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Serum magnesium levels in patients with pre-eclampsia and eclampsia with different regimens of magnesium sulphate

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ABSTRACT

Background **Pre-eclampsia and the subsequent eclampsia account for a common cause of maternal mortality worldwide and efforts aimed at reducing its menace are vital.**

Objective **To estimate the serum magnesium levels in pre-eclampsia and eclampsia and to study the effect of using different regimens of magnesium sulphate.**

Methods **70 cases of pre-eclampsia and eclampsia and 35 normal pregnant women as controls were studied. Serum magnesium levels were estimated using Atomic Absorption Spectrophotometer (Model AAS-4139) at baseline and at frequent intervals during gestation and the overall parameters were meticulously observed.**

Results **Majority (60%) of studied cases was nullipara with gestation age of 36-40 weeks. Statistically significant reduction of mean diastolic blood pressure and protein-urea was observed after using both intramuscular and intravenous regimens of magnesium sulphate. Mean initial serum magnesium level (mg/dl)±SD was 1.81±0.58 in group A,1.55±0.41 in group B and 1.49±0.41 in group C. Mean serum magnesium levels during first 4 hours after therapy were statistically significant between intramuscular and intravenous regimen groups while same were statistically insignificant at 8,12,16,24 and 32 hours. Besides, few minor side effects including headache, vomiting, reduced tendon reflexes and thrombocytopenia, no severe side effects and no maternal mortality were seen.**

Conclusion **Hypomagnesemia occurs during states of preeclampsia and eclampsia, and, administration of magnesium sulphate is effective and safe in preventing maternal mortality.**

Keywords: Pre-eclampsia, eclampsia, maternal mortality, magnesium sulphate.

INTRODUCTION

Pre-eclampsia is a common medical complication of pregnancy affecting 5% to 10% of all pregnancies[1]. It is best described as a pregnancy specific syndrome of reduced organ perfusion secondary to vasospasm and endothelial activation, characterized by hypertension and proteinuira that may lead to multisystem involvement including renal, hematological, hepatic and cerebral impairment[2,3].Eclampsia defined as generalized tonic clonic seizures and/or coma in a pregnancy complicated with hypertension is a common cause of maternal mortality worldwide, particularly in the developing countries with about 50,000 maternal deaths each year[3,4]. The exact cause of pre-eclampsia is currently unknown, the disorder is

associated with endovascular abnormalities in the presence of placental trophoblastic tissue and may even occur in absence of fetus as seen in patients with hydatidiform mole. Placental factors such as regulators of angiogenesis, growth factors, cytokines and regulators of arterial tone are released into maternal circulation leading to systemic endothelial cell dysfunction resulting in development of multisystem disease[3,5].

Diverse medical conditions predispose women to develop pre-eclampsia. These include nulliparity, multiple gestations, diabetes mellitus, pre-existing renal disease, chronic hypertension, prior history of preeclampsia, extremes of maternal age(>35 years or<15 years),obesity ,connective tissue disorders, factor V Leiden mutation, angiotensinogen gene T235, G20210A prothrombin gene mutation and antiphospholipid antibody syndrome[3,5,6].

Pregnancy is a state of magnesium depletion. The total and ionized magnesium levels are significantly lower in normal pregnancy compared to non-pregnant women[7,8]. The levels tend to fall during pregnancy and further decrease in women who develop preeclampsia later[8].It is also mentioned in previous studies that the concentration of magnesium during pregnancy exceeds the intake creating a state of *physiological hypomagnesemia*[9].Although, the definitive treatment of pre-eclampsia includes delivery of the fetus and placenta, magnesium sulpahte is the modality of choice for prevention and treatment of eclamptic seizures. Currently there is better understanding of the mechanisms of action of magnesium sulphate in regulating the neuromuscular excitability by acting directly on the myoneural junction and antagonizing N-methyl-D-aspartate receptor activation[10-12].The presynaptic release of acetylcholine is also reduced, thereby altering neuromuscular transmission[13].Dilatation of cerebral blood vessels takes place thus reducing cerebral ischaemia. Also the peripheral arteriolar dilatation reduces the blood pressure[14,15].The precise mechanism of action for the tocolytic effects may be related to the action of magnesium as a calcium blocker thus inhibiting muscle contractions[16,17].Consequently,many studies have been conducted so far showing the efficacy and safety of magnesium sulphate compared to placebo, diazepam and phenytoin in the treatment of preeclampsia and eclampsia[18-20].

