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DIFFERENT REGIMENS OF MAGNESIUM SULFATE FOR MANAGEMENT OF WOMEN WITH SEVERE PREECLAMPSIA

By

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ABSTRACT

Background: Preeclampsia is serious syndrome that can affect human pregnancy causing serious complications. Preeclampsia is pregnancy-specific syndrome of reduced organ perfusion secondary to vasospasm and endothelial activation.

Objective: To assess the comparative effects of three regimens for the administration of the magnesium sulfate when used for the care of women with severe preeclampsia to determine the minimal effective dose of magnesium sulfate in controlling cases with severe preeclampsia and prevention of eclampsia and to determine whether only loading dose of magnesium sulfate is effective in prevention of eclampsia or not.

Patients and Methods: 240 patients were recruited and divided into three groups. Each group contains 80 patients, the first group received only the loading dose of MgSO4 and the second group received loading dose plus 12 hours maintenance dose while the last group received the loading dose and the full maintenance dose of MgSo4 for 24 hours.

Results: Although strong evidence supports the use of magnesium sulfate for prevention and treatment of eclampsia, there was no significant difference between occurrence of eclampsia in the three groups after either administration of loading dose of MgSO4 only or administration of loading dose with maintenance dose for 12 hours or maintenance dose for 24 hours in the studied patients.

Conclusion: Magnesium sulfate proved to cause many hemodynamic changes as it has vasodilator effect on maternal and fetal blood vessels; however, magnesium sulfate should be given to all patients with severe preeclampsia.

Key words: Magnesium sulfate, management, severe preeclampsia.

INTRODUCTION

Preeclampsia is a multisystem disorder of pregnancy which is a major cause of maternal and fetal morbidity and mortality worldwide. The cardinal clinical features of the condition are hypertension and proteinuria occurring after 20 weeks gestation in women who were not previously known to be hypertensive *(Uzan et al., 2011).*

Pre-eclampsia often affects young and nulliparous women, whereas older women are at great risk of chronic hypertension with superimposed preeclampsia *(Young et al., 2010).*

Preeclampsia is considered severe if one or more of the following:, Blood pressure of 160 mmHg systolic or higher or 110 mmHg diastolic or higher on two

occasions at least 6 hours a part while the patient on bed rest., Proteinuria of 3 gm. in 24 hours urine specimen or +2 > on two random urine samples collected at least 4 hours apart., Oliguria of less than 500 ml in 24 hours., Cerebral or visual disturbance, pulmonary edema or cyanosis., epigastric or right upper quadrant pain., Impaired liver function., thrombocytopenia., Fetal growth restriction *(Al-Jameil et al., 2014).*

In normal pregnancy the spiral arteries in the placental bed are invaded by trophoblast, which becomes incorporated into the vessel wall and replaces the endothelium, muscular layer and neural tissue. These physiological changes convert the spiral arteries from narrow muscular vessels to wide non-muscular channels independent of maternal vasomotor control. Pre-eclampsia is thought to be the consequence of impaired trophoblastic invasion of the maternal spiral arteries *(Cui et al., 2012).*

Magnesium sulfate is widely used in obstetrics and is a drug of choice in two important complications of pregnancy, preeclampsia and preterm labor. Magnesium sulfate is used to prevent seizures in preeclampsia patients *(Smith et al., 2013).*

The most common side effect is flushing. Others are far less common and include nausea, vomiting, muscle weakness, thirst, headache, drowsiness and confusion. Although magnesium sulfate can lead to respiratory depression and respiratory arrest, these hazards appear to be rare. Higher dose regimens may be associated with a great risk of side effects and adverse effects. If magnesium sulfate toxicity does occur, intravenous calcium gluconate is an effective antidote *(Duley et al., 2010).*

Magnesium sulfate remains the drug of choice for both prevention and treatment of women with eclampsia. Regimens for administration of this drug have evolved over the years, but have not yet been formally evaluated *(Dhakal et al., 2012).*

In past, MgSO4 was given according to Pritchard regime in which 5 grams of magnesium sulfate was administered four-hourly for 24 hours after loading with 14 grams. It was observed that many patients did not receive maintenance therapy due to suspicion of toxicity but they did not convulse any further. On the basis of this observation, many studies were planned to compare the efficacy of loading dose of magnesium sulfate versus the standard regime in the management of preeclampsia to prevent fits.

