). In the control group no patient showed failure of therapy. The difference in both the groups was statistically significant (Table 5).

In the study group, decreased urine output was seen in no patient. Nonprogression of labor was seen in 3 cases (12%) and fits recurred in 4 cases (13.3%). None of the cases showed loss of DTR, respiratory depression PPH, or fetal distress. In the control group, decreased urine output was seen in 4 cases (13.3%), loss of DTR was also observed in 3 cases (10%), and respiratory depression, PPH, fetal distress occurred in just 1 patient. Recurrence was seen in

Table 1: Patient profile

Parameter	*Study group*	*Control group*	*p value*
Mean age (years)	24.4	25.4	NS
Parity	Primipara (60%)	Primipara (66.7%)	NS
Education	Illiterate (83.3%)	Illiterate (80%)	NS
SE status	Middle class (40%)	Middle class (33.3%)	NS
Type of eclampsia			
Antepartum	25 (83.3%)	26 (86.7%)	NS
Intrapartum	00	00	
Postpartum	05 (16.7%)	04 (13.3%)	

Table 2: Distribution of cases according to mode of delivery

	Study group (n = 25)		*Control group (n = 26)*		
Mode of delivery	*n*	*%*	*n*	*%*	*p value*
Vaginal	20	80	19	73.1	0.74
Cesarean section	5	20	6	23.1	1
Instrumental	0	0	1	3.8	1

Table 3: Distribution of cases according to serum magnesium levels during treatment

Serum magnesium level (in mEq/L)	*Study group*		*Control group*		
	n	*%*	*n*	*%*	*p value*
<1.5	1	3.3	1	3.3	1.00
1.5–2	29	96.7	22	73.3	0.61
>2	0	0	7	23.3	0.012

Table 4: Distribution of cases according to total dose of magnesium sulfate required in the study group

Dose of magnesium sulfate (in g)	*Study group*		*Control group*	
	n	*%*	*n*	*%*
23.2	5	16.7	00	
23.2–32.8	11	44	00	
32.8–42.4	10	40	00	
42.4–43.9	4	13.3	00	
44	00		6	20
45–59	00		10	33.3
60–74	00		10	33.3
>74	00		4	13.3

Table 5: Distribution of cases according to failure of therapy

	Study group		*Control group*		
	n	*%*	*n*	*%*	*p value*
Switch over to conventional IV dose (1 g/hour)	3	10	0	0	0.0412
Need of repeated dose (2 g IV)	1	3.3	0	0	0.617

no patient in the control group and 4 cases (15.4%) ended up with nonprogression of labor. The difference in both the groups was statistically significant as far as decreased urine output and loss of DTRS is concerned (Table 6).

Maternal mortality occurred in 2 cases of the study group (6.7%) and 3 cases in the control group (10%). Three cases (10%) in the study group and 4 cases (13.3%) in the control group were shifted to ICU. HELLP Syndrome occurred in none of the cases in the study group and in 1 patient (3.3%) in the control group. Renal failure was seen in 1 patient (3.3%) of the study group and in 2 cases (6.7%) in the control group. None of the value was, however, statistically significant.

Out of the 25 antenatal cases in the study group, 10 (40%) babies were stillborn. Four babies (26.7%) were asphyxiated and 3 (20%) were admitted to NICU. In the control group, out of the 26 antenatal cases, 9 (34.6%) were stillborn. Seven babies (41.2%) of the control group were asphyxiated and 5 (29.4%) were admitted to NICU. Early neonatal death was observed in 1 baby (6.7%) of the study group and in 3 babies (11.5%) of the control group. The difference in these parameters was not statistically significant (Table 7).

Discussion

Different regimens for the administration of magnesium sulfate have been tried, and the most commonly recommended regimen is the Pritchard's regimen, which is still in use. The dose of magnesium sulfate used in this regimen is based on the height and weight parameters of western women. Indian women have a less weight, height and BMI than their western counterparts. So these doses frequently cause toxicity in Indian women. The aim of our study was to compare the efficacy and safety of low dose intravenous magnesium sulfate with Pritchard's regimen in terms of maternal and fetal outcome.

