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Parameters to Individualize Dose of Magnesium Sulfate to Prevent Toxicity

Nitisha Vijayvargia[1], Sudha Gandhi[2]

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[1]Resident, [2]Senior Professor and Unit Head, Department of Obstetrics and Gynecology, R.N.T. Medical College, Udaipur, Rajasthan 313001, India.

Corresponding Author: Sudha Gandhi, Senior Professor and Unit Head, Department of Obstetrics and Gynecology, R.N.T. Medical College, Udaipur, Rajasthan 313001, India.

E-mail: sbapna.1@gmail.com

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Abstract

Objective: Objective of this study was to assess the impact of deranged renal function and severity of disease in terms of number of fits and mean arterial pressure on incidence of toxicity of $MgSO_4$ and to compare the standard regimes of Magnesium sulfate by IM and IV routes.

Method: A prospective study was performed on patients of eclampsia and severe preeclampsia.

Result: Subjects with creatinine levels > 0.80 mg/dl, mean arterial pressure ≥ 130 mmHg and No. of fits >3 have significantly higher percentage of patients with loss of DTR (p value = 0.002; 0.05; 0.04 respectively). At higher creatinine levels >0.80 mg/dl significantly less percentage of patients with loss of DTR were found (p value = 0.009) with IV route compared to IM route. At mean arterial pressure ≥ 130 mmHg and No. of fits >3 results were comparable with IM and IV routes of $MgSO_4$.

Conclusion: IV route was found safer in patients with higher creatinine values. But with further increase in severity as evident by mean arterial pressure ≥ 130 mmHg and No. of fits >3 route of $MgSO_4$ did not matter.

Keywords: Magnesium Sulfate; DTR; MAP.

Introduction

In severe pre-eclampsia and eclampsia magnesium sulfate administered intravenous or intramuscular is an effective anticonvulsant that avoids producing central nervous system depression in either mother or infant. It is used in IM form intermittently or IV form as continuous infusion.

Magnesium is cleared almost totally by renal excretion. Whenever plasma creatinine levels are >1.0 mg/dl, serum magnesium levels are measured to guide infusion rates [1].

Monitoring for magnesium toxicity is done clinically by assessment of deep tendon reflexes, respiratory rate and urine output periodically. However the precise significance of serum creatinine levels in predicting the chances of magnesium toxicity must be established.

The review of available data on pharmacokinetic properties of $MgSO_4$ when used for women with preeclampsia and/or eclampsia was done by Okusanya *et al.* in 2015. It was found that 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 volume of distribution of magnesium varied significantly but plasma clearance was fairly similar across populations [2].

Thus route of administration could influence the effects as well as toxicity of magnesium in the body. A retrospective review of on-admission factors on attainment of therapeutic serum concentrations of magnesium sulfate in women treated for a diagnosis of preeclampsia by Jarunee Leetheeragul *et al.* [3] in Feb 2018 observed 360 women with PE who received intravenous $MgSO_4$. Women with mild PE were less likely to attain therapeutic serum magnesium levels compared with those with severe phenotypes. They also concluded that on-admission factors, especially BMI and renal clearance indices, of women with PE may affect timely attainment of therapeutic serum magnesium levels [2].

Thus it could be inferred that renal functions and severity of disease in terms of mean arterial pressures and number of fits could influence the attainment of therapeutic levels of magnesium sulfate and occurrence of its toxicity in a significant way.

Aims and Objective

- To assess the impact of deranged renal function and severity of disease in terms of number of fits and mean arterial pressure on incidence of toxicity of $MgSO_4$.
- To assess the incidence of toxicity of $MgSO_4$ with standard IM and IV regimens.
- To compare the effect of route of $MgSO_4$ with increasing severity of disease and deranged levels of renal functions

Methodology

A prospective study was performed on patients of eclampsia and severe preeclampsia admitted in Pannadhay Zanana Chikitsalaya, R.N.T. Medical College, Udaipur during the period July 2018 to October 2018. We investigated each of the patient for renal and liver function tests as per the management protocols. We also 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 (total of 52 gms). The IM group was given intramuscular magnesium sulfate (IM $MgSO_4$) by Pritchard regime (total of 42 gms). Maintenance dose was given for 24 hours provided delivery has occurred. We used 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 all women with severe pre-eclampsia where decision had been made to deliver or was 24 hours or less postpartum and where anyone of following criteria was met:

1. Premonitory symptoms like headache, visual disturbance, persistent epigastric pain;
2. Oliguria 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

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

We made groups according to regime of $MgSO_4$ (IV or IM) used, serum creatinine levels (> or < 0.80 mg/dl), mean arterial pressure (>/ < 130 mmhg) and no. of fits (> or <3). A comparative analysis was made between the groups on the basis of percentage of patients having loss of deep tendon reflexes i.e. the first clinical sign of magnesium toxicity. The confidence limit of the study was kept at 95%, a p value ≤ 0.05 was taken as a level of statistically significant difference.