The present study was conducted with the aim of estimating serum magnesium levels in normal pregnant women and in those with preeclampsia and eclampsia and also to study the serum levels following intramuscular and intravenous administration of magnesium sulphate in recommended doses.

MATERIAL & METHODS

This prospective clinico-pharmacological study was carried out in the Department of Pharmacology in collaboration with Department of Obstetrics and Gynaecology of S.N. Medical College and Hospital, Agra, Uttar Pradesh, India from November 2005 over a period of 2 years.

Study population

A total of 105 cases aged 16-40 years of preeclampsia, eclampsia and normal pregnant women were included in the study. The study group comprised of 70 cases of pre-eclampsia and eclampsia. The control group included 35 normal pregnant women. The preeclampsia cases were selected on the basis of evidence of hypertension (blood pressure 140/90 mmHg or more), proteinuria and edema with/without history of convulsions in the last trimester of pregnancy, during labor or within 48 hours of delivery. We have chosen this study in women at their last trimester of pregnancy as majority of cases of gestational hypertension and preeclampsia develop at or near term.

Exclusion Criteria

Subjects having pre-existing hypertension, renal disease, diabetes mellitus, thyrotoxicosis or other secondary causes of hypertension, hydatidiform mole were excluded from the study.

Magnesium sulphate administration

For this purpose the subjects were divided into 3 groups. Group A was a control, group B received intramuscular (IM) magnesium sulphate while group C received intravenously (IV) magnesium sulphate. For

the IM and IV regimens protocols of Pritchard[21] and Sibai[22] were followed respectively.

The IM regimens consisted of loading dose of 10ml of 50% magnesium sulphate (5g) deep IM in each buttock, followed by IV dose(only for eclampsia cases) with dilute 8 ml of 50% magnesium sulphate(4g) with 12ml of sterile water or 20 ml of a 20% solution (4g)within 3 to 5 minutes. The IV regimen was prescribed as 12 ml of 50% magnesium sulphate (6g)in 100 ml of 5% dextrose over 10 to 15 minutes and for maintenance 20 g of magnesium sulphate were added to 1000 ml of dextrose 5% given at a rate of 100 ml per hour(2g/h).

Collection of Sample

Samples of serum for estimation of magnesium were obtained before and after administration of magnesium sulphate in both the groups B and C. The collection of samples was done with great care to prevent any contamination. 2-3 ml of blood was withdrawn from vein by a sterile syringe into plastic vials that were dipped overnight in 0.1 N nitric acid bath and subsequently rinsed in deionized water. The samples were kept in water bath at 37°C for one hour and the serum was separated by centrifugation at 3000 rpm for 10 minutes. Each sample was stored at 0.4°C and analyzed within one week of collection.

Estimation of serum magnesium levels

This was performed by Atomic Absorption Spectrophotometer (Model AAS-4139) where measurement of radiation absorbed by the unexcited atoms of a chemical substance is estimated and its quantitative correlation with the concentration of the metal ions originally present in a sample is calculated. The elements are transformed into atomic vapor form by drawing an aerosol of the sample solution in the flame, while a light beam is directed through the flame into monochromater and into a detector that measures the amount of light (radiation) absorbed by the atomized element in the flame. Each metal has its own characteristic absorption wave length which is to the tune of 285.2 nm for magnesium. Finally, the amount of energy of the characteristic wavelength absorbed in the flame is proportional to the concentration of magnesium in the sample. For final determination of magnesium, serum samples were diluted to 1:50 with 0.1% (w/v) lanthanum diluent. Standards were also prepared by diluting the stock standard solutions (1.000 gm magnesium ribbon dissolved in a volume of (1+1) HCl with 0.1% (w/v) lanthanum as chloride. The serum magnesium levels were compared between groups B and C at 0, 4, 8,12,16,24 and 30 hours during magnesium sulphate therapy.

