

Comparison of intravenous magnesium sulphate versus placebo in the management of women with severe pre-eclampsia.

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Abstract:

Objective: To investigate the effectiveness of prophylactic intravenous magnesium sulphate in management of pre-eclampsia in terms of prevention from convulsions and development of eclampsia. **Methodology:** This prospective randomised trial was conducted in the department of Obstetrics and gynaecology Bahawal Victoria Hospital, Bahawalpur. From September 2016 to September 2017. Information was entered in SPSS computer software version 23.1 and analyzed for possible results. Mean and SD was calculated and presented for quantitative data like maternal age, Gestational age, Parity and Blood pressure. Frequency (percentages) were calculated and presented for qualitative data such as gender protienurea (Yes/No), C-section, development of eclampsia and maternal death. Post stratification statistical chi square test was used to see effect modification. P value ≤ 0.05 was considered as significant. **Results:** In this study, a total number of 100% (n=318) patients were

included, divided into two equal groups, 159 in each i.e. magnesium sulphate group and placebo group. The outcomes were observed as Convulsions 2.5% (n=4) and 8.2% (n=13), maternal death 1.3% (n=2) and 6.3% (n=10), adverse reaction 0.6% (n=1) and 8.2% (n=13), anti-hypertensive therapy 73.6% (n=117) and 81.8% (n=130), caesarean Section 59.7% (n=95) and 48.4% (n=77), live births 88.1% (n=140) and 97.5% (n=155) and stillbirths 21.4% (n=34) and 12.6% (n=20) for magnesium sulphate group and placebo group respectively. In Mgso4 group 95% patients have good efficacy and placebo group have 84.3% good efficacy. **Conclusion:** Relative small incidence of convulsions (2.5%) was found in Mgso4 group, so administration of Magnesium sulphate should be considered in management of pre-eclampsia.

Introduction:

Mgso4 is an intravenous or intramuscular agent commonly used in treatment of pre-eclampsia or eclampsia as a prophylaxis. Mechanism of action of magnesium sulphate in prevention of pre-eclampsia is still completely unclear (1). It is claimed that this prevention may be due to the vasodilatation of brain vessels to prevent the brain ischemia through which blood pressure becomes reduced, Mgso4 also involved in peripheral vasodilatation. Another thought is that Mgso4 involved in blocking of calcium to alter the neuromuscular transmission by inhibiting its entry in synaptic endings. It blocks the action of N-methyl-D-aspartate receptors in the brain cells (2).

Round about 40% of plasma Magnesium bound with protein and remaining unbound Magnesium diffused into extracellular space across placental barrier in amniotic fluid (3). It also accumulates in bones. When it was given in pregnancy, it reaches at its maximum level within fourth and fifth hour of drug administration. Mg eliminated through kidneys via urine, almost ninety percent in early 24 hours and remaining slowly in next 24 hours (4).

Side effects of Magnesium Sulphate are dose depending. Convulsions due to eclampsia can be controlled when its concentration reaches at level of 1.8-3.0 mmol/l (5). The real value of mgso4 not estimated yet as prophylaxis. Patellar reflex, respiratory paralysis and Cardiac conduction abnormalities are main side effects of mgso4 occurs at 3.5-5 mmol/l, 5-6.5 mmol/l and 7.5 mmol/l concentrations respectively (6). It may cause cardiac arrest when exceeded 12.5 mmol/l. Its toxicity and side effects are minimum when administered under strict monitoring.

Long term use of Mgso4 during gestation may cause hypocalcemia, hypermagnesemia and demineralization in fetal skeletal system (7,8). Renal toxicity also reported in these patients, hypo magnesium may lead to hypokalemia and cardiac arrhythmias (9). So administration of magnesium must be under observation and monitoring of respiratory rate, blood pressure and tendon reflex. Coetzee EJ et al (10) conducted a study on this topic and reported in Mgso4 group 0.3% patients develop eclampsia and in placebo group 3.2% patients develop eclampsia.

We conducted this randomized trial to determine the role of magnesium sulphate in management of pre-eclampsia and study will be used as new gate towards pre-eclampsia management.

Methodology:

This prospective randomized trial was conducted in the department of Obstetrical and gynecology Bahawal Victoria Hospital, Bahawalpur from September 2016 to September 2017. Women of severe eclampsia admitted from outdoor department and antenatal wards of hospital were included in the study by using non probability consecutive sampling. Study was started after approval from the institution ethical board and informed consent was also obtained from patients. Patients with diastolic blood pressure ≥ 110 mmHg and proteinuria were considered as pre-eclamptic. Efficacy was measured in terms of prevention from convulsions or seizures after the use of drug. Women having age less than 16 years and hypertensive disorder were excluded from the study. Sample size was obtained by assumption of previous study that P1 in Mgso4 group 0.3% patients develop eclampsia but P2 in placebo group 3.2% patients develop eclampsia; CI 95%, power 80% and calculated sample size was 318 patients.

