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Comparison of safety and efficacy of intramuscular and intravenous regime of magnesium sulfate in Eclampsia and severe preeclampsia

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Abstract
Background: Magnesium sulfate is the ideal drug for the prevention and treatment of eclampsia. Nevertheless, the best regimen for protection against eclampsia with minimal side effects remains to be established. This study aimed to compare between intramuscular (IM) and intravenous (IV) magnesium sulfate regimes in severe preeclampsia and eclampsia in terms of efficacy, toxicity, maternal and fetal outcome.
Material & Methods: A prospective study will be performed on patients of eclampsia and severe preeclampsia admitted in mahila chikitsalya, J.L.N. Medical College, Ajmer during the period July 2019 to October 2019. We will compare IV and IM group, each group with equal number patients of eclampsia and severe pre-eclampsia.
Results: Average age being 23.62±3.74 years for group receiving IM regime 25.225±3.27 years for group receiving IV regime. We found 3 /40 (7.5%) patients with recurrence of fits of those who received the IM regime of MgSO4 and none of the patients who received IV regime had recurrence or occurrence of fits. In our study we found significantly higher incidence of signs of impending magnesium toxicity as of loss of DTR at creatinine levels >0.80 mg/dl.
Conclusion: We found that IV regime was significantly more efficacious in preventing recurrence or occurrence of seizures then IM regime. Percentage of caesarean section was more in IM regime With Increase in serum creatinine levels the significance of route of regime was increased with IV regime being safer.

Keywords: Magnesium sulfate, eclampsia, severe preeclampsia, IV, IM, deep tendon reflex

Introduction
Patients Eclampsia and preeclampsia are important causes of morbidity and mortality during child birth and perpurium. Eclampsia alone accounts for approximately 50000 maternal deaths worldwide annually [1]. Incidence of eclampsia is one in 2000 deliveries in developed countries and one in 50 to 500 deliveries in developing countries [2]. The WHO notes that high blood pressure during pregnancy (preeclampsia and eclampsia) was one of the major direct cause of maternal deaths globally and its contribution in 2014 was 14% [3]. Hypertension and its complications are the third leading cause of pregnancy- related deaths, superseded only by hemorrhage and associated with increased risks of placental abruption, acute renal failure, cerebro-vascular and cardiovascular complications, disseminated intravascular coagulation, and maternal death [4]. In many developing countries like ours, particularly in rural areas; eclampsia may present for treatment in deep coma after many fits at home. Amongst the principles of management of eclampsia the first and the foremost is the control of convulsions. The results of collaborative eclampsia trial suggested that magnesium sulfate ($MgSO_4$) is the drug of choice for routine anticonvulsant management of women with eclampsia rather than diazepam and phenytoin [5]. The major breakthrough in the management of eclampsia came when Dr. J.A. Pritchard published his standardized treatment protocol in 1984. His protocol for management is popularly known as Pritchard regimen" [6]. Zuspan and Sibai Baha both have proposed protocol which consists of continuous infusion of magnesium sulfate in which toxicity caused due to $MgSO_4$ can be kept under control and complications due to toxicity could be prevented. Ekele BA, Badung SL in 2002 concluded that the routine estimation of magnesium cation is not necessary.

It is suggested that serum estimation be limited to cases where clinical monitors suggest toxicity [7]. Most of the health centers in world administer $MgSO_4$ by continuous IV infusion because the IV route for $MgSO_4$ administration has some advantage over IM $MgSO_4$ in terms of easy administration, less painful to patient and mean magnesium level can be easily controlled but in India most medical centers prefer IM administration as described by Pritchard because in poor resource sets ups giving IV magnesium sulfate is not practical due to non- availability of infusion sets, too busy nursing staff, taking sample for serum magnesium level at frequent interval is not cost effective. This encouraged us to do a study where both the route for $MgSO_4$ administration were compared and magnesium toxicity was measured by clinical parameters so that an institutional study might help the primary and other referral units to use $MgSO_4$ without any fear and delay.