Implementation of magnesium sulfate would be strengthened if guidelines and recommendations for practice could be based on reliable evidence about the comparative effects of alternative regimens. It is therefore relevant to assess the pros and cons of alternative strategies for administration. As administration of magnesium sulfate requires regular supervision by trained staff, which is costly, and higher doses may be associated with a greater risk of side effects and adverse events, it is particularly important to assess the minimum effect dose and duration of treatment *(Greenberg et al., 2013).*

In our study we will try to assess the comparative effects of three regimens for the administration of magnesium sulfate when used for the care of women with severe pre-eclampsia.

The aim of the study was to assess the comparative effects of three regimens for the administration of the magnesium sulfate when used for the care of women with severe preeclampsia to determine the minimal effective dose of magnesium sulfate in controlling cases with severe preeclampsia and prevention of eclampsia and to determine whether only loading dose of magnesium sulfate is effective in prevention of eclampsia or not.

PATIENTS AND METHODS

The study is prospective randomized comparative study that compares three regimens for administration of MgSO4 used for the cases of severe pre-eclampsia that were performed in Al-Galaa Maternity Teaching Hospital.

The study included 240 pregnant women presenting to the casualty unit diagnosed as a case of preeclampsia with criteria of severity in the form of the following:

Systolic blood pressure > 160., Diastolic blood pressure >110., Proteinuria > +2 by dip stick (3 gm/24 hrs)., Presence of alarming symptoms (headache, visual disturbance, epigastric pain, vaginal bleeding).

The study included pregnant1 females >37 weeks living fetus, pregnant females with criteria of severe pre-eclampsia, single pregnancy and primigravida.

While pregnant females with history of epilepsy, medical disorders: pregnant females with mild preeclampsia, pregnant females with eclampsia and superimposed patients will be excluded from the study.

After obtaining an informed consent the patients were subjected to the following: Careful history taking including age, parity, gestational age. Complete physical examination and assessment of the blood pressure. Urine analysis by dipstick. Blood sample was taken from the patient for laboratory investigations in the form of CBC, coagulation profile, liver function tests and kidney function tests. Ultrasound was done for each patient for assessment of fetal wellbeing, liquor and placenta.

In All groups, women took initial loading dose MgSO4 (6 grams of MgSO4 on 250 ml ringer solutions over 20 minutes by IV drip).

Using Random Number Table, the sample was divided into three categories:

- Category A - 80 patients who took only loading dose of MgSO4 (6 grams of MgSO4 on 250 m l ringer solutions over 20 minutes) with no postpartum maintenance sulfate.
- Category B ->80 patients given after initial loading dose, abbreviated doses of MgSO4 (4 grams of MgSO4 on 250 ml ringer solution over 4 hours every 4 hours by IV drip only for 12 hours) in the postpartum period.
- Category - C 80 patients given after initial loading dose, full dose of maintenance MgSO4 (4 grams of MgSO4 on 250 ml ringer solution over 4 hours every 4 hours by IV drip for 24 hours) in the postpartum period.

Technique of Blood Pressure Measurement:

For the measurement of maternal blood pressure, a mercury sphygmomanometer was used, with a cuff of 20 x 60 cm.

- The initial measurement for the diagnosis of severe preeclampsia was performed while the patient being seated, holding her right arm at heart level, being considered the last value obtained.
- After loading dose of magnesium sulfate, new blood pressure measurement was performed. Diastolic pressure was determined by Korotkoff phase V. All measurements were performed by the same researcher.

Statistical analysis:

Data were statistically described in terms of mean ± standard deviation (± SD), median and range, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using one way analysis of variance (ANOVA) test. For comparing categorical data, Chi square (x3) test was performed. Exact test was used instead when the expected frequency is less than 5. p values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows.

RESULTS

Mean age of patients was; 26.65 years, SD 5.113 (range; 16-42). Mean gestational age was; 38.88 weeks, SD 2.769 (range; 38-40). Mean systolic BP was; 161.88mmHg, SD 17.121 (range; 100-210). Mean diastolic BP was; 103.15, SD 12.127 (range; 50-120) **(Table 1)**.