Results

In our study overall incidence of magnesium toxicity in terms of loss of DTR was 17%.

Effect of Serum Creatinine on Sign of Impending Toxicity of $MgSO_4$"

Table 1: 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

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 1 and Graph 1.

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

Effect of Mean Arterial Pressures and Number of Fits on Signs of Impending Toxicity

It was observed that those patients with higher mean arterial pressures and /or who had experienced more number of fits had greater morbidity with dose of $MgSO_4$.

Table 2: MAP and loss of DTR

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

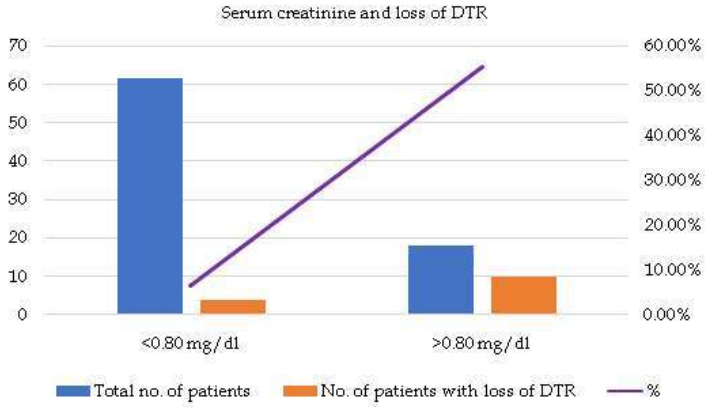
p value: 0.05

Subjects with mean arterial pressure ≥ 130 mmhg have higher percentage of patients with loss of DTR and the difference was significant (p value = 0.05). (Table 2)

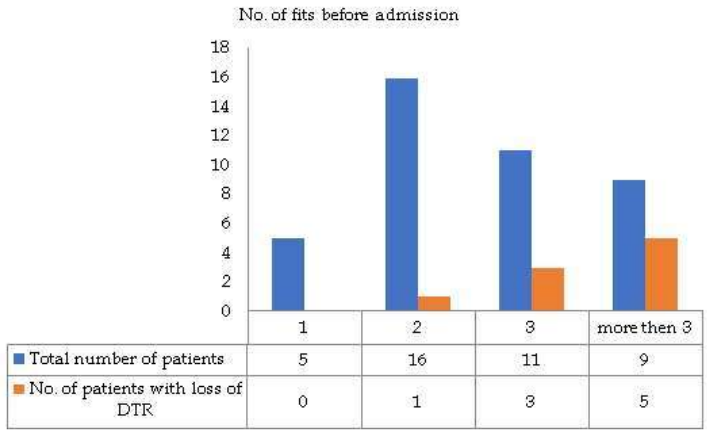
Table 3: No. of fits before admission and loss of DTR

No. of fits before admission	Total no. of patients	No. of patients with loss of DTR	%
< 3	32	4	12.50%
3	9	5	55.55%
Total	41	9	21.95%

p value: 0.0420



Graph 1: Serum creatinine and loss of DTR



Graph 2: No. of fits before admission and loss of DTR

No. of fits > or equal to 3 significantly increases the percentage of patients with signs of impending toxicity of magnesium (p value: 0.04). (Table 3 and Graph 2).

As in tables 4 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 = 0.022. However in our study respiratory depression was found at the same rate i.e. 1/40 in both groups.

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 5.

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 (Table 6).

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

Overall the significance of route of administration was not significant with further increased severity of disease which is implicated by no. of fits > 3 before admission and mean arterial pressure >130 mmHg at admission (Table 7). Here the higher morbidity of patients has an impact causing signs of impending toxicity at lower doses of the drug.

Other Maternal Outcomes

Recurrence or Occurrence of Fits

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.

Induction Delivery Interval

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 of induction delivery (13/19) compared to IM regimen (9/19) interval but the difference was not significant.