Material & Methods

A prospective study performed on patients of eclampsia and severe preeclampsia admitted in mahila chikitsalya, J.L.N. Medical College, Ajmer during the period July 2019 to October 2019. We compared IV and IM group, each group with equal number patients of eclampsia and severe pre-eclampsia. IV group was given continuous IV magnesium sulfate (IV $MgSO_4$) consisting of 4gm of loading dose, administered over 15 minutes followed by maintenance dose of 2gm/hour. The IM group will be given intramuscular magnesium sulfate (IM $MgSO_4$) by Pritchard regime. Maintenance dose will be given for 24 hours provided delivery has occurred. We will use 22 gauge needle of 3 cm for IM injections instead of 20 gauge needle of 3 inches to minimize patient's discomfort

Inclusion criteria

The study included women with **s**evere pre-eclampsia and eclampsia

The study included all women with **s**evere pre-eclampsia where decision had been made to deliver or was 24 hours or less postpartum and where any one of following criteria was met:

1. Premonitory symptoms like headache, visual disturbance, persistent epigastric pain.
2. Oligouria or abnormal biochemical findings: platelet count <100000/µL, ALT >50 IU/L, markedly increased creatinine >2 mg/dl
3. Severe hypertension (> or equal to 160/110 mmHg) with proteinuria of at least 2+ assessed by semi quantitative dipstick method

Eclampsia: Eclampsia was diagnosed by taking history of generalized tonic clonic convulsions with or without elevated blood pressure and proteinuria (by dipstick method) in the absence of any underlying seizure disorders after 20 weeks of gestational age. All cases of antepartum, intrapartum and postpartum eclampsia, presenting in obstetric emergency (labor room) were included in the study.

Exclusion Criteria

Patient with severe preeclampsia or eclampsia with

1. Renal failure
2. Severe pulmonary edema with respiratory failure.
3. Cerebrovascular accident and Disseminated Intravascular Coagulation (DIC)
4. Hydatidiform mole, diabetes mellitus, thyrotoxicosis and epilepsy.
5. Those if received magnesium sulfate and/or other anticonvulsant before coming to our hospital will be excluded from the study.

Results

A total of 80 patients were included in the study. Average age being 23.62±3.74 years for group receiving IM regime 25.225±3.27 years for group receiving IV regime. We had 19 patients of eclampsia and 21 patients of severe preeclampsia in IM group and 21 patients of eclampsia and 19 patients of severe preeclampsia in IV group**.** We had 38 booked and 42 unbooked patients. Most of the patients of eclampsia were unbooked (30/40). Most of the patients of severe preeclampsia were booked (28/40). We had almost equal number of booked and unbooked patients in IM and IV regime groups.

We found 3 /40 (7.5%) patients with recurrence of fits of those who received the IM regime of MgSO4 and none of the patients who received IV regime had recurrence or occurrence of fits. This was significant with P Value 0.02.

In the study by Kanti V *et al.* on comparison of IM and IV regime MgSO4 both the group had 1/17 (5.88%) cases each with recurrence of convulsion after the loading dose. The difference between the two groups was statistically insignificant (P = 1) [11].

The recurrence rate reported in collaborative eclampsia trial using Pritchard's regimen ranged between 5.7 and 13.2%. There was no occurrence of convulsion in any subject with severe preeclampsia [15].

Coetzee *et al.*13 found occurrence of convulsion rate of 0.3% in severe eclampsia group after receiving IV magnesium sulfate.[8]

Eclamptic convulsions are almost always prevented or arrested by plasma magnesium levels maintained at 4-7 meq/l, 4.8-8.4 mg/dl, or 2-3.5 mmol/l [14].

The review of available data on pharmacokinetic properties of MgSO4 when used for women with preeclampsia and /or eclampsia was done by Okusanya *et al.* in 2015 [12].

It was found that maintenance infusion of 2 g/hour following either a 4- or a 6-g loading dose had a higher likelihood of producing mean concentrations between 2 and 3 mmol/l with fewer fluctuations during the period of administration.

The Pritchard regimen inconsistently produced serum concentrations between 2 and 3 mmol/l but the repeated intramuscular injections resulted in more fluctuations compared with continuous intravenous maintenance regimens.

The inconsistency in maintenance of serum concentrations between 2 and 3 mmol/l can be correlated with increased rate of recurrence or occurrence of fits in patients who were given IM regime as compared to IV regime.