A total of 60 cases were included in our study. In our study 83.3% and 86.7% in the study and control groups, respectively, were antenatal and the remaining had postnatal eclampsia, while there was no case of intrapartum eclampsia. This distribution was almost similar in the study and control groups (Table 1).

In a large study conducted by Say[5] (1997–1985) at EH Crump Women's Hospital and Perinatal Centre of the City of MEMPHIS Hospital, out of 179 cases of eclampsia, 130 cases (73%) had an onset of convulsion before delivery and 49 (27%) cases had postpartum eclampsia. Our center being a tertiary center, most of the complicated cases were referred from periphery for delivery. This accounts for a high incidence of antepartum eclampsia. Proper monitoring of preeclamptic cases post-delivery accounted for a lower incidence of postpartum eclampsia. Out of 25 antenatal cases in the study group, 80% delivered by the vaginal route and only 20% underwent cesarean section. In the control group, 73.1% delivered by the vaginal route and 23.1% underwent cesarean section while 3.8% had instrumental delivery, as shown in Table 2. In a retrospective study at Dhaka Medical College, by Begum et al.,[6] there were 66% lower segment cesarean section in cases of eclampsia in 1997 and 82% cesarean section in cases of eclampsia in 1998. The remaining cases delivered vaginally in both the years. The results of this study were contradictory to our findings. On the contrary, the cesarean section rate was much lower in the study by Sardesai et al.[4] In 570 cases of eclampsia at the Medical College, Solapur, they reported cesarean section in 13.68% cases. The results were similar to our study. Vaginal delivery is the preferred route of delivery in our hospital, and we resorted to cesarean section only for obstetric indications.

In our study, it was seen that during therapy, serum magnesium level was found to be <1.5 mEq/L in 1 patient (3.3%) in both the study group and the control group. It ranged from 1.5 to 2 mEq/L in 29 cases (96.7%) in the study group and 27 cases (90%) in the control group. The level was found to be >2 mEq/L in none of the cases in the study group and 7 cases (23.3%) in the control group. This value was found to be statistically significant (p value = 0.012). The mean serum magnesium level was 1.66 mEq/L in the study group and 1.9 mEq/L in the control group (Table 3).

The findings were compared with a study done by Singh et al.[7] in the year 2010 to estimate the serum magnesium levels in pre-eclampsia and eclampsia and to study the effect of using different regimens of magnesium sulfate. Mean initial serum magnesium level was 1.81 ± 0.58 (mg/dL) in the group receiving Pritchard's regimen and 1.55 ± 0.41 in the group receiving the low dose regimen. The difference between mean serum magnesium levels during the first 4 hours after therapy was statistically significant between intramuscular and intravenous regimen groups. Similarly in a study done by Das et al.[8] in Burdwan Medical College in the year 2015, the mean maternal serum magnesium level was 2.3 mmol/L for cases that received 8 g magnesium sulfate, and 3.46 mmol/L for cases received >8 g magnesium sulfate (difference of means: 1.16, 95% confidence interval: 1.08–1.38).

Table 6: Distribution according to complications

	Study group		*Control group*		
Complication	*n*	*%*	*n*	*%*	*p value*
Decreased urine output	0	0	4	13.3	0.042
Loss of DTR	0	0	3	10	0.031
Respiratory depression	0	0	1	3.3	1.00
PPH	0	0	1	3.9	1.00
Recurrence of FIT	4	13.3	0	0	0.042
Fetal distress	0	0	1	3.9	1.00
Nonprogression of labor	3	12	4	15.4	1.00
HELLP syndrome	0	0	1	3.3	1.0
Renal failure	1	3.3	2	6.7	1.0
Need for ICU	3	10	4	13.3	1.0
Maternal mortality	2	6.7	3	10	1.0

Table 7: Fetal outcome

	Study group		*Control group*		
Fetal outcome	*n*	*%*	*n*	*%*	*p value*
Live birth	15	60	17	65.4	0.79
Stillbirth	10	40	9	34.6	1.0
Asphyxia	4	26.7	7	41.2	0.5
Early neonatal death	1	6.7	3	11.5	0.52
Intrauterine death	10	40	9	34.6	1.00
NICU admission	3	20	5	29.4	0.70
Apgar score <6 AT 1 minutes	2	13.3	1	5.9	1.0
Apgar score <6 AT 5 minutes	3	20	2	11.8	1.0