The readings of serum magnesium levels in each subject were recorded in the proforma prescribed for the purpose in addition to demographic profile and relevant investigations.

Statistical Analysis

After compiling the data, final analysis was performed by experienced statistician. Comparison was made between the variables using students' t-test and chi-square test wherever appropriate. Data were presented as the mean±SD, and p values of <0.05 was considered statistically significant.

RESULTS

Majority of the cases (48.75%) in all the groups belonged to the age between 20 to 25 years, with the age range of 15-35 years (mean, 24.17 ± 4.04, 23.65±3.94 and 23.51±4.04 for groups A to C respectively). Majority (60%) of cases were nullipara followed by primipara (26.6%) and 57(54.2%) of the subjects had gestation age of 36-40 weeks. There was no statistically significant difference between the age and gestational age with the serum magnesium levels (p>0.5). The mean initial diastolic blood pressure in the control group was 74.97 ±8.10 mmHg while it was 112.17 ±12.66 and 111.48 ±12.29 mmHg in the groups B and C, respectively. Statistically, a highly significant difference in the blood pressure (p<0.01) was found between both study groups compared to control. Mild edema was seen in 28.5%, 42.8% and 40.0% cases among the groups A to C, respectively. No case in any group had severe edema. Proteinuria was present in all the cases of the study groups; however, it was more noticed among cases of group B (57.1%) and group C

Table 1 Distribution of cases according to initial (baseline) serum magnesium levels

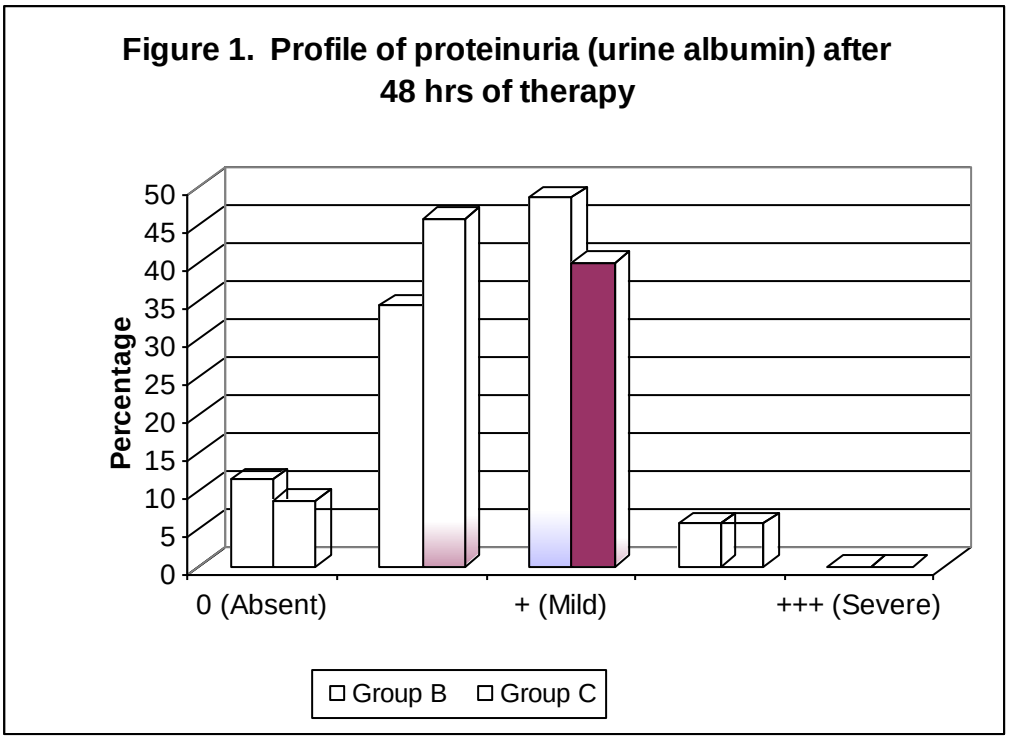
Initial (baseline) serum magnesium levels, mg/dl	Group A No. (%)	Group B No.(%)	Group C No.(%)
0-0.5	0(0)	1 (2.85)	1 (2.85)
0.5-1.0	5(14.28)	3 (8.75)	3 (8.75)
1.0-1.5	7(20)	11(31.42)	12 (34.28)
1.5-2.0	16 (45.71)	17(48.57)	17 (48.57)
≥ 2	7 (20)	3(8.75)	2 (5.71)
Total	35 (100)	35(100)	35 (100)
Mean±SD	1.81±0.58	1.55±0.41	1.49±0.41