Sealed envelopes were divided to the patients, each envelope consist of a card directing to the use of solution A and B. Cards have consecutive numbers and envelopes were divided into patients randomly. Solutions were made by a third person (4g of Mgso4 in 200 ml N/S and 200 ml N/S only). Identification of the solutions altered randomly without information to the researcher and at the end of study solutions were exposed.

Routine investigations (urea, creatinine, complete blood count, serum electrolytes) were done except serum Mg level. All women were observed under special monitoring for blood pressure, and urine output. Desired level of blood pressure (diastolic 100-110 mmHg) was achieved where it is necessary by giving 25 dihydralazine i/v infusion in 200 ml N/S. After keeping the patient stable labour was induced artificially or delivered through C-section.

Collected Information was entered in SPSS computer software version 23.1 and analyzed for possible results. Mean and SD was calculated and presented for quantitative data like maternal age, Gestational age, Parity and Blood pressure. Frequency (percentages) were calculated and presented for qualitative data such as gender protienurea (Yes/No), C-section, development of eclampsia, maternal death and efficacy. Post stratification statistical chi square test was used to see effect modification. P value ≤ 0.05 was considered as significant.

Results:

In this study, a total number of 100% (n=318) patients were included, divided into two equal groups, 159 in each i.e. magnesium sulphate group and placebo group. The Mean \pm S.D maternal age, parity, gestational age, birth weight, systolic blood pressure, diastolic blood pressure and modal proteinuria (+) of the patients of group magnesium sulphate was 23.05 \pm 2.18 years, 0.08 \pm 0.405 parity, 34.94 \pm 3.57 weeks, 2119.13 \pm 24.61 g, 173.77 \pm 4.51 (mmHG), 118.64 \pm 3.80 (mmHG), 3.50 \pm 0.50 respectively. While, the Mean \pm S.D maternal age, parity, gestational age, birth weight, systolic blood pressure, diastolic blood pressure and modal proteinuria (+) of the patients of group magnesium sulphate was 26.16 \pm 4.15 years, 0.04 \pm 0.22 parity, 35.86 \pm 1.17 weeks, 2244.33 \pm 68.83 g, 178.70 \pm 9.64 (mmHG), 118.36 \pm 2.33 (mmHG), 4.94 \pm 1.20 respectively. No. twin pregnancies was observed as 3.1% (n=5) and 6.3% (n=10) in magnesium sulphate group and placebo group respectively. Symptoms of imminent eclampsia were noted 58.5% (n=93) and 62.3% (n=99) for magnesium sulphate group and placebo group respectively. (Table. 1)

The outcomes were observed as Convulsions 2.5% (n=4) and 8.2% (n=13), maternal death 1.3% (n=2) and 6.3% (n=10), adverse reaction 0.6% (n=1) and 8.2% (n=13), anti-hypertensive therapy 73.6% (n=117) and 81.8% (n=130), caesarean Section 59.7% (n=95) and 48.4% (n=77), live births 88.1% (n=140) and 97.5% (n=155) and stillbirths 21.4% (n=34) and 12.6% (n=20) for magnesium sulphate group and placebo group respectively. (Table. 2). In Mgso4 group 95% patients have good efficacy and placebo group have 84.3% (n=134) good efficacy, this difference was statistically significant (p=0.002). (Table-2).

Association was found between maternal age (p=0.000), gestational age (p=0.002), birth weight (p=0.000), systolic blood pressure (p=0.000) and Modal proteinuria (+) (p=0.000). (Table. 1). There were statistically significant differences in women receiving placebo or magnesium sulphate solution intravenously, apart from the incidence of eclampsia. After applying chi-square. (Table. 2).