Study	*Serum magnesium level mEq/L*
Arpita Singh et al., 2010	1.55
Monalisa Das et al., 2015	2.3
Our study	1.43

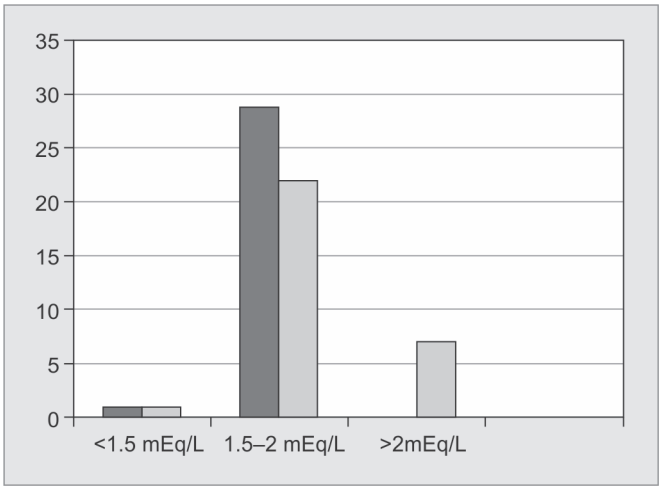

Fig. 1: Distribution of cases according to serum magnesium levels during treatment

The observations in serum magnesium levels during and after treatment show that serum magnesium in blood is lower in cases which were given low-dose IV magnesium sulfate than in those in which Pritchard's regimen was administered. The lower serum magnesium level during and after therapy in the study is attributed to the lower dose being administered as compared to standard Pritchard's regimen (Fig. 1).

Failure of therapy was observed with a recurrence of 2 or more fits after 30 minutes of administration of magnesium sulfate. In the study group, it was seen in 4 cases, out of which 3 cases (10%) were switched over to the conventional IV dose. In the control group, no patient showed failure of therapy. The difference in both the groups was, however, statistically significant (Table 5). A similar study was performed at the Kasturba Medical College, Mangaluru, by Malapaka et al. in the year 2011, on the comparison of low dose magnesium sulfate with Pritchard's regimen. Out of the 73 women of the eclampsia group, none of the women of Pritchard group showed failure of therapy while it was seen in 6 women (17.1%) in the low-dose group.[9]

Study	*Failure rate (%)*
Malapaka, 2011	17.1
Our study	13.3

Lower serum magnesium levels below the therapeutic range could be the reason for failure. However, because of the lean built and lower BMI of the Indian women, this regimen was still successful in more than 80% of cases.

The recurrent fits were controlled by 2 g IV dose of magnesium sulfate. The risk of failure of low-dose magnesium sulfate with this regimen needs to be weighed against the benefits of almost no chances of toxicity, especially when it is being used at the peripheral health center. In the study group, decreased urine output was seen in no patients. Nonprogression of labor was seen in 3 cases (12%) and fits recurred in 4 cases (13.3%). None of the cases showed loss of DTR, respiratory depression PPH or fetal distress. In the control group, decreased urine output was seen in 4 cases (13.3%), loss of DTR was also observed in 3 cases (10%), and respiratory depression, PPH, and fetal distress occurred in the control group in just 1 patient. Recurrence was seen in no patient in the control group and 4 cases (15.4%) ended up with nonprogression of labor. The difference in both the groups was statistically significant as far as decreased urine output and loss of DTRS is concerned (Table 6).

In a prospective study at Dhaka Medical College (1997), by Begum et al.,[6] using low doses of magnesium sulfate, of the 65 cases only 5 had diminished knee jerk. A study was done by Lynsal Tinda in Bengaluru Medical College in the year 2011 for comparing the efficacy of low-dose magnesium sulfate with Pritchard's regimen. In this study, recurrence of convulsions was seen 6% of cases treated with low-dose magnesium sulfate and 4% patients treated with Pritchard's regimen. In a similar study performed at Kasturba Medical College, Mangaluru, by Malapaka et al. in the year 2011,[9] it was seen that Pritchard's regimen showed severe toxicity, resulting in 1 death due to severe respiratory depression. For 12 eclamptic women (31.6%), Pritchard's regimen was discontinued because of toxicity. The low-dose regimen was associated with a significantly lower magnesium toxicity than Pritchard's regimen. The results were not statistically significant, thereby inferring that low dose regimen has less chances of toxicity than Pritchard's regimen.