In both groups 19 of 40 patients in each group delivered normally. As shown above, in our study higher percentage of subjects given IV regime had induction delivery interval greater than 12 hours (13/19) compared to IM regimen (9/19) interval but the difference was not significant. In study to compare Intravenous and intramuscular magnesium sulphate regimens in severe pre-eclampsia was done by Chissell S1, Botha JH, Moodley J, McFadyen L mean delivery time after start of $MgSO_4$ therapy was more (5.8±4.2 hours) (N=9) in patients with IM regimen and 5.3±3.1 (N= 8) hours in patients who were given IV regimen. However the difference was not significant [10].

We also observed that total percentage of induction failures were higher in the group receiving IM regimen then in those who were given IV regimen. But the difference was not significant.

Comparing the signs of impending toxicity

Signs of impending toxicity had more occurrence in IM group as

compared to IV group. Loss of Deep tendon reflex was present in 10/40 (25%) subjects of IM group and only in 4/40(10%) in IV group and this was statistically significant. P = (0.02298). However on our study respiratory depression was found at the same rate i.e. 1/40 in both groups. Another study by V. Kanti *et al.* IV regime and IM regime comparison also found higher incidence of loss of patellar reflexes in subjects receiving IM dose (24.3%) than those receiving IV dose (7.3%) [10].

Similar results were obtained in study by Rakesh Kumar *et al.* on 100 patients for comparison of IM and IV regimes of $MgSO_4$. They found 2% incidence of loss of deep tendon reflexes in IV group as compared to 14 % in IM group. However they used 1 gm / hour MgSO4 maintenance dose in IV regime [11].

Effect of serum creatinine on sign of impending toxicity of MgSO4

Magnesium is cleared almost totally by renal excretion. Maintenance dose should be altered with diminished renal function. Its recommended that Whenever plasma creatinine levels are> 1.0 mg/dl, serum magnesium levels are measured to guide infusion rates. In our study we found significantly higher incidence of signs of impending magnesium toxicity as of loss of DTR at creatinine levels >0.80 mg/dl as shown in the table above.

Of all 80 patients only 2 had oliguria and both had serum creatinine values > 1 mg/dl. These 2 patients had respiratory depression due to magnesium toxicity both had serum creatinine values of 1.21 and 1.3 given IV and IM regimen respectively.

Our study was in collaboration with results of Jarunee Leetheeragul *et al.* in Feb 2018 who observed 360 women with PE who received intravenous $MgSO_4$ for seizure prophylaxis retrospectively. Women with mild PE were less likely to attain therapeutic serum magnesium levels compared with those with severe phenotype, which was explained probably due to significantly lower creatinine levels ($p < .05$) [13].

We found increase in incidence of signs of impending toxicity with increasing severity of disease as indicated by the mean arterial pressure and no. of fits at the time of admission of patient.

No. of fits >3 significantly increases the percentage of patients with signs of impending toxicity of magnesium (P value: 0.04).

Similar implications could be derived from the observational study by Jarunee Leetheeragul *et al.* in Feb 2018 who found early achievement of therapeutic levels of MgSO4 associated with increasing severity of the disease [13].

We had 2 patients with respiratory depression due to magnesium toxicity. Both had mean arterial pressure 140 mmHg and 136.5 mmHg and presented with > 3 fits on admission of given IV and IM regimen respectively.IM regime is associated with higher incidence of loss of deep tendon reflex then with IV regime even in those with higher mean arterial pressures but the difference is not significant.

Thus with increasing severity of disease significance of route of administration decreases.

Effect on neonate

In our study we compared the effect of IM and IV regime of $MgSO_4$ on neonatal APGAR as follows

APGAR was <7 in more of the subjects who were given IM regime then those who were given IV regime but the difference was not significant (P value = 0.2680).

Also after grouping for different gestational ages the neonates of subjects who were given IM regime had higher number of those with APGAR score <7 then in those neonates of subjects who were1 given IV regime but the difference was not significant

During evaluation we excluded the neonates of 28 to 32 weeks of gestation as in this group prematurity itself is a significant factor causing low APGAR score

Overall in the study we had 6 still births 2 in IM regimen group and 4 in IV group regimen but all were < 28 weeks so we did not consider it for comparison as prematurity itself is a significant factor here. We did not have any still birth at greater than 28 weeks in our study.

4 of 61 live birth expired in nursery. We again excluded < 32 weeks gestational age for evaluation due to significant effect of prematurity In greater than 32 weeks we had more percentage of neonates expired in the IV group but the difference was not significant In the study by V. Kanti *et al.* a higher perinatal mortality in IM group when compared to IV (17.07% in IV 13.95% in IM) was found but it was insignificant [10].