Table 4: Analysis on the basis of route of administration

	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	40	10	25.00%	40	4	10%

Table 5: 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%

p value 0.0093

Table 6: MAP and loss of DTR: Comparison of IM and IV regime

MAP	IM			IV		
	Total no. of patients	**No. of patients with loss of DTR**	**%**	**Total no. of patients**	**No. of patients with loss of DTR**	**%**
<130 mmHg	22	4	18.18%	17	0	0%
≥ 130mmHg	18	6	33.33%	23	4	17.39%

p value = 0.1383

Table 7: No. of Fits at admission and loss of DTR: Comparison of IM and IV Regime

No. of fits before admission	**IM-Total number of patients**	**IM-No.of patients with loss of DTR**	**%**	**IV-Total number of patients**	**IV-No. of patients with loss of DTR**	**%**	**p-value**
≤ 3	16	4	25.00%	16	1	6.25%	0.18
>3	4	2	50.00%	5	3	60.00%	0.76

p value = 0.5501

Table 8: Neonatal Outcome

0 min APGAR < 7 per total no. of live birth	
IM	**IV**
10\32	6\29
31.20%	20.60%

As shown in Table 8 neonatal 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.

Discussion

Subjects with creatinine levels >0.80 mg/dl, mean arterial pressure ≥ 130 mmHg and No. of fits >3 have significantly higher percentage of patients with loss of DTR (p value = 0.002; 0.05; 0.04 respectively).

Our study was in collaboration with results of Jarunee Leetheeragul *et al.* [3] 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 ($p < 0.05$) in mild PE [3].

The review of available data on pharmacokinetic properties of $MgSO_4$ when used for women with preeclampsia and /or eclampsia was done by Okusanya *et al.* in 2015 [2].

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 volume of distribution of magnesium varied significantly but plasma clearance was fairly similar across populations.

However in our study IV regime was significantly safer in patients with higher creatinine levels indicating more clearance of magnesium with IV regime.

Another study done on 100 patients of eclampsia by R. Kumar *et al.* [5] for comparison of intramuscular and intravenous regime of magnesium sulfate in 2015. The 100 patients were randomly allocated to group 1 for $MgSO_4$ IM regime and group 2 to $MgSO_4$ IV regime (maintenance dose of 1 gm/hr). They found that both the treatment regimens were comparable with regard to recurrence of convulsions (6% in IM group and 4% in IV group p value 0.646). Incidence of loss of knee jerk reflex was significantly higher in IM group (14%) as compared to IV group (2%) compared to IM regime [5].

In 2015 a prospective study was done on 82 patients by V. Kanti *et al.* [6] on comparison between intramuscular and intravenous regime of magnesium sulfate in management of severe preeclampsia and eclampsia. In this study they evaluated the impending signs of toxicity clinically; loss of patellar reflex, which was higher in IM 10/41 (24.39%) as compared to IV 3/41 (7.31) group, which was significant, (p = 0.034). Local site abscess was seen in 1 case of eclampsia IM group which was managed conservatively. No patient in IV group had respiratory depression, or any local site complication such as phlebitis. Overall signs of impending toxicity were more common in IM group compared to IV group (39.02% IM/12.19% IV) but it was not statistically significant [6].

Serum magnesium along with GFR levels is a good indicator of toxicity. Since it was not available in government setup, we used clinical signs of magnesium toxicity i.e. loss of Deep tendon reflexes and respiratory depression in our study. We recommend further studies using serum magnesium levels and GFR for accomplishing further accuracy in the results.

However in a study by Indumati *et al.* [4] on Serum Lactate Dehydrogenase in Eclampsia and Serum Magnesium Levels in Patients with Eclampsia Undergoing Magnesium Sulfate Therapy it was suggested that routine estimation of magnesium cation is not necessary. Even where the laboratory facility is available, it is suggested that serum estimation of magnesium be limited to cases where clinical monitors suggest toxicity [4].

Conclusion

- We observed a significantly higher incidence of signs of impending toxicity of magnesium with serum creatinine > 0.80, number of fits before admission > 3 and mean arterial pressure > 130 mmHg.
- When evaluated by loss of knee jerk reflex IV regime was significantly more safe as compared to IM regime. As number of subjects having loss of Deep tendon reflexes

was significantly more in IM group (25%) as compared to IV group (10%).

- With Increase in severity of disease as by increased serum creatinine levels the significance of route of regime was increased with IV regime being safer.
- With further Increase in severity as evident by mean arterial pressure > 130 mmHg and number of fits > 3 before admission of disease there was no significant difference in safety with both the regimes. Thus here dose alteration is required.
- 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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