In our study, maternal mortality was 6.7% in the study group and 10% in the control group (Table 7). In a prospective cohort study of eclamptic cases in Nigeria by Ekele et al., out of 121 cases, there were 12 maternal deaths (0.99%). In a study done by Lynsal Tinda in Bengaluru Medical College in the year 2011 for comparing the efficacy of low-dose magnesium sulfate with Pritchard's regimen, it was seen in 2% cases. The results were not statistically significant and were similar to our study. This is because in cases of failure of low dose, we immediately resorted to the conventional treatment therapy explaining nonsignificant differences. No study citing the incidence of HELLP syndrome with low-dose magnesium sulfate is available in the literature. It seems that Indian women need low doses of magnesium sulfate for the management of eclampsia as compared to Pritchard's regimen.

In our study, 20% of the babies required NICU admission in the low-dose group while in the control group 29.4% of the babies required NICU admission. This difference was, however, not statistically significant. Early neonatal death was seen in only 6.7% of the babies in the study group while it was seen in 41.25% of the babies of control group. This difference between the two groups was statistically significant (p value = 0.052) as shown in Table 7.

In the study conducted by ICMR at KGMC, Lucknow, 38% of the neonates of the study group and 30% of the neonates of the control group needed neonatal ICU admission. Out of the neonates requiring NICU care, 7.4% in the study group and 7.5% neonates in the control group were admitted because of prematurity. In a study done by Das et al. in Burdwan, from January 2011 to September 2012, assessment of serum magnesium levels and its outcome in neonates of eclamptic mothers treated with low dose magnesium sulfate regimen was done. The perinatal mortality rate was 8% in their study. There were 6 (6%) stillbirths and early neonatal deaths were 2 (2%). Birth asphyxia led to 1% neonatal death (1% neonatal death was due to causes other than complications related to neonatal hypermagnesemia). Birth asphyxia was observed in 14 (14.89%) newborns. Similar results were observed by researchers, using low-dose magnesium sulfate regimen, for the treatment of eclamptic mothers. Studies using standard dose magnesium sulfate regimen (Pritchard's regimen) in the same reported perinatal death 30.07%—stillbirth rate 22.7% and neonatal death 7.67%. Collaborative Eclampsia Trial using standard dose magnesium

sulfate regimen found perinatal mortality rate of 24–26% and birth asphyxia of 44–48% in eclampsia. The results were similar to our study.

Conclusion

Eclampsia still remains a significant problem worldwide. Control of convulsion and effective prevention in imminent eclampsia would greatly improve the outcome in cases of eclampsia and imminent eclampsia.

Magnesium sulfate is the drug of choice, which has been proved by various trials all over the world. A wide variety of protocols are in use throughout the world. From the results obtained by this study, it can be stated that low dose magnesium sulfate is as efficacious as Pritchard's regimen, which is most commonly used. No case of magnesium sulfate toxicity was encountered in this study. The low dose magnesium sulfate regimen is adequate for Indian women, who are smaller built. Both maternal and perinatal mortality rates are still disappointing. This cannot be improved by anticonvulsants alone. Other principles like early attention, intensive antihypertensive, and obstetric management are very essential for improving the maternal and perinatal outcome. A good NICU care remains a cornerstone to salvage many babies.

Low-dose regimen requires simple clinical monitoring and can be administered in any type of hospital setup where facilities for intensive monitoring or serum magnesium level estimation are not available. The loading dose of low-dose regimen can be administered by a medical officer at PHC prior to the transfer to a referral center and thus catastrophe of convulsion on the way can be avoided. There is no risk of any gluteal abscess as the drug is given intravenously in the low-dose regimen as compared to Pritchard's regimen.

More extensive and multicentric trials involving more number of cases are needed to prove the efficacy and safety of low-dose magnesium sulfate regimen in the management of eclampsia.

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