Chissell S showed 1/8 and 1/9 stillbirth in both IV and IM severe eclampsia group respectively. It was seen that subjects in IM group had no significant difference as regard babies with low APGAR score as compared to subjects in IV group (P = 0.751) [9].

Table 1: Booked/Unbooked

Type of patients	IM		IM Total	IV		IV Total	Grand Total
	E	Severe PE		E	Severe PE		
Booked	4	14	18	6	14	20	38
Unbooked	15	7	22	15	5	20	42
Grand Total	19	21	40	21	19	40	80

Comparison of efficacy of Mgso4 Via Im and Iv Route

Table 2: Recurrent or occurrence of Fit

	IM		IV	
	E	SPE	E	SPE
Recurrent or occurrence of Fit	2	1	0	0

P value: 0.02

Table 3: Effect on induction delivery interval

Induction delivery interval	IM	IV
>12 hours	9	13
<12 hours	10	6

P value= 0.1888

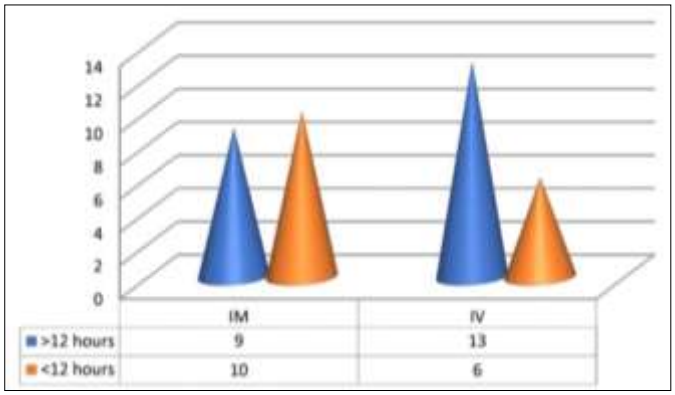

Fig 1: Induction delivery interval

Table 4: Loss of DTR

	IM			IV		
	Total	**No of Patients with loss of DTR**	**%**	**Total**	**No of Patients with loss of DTR**	**%**
Eclampsia	21	6	28.57 %	21	3	14.29 %
SPE	19	4	21.05%	19	1	5.263%
Grand Total	10	40	25.00%	40	4	10%

Table 5: Serum creatinine and loss of DTR

Serum creatinine	Total no. of patients	No. of patients with loss of DTR	%
</=0.80 mg/dl	62	4	6.43%
>0.80 mg/dl	18	10	55.50%

P Value: 0.0002

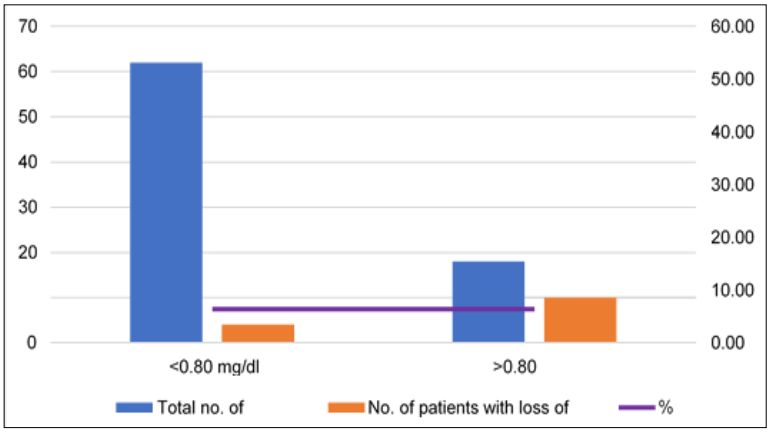

Fig 2: Serum creatinine and loss of DTR

Table 6: Serum creatinine and loss of DTR: comparison of IM and IV regime

Serum creatinine	IM			IV		
	Total no. of patients	**No. of patients with loss of DTR**	**%**	**Total no. of patients**	**No. of patients with loss of DTR**	**%**
< 0.80 mg/dl	30	3	10%	32	0	0%
≥ 0.80 mg/dl	10	7	70%	8	4	50%