Table (1): Demographic features of the studied patients

Groups \ Parameters		Age	GA	SBP	DBP
A	Mean	26.75	38.88	162.00	104.13
	N	80	80	80	80
	Std. Deviation	5.262	1.91	19.448	11.550
	Minimum	17	37	100	60
	Maximum	40	40	210	120
	Median	28.00	39	160.00	110.00
B	Mean	26.56	38.21	162.50	105.06
	N	80	80	80	80
	Std. Deviation	4.986	1.96	14.884	10.296
	Minimum	18	37	120	80
	Maximum	42	40	200	120
	Median	27.00	38	160.00	110.00
C	Mean	26.64	38.24	161.13	100.25
	N	80	80	80	80
	Std. Deviation	5.151	1.80	16.913	13.869
	Minimum	16	37	110	50
	Maximum	39	40	200	120
	Median	28.00	38	160.00	100.00
Total	Mean	26.65	38.71	161.88	103.15
	N	240	80	240	240
	Std. Deviation	5.113	1.86	17.121	12.127
	Minimum	16	37	100	50
	Maximum	42	40	210	120
	Median	28.00	39	160.00	110.00
	P value	.973	.761	.877	.028*

As regarding parity, mode of delivery and proteinuria there were no significant difference within the studied groups **(Table 2)**.

Table (1): Parity, mode of delivery and proteinuria of the studied patients

Parameters \ Groups			A	B	C	Total	P value
Parity	Multigravida	Count	50	50	51	151	0.98
		% within Group	62.5%	62.5%	63.8%	62.9%	
	Primigravida	Count	30	30	29	89	
		% within Group	37.5%	37.5%	36.3%	37.1%	
MOD	CS	Count	35	43	45	123	0.24
		% within Group	43.8%	53.8%	56.3%	51.3%	
	VD	Count	45	37	35	117	
		% within Group	56.3%	46.3%	43.8%	48.8%	
Protein uria	+2	Count	1	2	0	3	0.60
		% within Group	1.3%	2.5%	0.0%	1.3%	
	+3	Count	46	50	51	147	
		% within Group	57.5%	62.5%	63.8%	61.3%	
	+4	Count	33	28	29	90	
		% within Group	41.3%	35.0%	36.3%	37.5%	

There was no significant difference between occurrence of eclampsia occurrence of HELLP syndrome, maternal side effects and maternal ICU admission in the three groups after either administration of loading dose of MgSO4

only or administration of loading dose with maintenance dose for 12 hours or 24 hours in the studied patients where group C showing the highest rate for ICU admission while group A showing the lowest rate for ICU admission **(Table 3)**.

Table (2): Comparison between occurrence of eclampsia, HELLP, maternal side effects and maternal ICU admission after administration of MgSO4 in the studied patients

Parameters \ Groups			A	B	C	Total
Eclampsia	No	Count	80	79	80	239
		% within Group	100.0%	98.8%	100.0%	99.6%
	Yes	Count	0	1	0	1
		% within Group	0.0%	1.3%	0.0%	0.4%
Total		Count	80	80	80	240
		% within Group	100.0%	100.0%	100.0%	100.0%
HELLP	No	Count	78	77	75	230
		% within Group	97.5%	96.3%	93.8%	95.8%
	Yes	Count	2	3	5	10
		% within Group	2.5%	3.8%	6.3%	4.2%
Total		Count	80	80	80	240
		% within Group	100.0%	100.0%	100.0%	100.0%
Maternal Side effect	Flushing	Count	8	5	11	24
		% within Group	10.0%	6.25%	13.8%	10%
	No	Count	72	75	69	216
		% within Group	90.0%	93.75%	86.3%	90%
Total		Count	80	80	80	240
		% within Group	100.0%	100.0%	100.0%	100.0%
MICU	No	Count	73	66	50	189
		% within Group	91.3%	82.5%	62.5%	78.8%
	Yes	Count	7	14	30	51
		% within Group	8.8%	17.5%	37.5%	21.3%
Total		Count	80	80	80	240
		% within Group	100.0%	100.0%	100.0%	100.0%

In more detailed analysis of the significant difference between groups, we found that maternal ICU admission was significant between Group A and Group C, and non-significant between Group A & B as Group A showed the lowest percentage in maternal ICU admission while Group C shows the highest maternal ICU admission with P value less than 0.0001 **(Table 4)**.