Table-1: Demographic Variables

Variable	Magnesium Sulphate (n=159)	Placebo (n=159)	Test of Sig.
Maternal age	23.05 \pm 2.18 years	26.16 \pm 4.15 years	t=-8.36,p=0.000
Parity	0.08 \pm 0.405 parity	0.04 \pm 0.22 parity	t=1.20,p=0.230
Gestational age (weeks)	34.94 \pm 3.57 weeks	35.86 \pm 1.17 weeks	t=-3.06,p=0.002
Birth weight (g)	2119.13 \pm 24.61 g	2244.33 \pm 68.83 g	t=-21.60,p=0.000
Systolic blood pressure	173.77 \pm 4.51(mmHG)	178.70 \pm 9.64(mmHG)	t=-5.84,p=0.000
Diastolic blood pressure	118.64 \pm 3.80(mmHG)	118.36 \pm 2.33(mmHG)	t=0.799,p=0.425
Modal proteinuria (+)	3.50 \pm 0.50	4.94 \pm 1.20	t=-13.85,p=0.000
Symptoms of imminent eclampsia	58.5% (n=93)	62.3% (n=99)	$\chi^2=473,p=0.492$
No. twin pregnancies	3.1% (n=5)	6.3% (n=10)	$\chi^2=1.75,p=0.186$

Table-2: Inferential Results (Outcomes)

Variable	Magnesium Sulphate (n=159)	Placebo (n=159)	Test of Sig.
Convulsions	2.5% (n=4)	8.2% (n=13)	$\chi^2=5.034, p=0.025$
Efficacy			
Good	95 % (n=151)	84.3% (n=134)	$\chi^2=9.772, p=0.002$
Poor	5% (n=8)	15.7% (n=25)	

Table-3: Effect Modifiers of study

Maternal death	1.3% (n=2)	6.3% (n=10)	$\chi^2=5.542, p=0.019$
Adverse reaction	0.6% (n=1)	8.2% (n=13)	$\chi^2=10.76, p=0.001$
Anti-hypertensive therapy	73.6% (n=117)	81.8% (n=130)	$\chi^2=7.825, p=0.005$
Caesarean Section	59.7% (n=95)	48.4% (n=77)	$\chi^2=4.103, p=0.043$
Live births	88.1% (n=140)	97.5% (n=155)	$\chi^2=10.55, p=0.001$
Stillbirths	21.4% (n=34)	12.6% (n=20)	$\chi^2=4.372, p=0.037$

Discussion:

Results of study revealed that use of magnesium sulphate in pre-eclamptic phase save the patient from complications of eclampsia. Its use in all cases of pre-eclampsia and daily use is not justified yet, in milder cases it is useful but in severe cases its use is not usefull and side effects of magnesium sulphate should be kept in mind before its administration (11). Close monitoring also reduce its incidence Sibai et al (12) recommended its doses 1 g/hour , 2-3 g/ hour can also be administered but without margin of safety. A recent trial was conducted on this topic of efficacy of Mgso4 and reported that our women are reluctant to use of placebo and it is considered as unethical in our society.

Burrows and Burrows et al (13) conducted a similar study and reported 1.3 % incidence of eclampsia in placebo group and justified the use of placebo which is much lower percentage, these finding are compareable with our finding in a study by Coetzee EJ et al (10) reported 3.2 % incidence in placebo group. This percentage is close to our results.

Chien et al (14) conducted a randomized control trial between placebo and Mgso4 in management of eclampsia and pre eclampsia and concluded that Mgso4 is very effective in the management of convulsions due to eclampsia and Mgso4 can be used in eclamptic patients but this study was conducted on sample size trials on larger scale are required for complete and definite treatmet. These results are also identical to our results.

In an another trial by Duley and Johnson et al (15) same results were reported that for the management of pre-eclampsia with Mgso4 recommendations require larger scale studies more precisely. Sample size of this trial should be at least 1200 or more. Lucas et al (16) conducted a study on comparison of Mgso4 and phenytoin in management of eclampsia. This study was on larger scale about 2138 patients included and reported no case of eclampsia in magnesium sulphate group but phenytoin group have almost ten women who develop convulsion of eclampsia. All patients of mild to severe disease and with or without protienturia were selected for this trial.

There is another trial by Roberts et al (17) concluded that there may be some other beneficial effects of Mgso4 for but in management of convulsion and seizures role of Mgso4 is outstanding, convulsions are very rare after use of Mgso4 in pre-eclampsia phase. But in our trial we didn't evaluate its beneficial effects. There were lot of other factors which can cause convulsions and eclampsia, all selected women should be given clonazepam and antihypertensive medication at the time of admission and monitored under intensive care with all essential monitoring systems (18, 19). Eclampsia and pre eclampsia may lead to hemorrhage, cerebral infarctions and may be death. It causes vasoconstriction of relevant area and results into ischemia or stroke. Magnesium sulphate found to be drug of choice in many studies for the management of pre-eclampsia (20).

Conclusion: Relative small incidence of convulsions (2.5%) was found in Mgso4 group, so administration of Magnesium sulphate should considered in management of pre-eclampsia.

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