Table 2Distribution of cases in study groups according to the total dose of magnesium sulphate used during the therapy

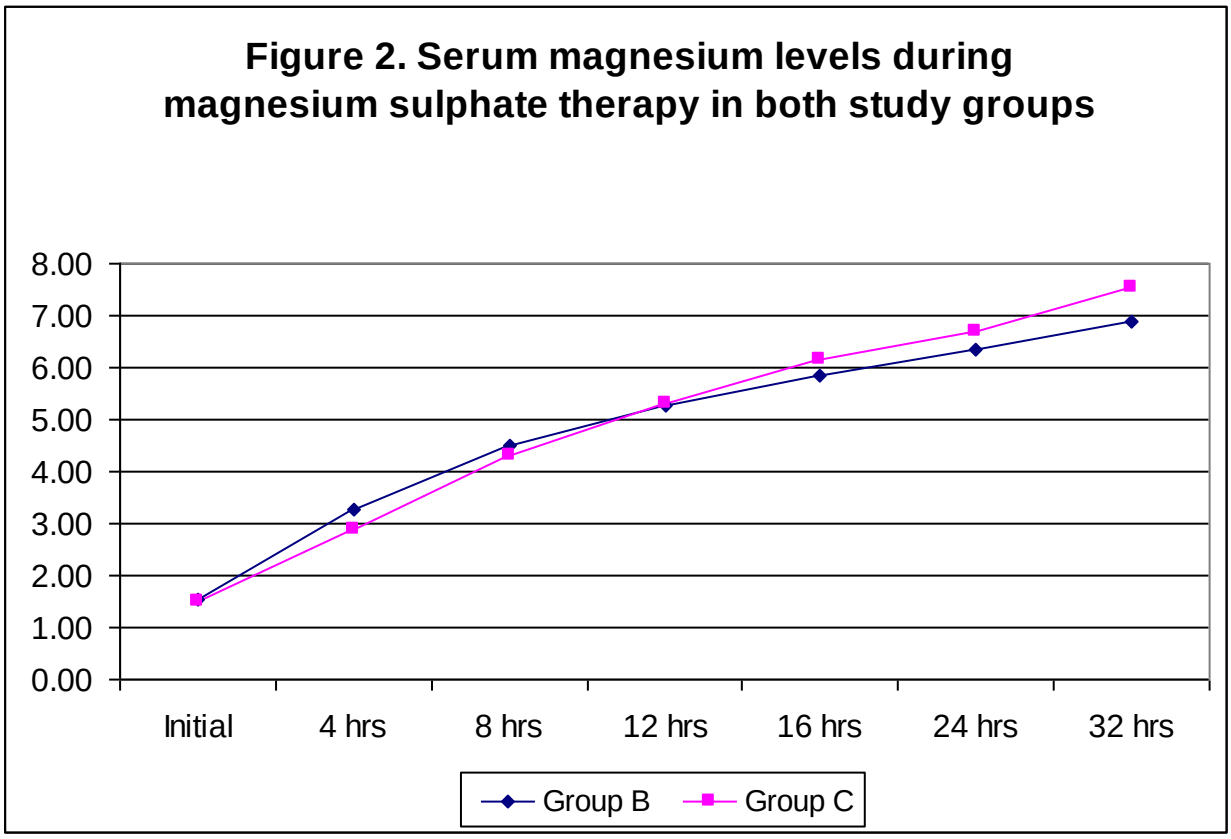
Total dose of magnesium sulphate, grams	Group B No. (%)	Group C No. (%)
10-20	8 (22.85)	4 (11.42)
20-30	4 (11.42)	4 (11.42)
30-40	5 (14.28)	5 (14.28)
40-50	9 (25.71)	13 (37.14)
50-60	6 (17.14)	5 (14.28)
≥ 60	3 (8.57)	4 (11.42)
Total	35 (100)	35 (100)
Mean ± SD	37.37±16.49	41.62±14.02