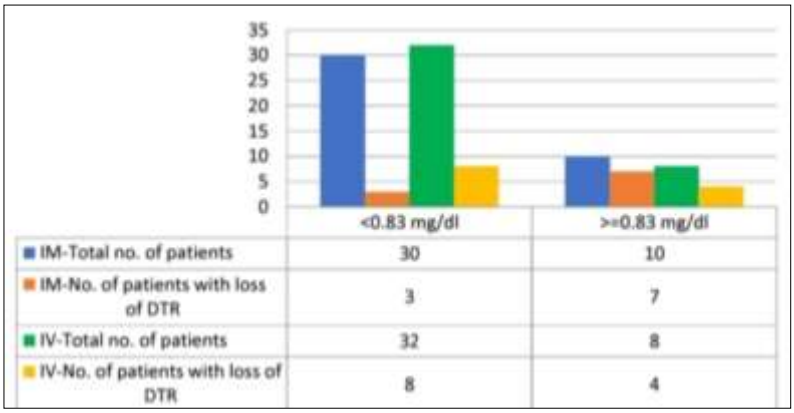

Fig 3: Serum creatinine and loss in DTR

P value 0.0093

Comparing effect of route of MgSO4 in those with higher creatinine levels. We found significantly higher incidence of loss of DTR with IM regime as compared to IV regime in those with higher creatinine levels as shown in table above.

Effect of severity of disease on signs of impending toxicity

Table 7: MAP and loss of DTR

MAP	Total no. of patients	No. of patients with loss of DTR	%
<130mmHg	39	4	10.25%
≥130mmHg	41	10	24.39%

P value: 0.057

As shown above subjects with mean arterial pressure ≥ 130 mmhg have higher percentage of patients with loss of DTR but the difference was not significant (P value = 0.057).
P value: 0.0420.

Table 8: Gestation weeks

Gestation weeks	IM			IV			Total no. of birth
	< 7 1 min APGAR	No. of birth	%	< 7 1 min APGAR	No. of birth	%	
33-36.6	5	17	29.41	2	15	13.33	32
37-41.0	4	13	30.77	1	7	14.29	20

P value: 0.2680

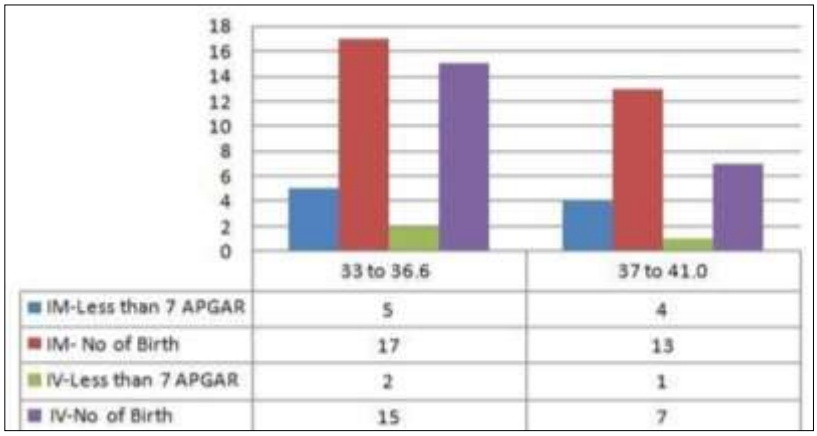

Fig 4: Gestation weeks

Conclusion

We found that IV regime was significantly more efficacious in preventing recurrence or occurrence of seizures then IM regime. Percentage of caesarean section was more in IM regime. However the difference was not significant. Induction delivery interval was more in IV group but the difference was not significant. When evaluated by loss of knee jerk reflex IV regime was significantly safer as compared to IM regime. As number of subjects having loss of Deep tendon reflexes was significantly more in IM group as compared to IV group. With Increase in serum creatinine levels the significance of route of regime was increased with IV regime being safer. With Increase in severity as evident by mean arterial pressure and number of fits before admission of disease there was no significant difference in safety with both the regimes. There was no significant difference in the incidence of respiratory depression in both the groups. There was no maternal mortality in our study. No. of neonates with 0 minute APGAR <7 was more in the IM group but the difference was not significant We did not have any still birth at greater than 28 weeks in our study. Thus we conclude that overall IV route has significantly better outcomes then IM route as far as safety and efficacy is concerned. However individualization of $MgSO_4$ dose should be done based on severity of the disease and renal function tests. Further studies are needed to accomplish the same.

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