Table (3): Comparison between maternal ICU admission in the group A vs group B, group B vs group C and group A vs group C after administration of MgSO4

Parameters \ Groups			A	B	Total	B	C	Total	A	C	
MICU	No	Count	73	66	139	66	50	116	73	50	123
		% within Group	91.3%	82.5%	86.9%	82.5%	62.5%	72.5%	91.3%	62.5%	76.9%
	Yes	Count	7	14	21	14	30	44	7	30	37
		% within Group	8.8%	17.5%	13.1%	17.5%	37,5%	27.5%	8.8%	37.5%	23.1%
p value			0.101			0.005			0.0001		

There was a significant difference between level of serum MgSO4 in the three groups after either administration of loading dose of MgSO4 only or administration of loading dose with maintenance dose for 12 hours or 24 hours in the studied patients as mean value of serum MgSO4 in Group A was; 3.785 mg/dl, SD 1.0528 (range; 0.9-6.1), Mean value of serum MgSO4 in Group B was; 4.881 mg/dl, SD 0.9783 (range; 1.9-8), Mean value of serum MgSO4 in Group C was; 5.851mg/dl, SD 0.9200 (range; 3.0-8) **(Table 5)**.

Table (4): Comparison between levels of serum MgSO4 in the studied population after administration of MgSQ4

Parameters \ Groups		Group A	Group B	Group C	Total
Mean		3.785	4.881	5.851	4.839
N		80	80	80	240
Std. Deviation		1.0528	0.9783	0.9200	1.2953
Minimum		0.9	1.9	3.0	0.9
Maximum		6.1	8.0	8.0	8.0
Median		3.800	5.000	5.800	5.000
(t) **Group**	(J) **Group**	**Mean Difference** (I-J)	**Std. Error**	**p value**	**95% Confidence Interval**
					Upper Bound

There was no significant difference between perinatal mortality in the outcome of pregnancy and neonatal ICU admission for the outcome of pregnancy in the three groups after either administration of loading dose of MgSO4 only or administration of loading dose with maintenance dose for 12 hours or 24 hours in the studied patients (Table 6).

Table (5): Comparison between perinatal fetus mortality, prematurity, NICU in the outcome of pregnancy in the studied groups after administration of MgSO4

Parameters \ Groups			A	B	C	Total
Perinatal death	IUFD	Count	4	3	9	16
		% within Group	5.0%	3.8%	11.3%	6.7%
	Neonatal mortality	Count	3	4	4	11
		% within Group	3.8%	5.0%	5.0%	4.6%
	no	Count	73	73	67	213
		% within Group	91.3%	91.3%	83.8%	88.8%
Total		Count	80	80	80	240
		% within Group	100.0%	100.0%	100.0%	100.0%
Prematurity	No	Count	41	47	40	128
		% within Group	53.9%	61.0%	56.3%	57.1%
	Yes	Count	35	30	31	96
		% within Group	46.1%	39.0%	43.7%	42.9%
Total		Count	76	77	71	224
		% within Group	100.0%	100.0%	100.0%	100.0%
NICU	No	Count	62	65	62	189
		% within Group	81.6%	84.4%	87.3%	84.4%
	Yes	Count	14	12	9	35
		% within Group	18.4%	15.6%	12.7%	15.6%
		Count	76	77	71	224
Total		% within Group	100.0%	100.0%	100.0%	100.0%

DISCUSSION

Preeclampsia is a major cause of perinatal and maternal morbidity and mortality, which affects 2-5% of pregnancies *(Ngwenya et al., 2017).*

Management of pre-eclampsia is based on stabilization, continued monitoring and delivery at an optimal time for mother and her baby. There is strong evidence from many randomized trials that supports the use of magnesium sulfate for the prevention and treatment of women with eclampsia *(Berhan et al., 2015).*

The incidence of seizures in untreated pre-eclamptic women is approximately 3-4%, whilst for those receiving magnesium sulfate; the rate is 0.8-1% *(Duley et al., 2011).*

There is a little reliable evidence from randomized trials assessing the minimum effective dose, the comparative effects of alternative routes of administration (intravenous or intramuscular), or the ideal duration of therapy *(Duley et al., 2011).*

In the present work, there was no significant difference between occurrence of eclampsia, HELLP syndrome, maternal side effects or perinatal mortality and neonatal ICU admission in the three groups after either administration of loading dose of MgSO4 only or administration of loading dose with maintenance dose for 12 hours or 24 hours in the studied patients However, there was a significant difference between maternal ICU admissions in the three groups with highest rate in Group C and lowest rate in Group A. Also, there was a significant difference between levels of serum MgSO4 in the three groups.