Table 3 Distribution of cases in the study groups according to the total duration of magnesium sulphate therapy

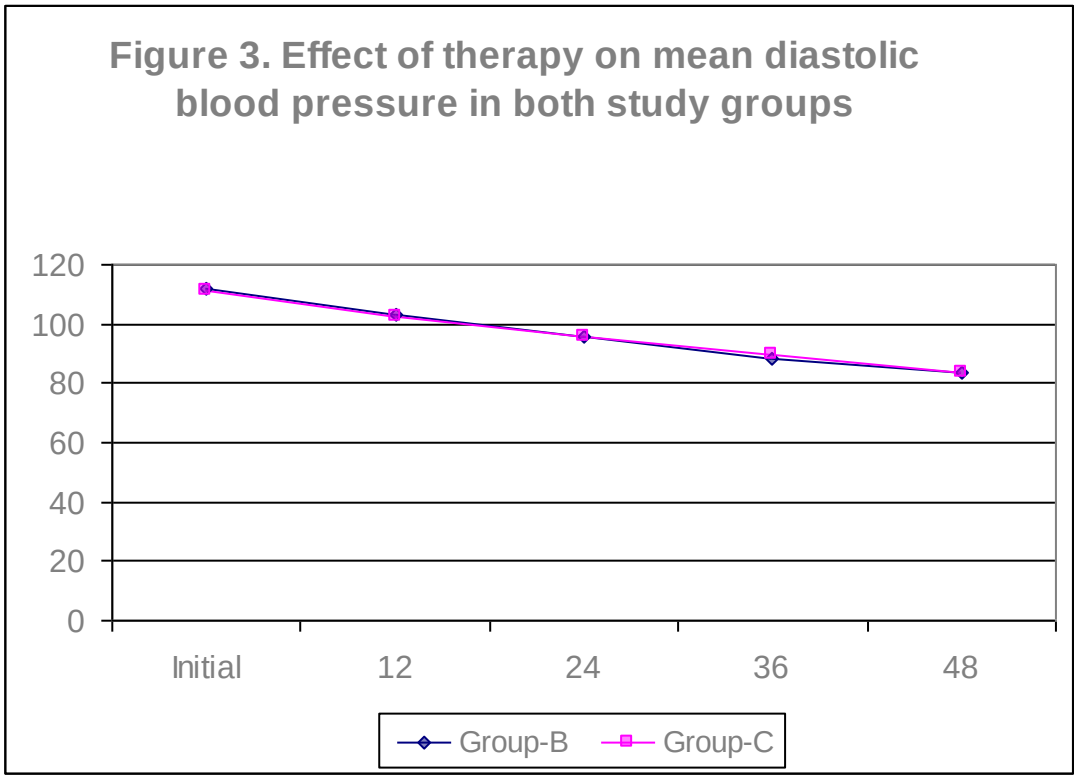
Total duration of magnesium sulphate therapy, hours	Group B No. (%)	Group C No. (%)
4-8	7 (20)	-
8-12	5 (14.28)	3 (8.75)
12-16	3 (8.75)	2 (5.71)
16-24	-	11 (31.42)
24-32	12 (34.28)	12 (34.28)
≥32	8 (22.85)	7 (20)
Total	35 (100)	35 (100)
Mean ± SD	20.74±10.84	24.20±7.93