Our study compared that three different regimens for .administration of MgSO4 (loading dose only, abbreviated regimen with maintenance sulfate for only 12 hours and standard regimen with maintenance dose for 24 hours) in management of severe preeclampsia.

Tabassum et al. (2009) found that there was no significant difference in the two groups in term of occurrence of seizures .In our study we include patients with severe preeclampsia not mild and we consider loading dose only as a comparative regimen. *Maia et al. (2014)* found that none of these women and none of the other cohort given the 24 hour magnesium infusion developed eclampsia. Other studies were conducted on women with eclampsia comparing the loading dose versus the standard regimen for MgSO4 with similar outcome. *Barber et al. (2009)* found that only loading dose of MgSO4 can control convulsion in eclampsia and it is as effective as standard regimen. *Calvin et al (2013)* found that the shortened postpartum course of magnesium sulfate is as effective as the standard Pritchard regimen in the management of eclampsia. *Regmi et al. (2010)* found that loading dose of magnesium sulfate is a good alternative for standard Pritchard regimen. It avoids multiple painful injections of magnesium Sulfate.

Bhattacharjec et al. (2011) found that low-dose intravenous magnesium sulfate was found to be as effective as the standard intramuscular regimen, while maintaining a high safety margin.

CONCLUSION

The early diagnosis of severe preeclampsia is very important in order to minimize maternal and fetal complications. We Magnesium sulfate proved to cause many hemodynamic changes as it has vasodilator effect on maternal and fetal blood vessels However; magnesium sulfate should be given to all patients with severe preeclampsia. Considering the equal effectiveness, fewer side effects, ease of monitoring and cost-effectiveness of loading dose, single loading dose of magnesium sulfate in the management of pre-eclampsia is preferable to other regimes of administration requiring multiple doses.

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النظم المختلفة لعقار سلفات المغناسيوم المستخدم فى علاج السيدات المصابة بمرض تسمم الحمل

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خلفية البحث: تسمم الحمل هو متلازمة خطيرة يمكن أن تؤثر على الحمل البشري وتسبب مضاعفات خطيرة. كما أنه متلازمة محددة للحمل من انخفاض نضح الجهاز الثانوي لتشنج الأوعية وتنشيط البطانية.

الهدف من البحث: لتقييم الآثار المقارنة لثلاثة أنظمة لإدارة سلفات الماغنسيوم عند استخدامها لرعاية النساء المصابات بتسمم الحمل الشديد لتحديد الحد الأدنى من الجرعة الفعالة من سلفات الماغنسيوم في السيطرة على الحالات مع تسمم الحمل الشديد والوقاية من تسمم الحمل.

المريضات وطرق البحث: تم تجميع 240 مريضة مقسمات إلى ثلاث مجموعات متساوية. تلقت المجموعة الأولى جرعة التحميل من سلفات الماغنسيوم ، بينما تلقت المجموعة الثانية جرعة تحميل بالإضافة إلى جرعة صيانة لمدة 12 ساعة، بينما تلقت المجموعة الأخيرة جرعة التحميل وجرعة الصيانة الكاملة من سلفات الماغنسيوم لمدة 24 ساعة.

نتائج البحث: لم يكن هناك فرق كبير بين حدوث تسمم الحمل في المجموعات الثلاث اللاتى شملتهن الدراسة.

الاستنتاج: سلفات الماغنسيوم تسبب العديد من التغيرات في الدورة الدموية لأنها لها تأثير موسع للأوعية الدموية للأم والجنين. غير أنه ينبغي إعطاء سلفات الماغنسيوم لجميع المرضى الذين يعانون من تسمم الحمل الشديد.