(54.2%). Mean baseline serum magnesium level in the (control) group A was 1.81±0.58 mg/dl, and, 1.55±0.41 and 1.49±0.41 mg/dl among the cases from groups B and C, respectively **(Table-1)**. Maximum dose of magnesium sulphate was 40-50 grams in most of the cases of groups B and C **(Table-2)** and no statistic difference was seen between groups B and C. The mean total duration of magnesium sulphate administration was 20.74±10.84 and 24.20 ± 7.93 hours among the groups B and C respectively **(Table-3)**. However the difference was not statistically significant (p>0.05).After 24 hours of magnesium sulphate therapy, there was a decrease in proteinuria, which was mild in 20 (57.14%) cases among group B and 19 (54.28%) in group C and there was a significant drop (p<0.05) in proteinuria among both the groups compared to baseline. **(Figure-1)**



Following 24 hours of magnesium sulphate administration, there was decrease in the severity of edema and no edema was present in 30(85.7%) and 29(82.85%) cases of group B and C respectively. Again this change was statistically highly significant (p<0.001).Overall, the mean serum magnesium level at 4 hours after magnesium sulphate therapy was significantly higher(p<0.05)in group B compared to group C, however, after 8,12,16,24 and 32 hours of therapy, the difference between the mean serum magnesium levels in the two study groups was statistically insignificant (**Figure 2**).



There was a fall in mean diastolic blood pressure in the study groups after magnesium sulphate administration. After 12,24 36 and 48 hours of therapy mean diastolic blood pressure decreased by 19.6±2.12 mmHg in group B and 19.03±2.12 mmHg in cases of group C. Therefore this fall in blood pressure as compared between group B and C was statistically not significant (**Figure 3**).

Overall during the study a statistically significant elevation of serum magnesium levels was observed after magnesium sulphate administration and no recurrence of seizures was found in cases of eclampsia. Magnesium sulphate was usually well tolerated. Among the known side effects, headache was frequent; more so in group B **(Table 4)**. No mortality was encountered during the study.

Table 4 Side effects of magnesium sulphate therapy

Headache	11(31.4)	6(17.1)
Vomitting	5(11.4)	1(2.8)
Reduced tendon reflexes	-	2(5.7)
Thrombocytopenia	3(5.4)	-

DISCUSSION

Although this is a well established fact that preeclampsia and eclampsia are more prevalent in extremes of age[3,5,6,23], none of the cases in the present study was less than 15 or over 35 years. Mabie and Sibai[24] also stated that one of the predisposing factor for pre-eclampsia is maternal age below 20 years, however in our study only 9 (12.8%) cases (4 in group B,5 in group C) belonged to the age group of 15- 20 years. Several studies have demonstrated that preeclampsia is more common to primigravidae[4,25]. In our series over 60% were nulliparous in both groups B and C, and the same was the observation made by Chelsey[23].

The baseline serum magnesium in our study group was lower compared to that of control cases. Kisters and co-workers[26] reported changes in magnesium metabolism in pre-eclampsia leading to development of hypertension. Condradt[27] demonstrated that a probable correlation of the level of serum magnesium plays an important role in the etiology of pre-eclampsia and reduced levels of serum magnesium may be because of excessive excretion of magnesium in urine in such patients.

In our study, during the first 4 hours of therapy the intramuscular regimens (group B) produced mean serum magnesium level that was higher than that obtained with the intravenous therapy and the observation was statistically significant (p value<0.05),although there was no significant difference between the two regimens at 8,12,16, 24 and 32 hours after administration of magnesium. Our findings are quite similar to the prospective study of Sibai and co-authors where comparison was made between the two regimens and significant difference during first 3 hours of using the drug was observed[22].

Magnesium sulphate toxicity was observed in a small proportion of patients. Headache was mostly noticed that too more with the intramuscular administration. However the most severe side effects reported previously include blindness, disseminated intravascular coagulation, cardiac arrhythmias, paralysis and respiratory failure[16,28,29]. Clinical assessment is therefore as important as serum magnesium levels for monitoring the toxicity. No maternal deaths were encountered during our study and similar outcome has been demonstrated previously as well[30,31]. However, for further substantiation more studies involving large samples of study populations are needed in future.

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