Intramuscular and intravenous routes of magnesium sulfate in preeclamptic with severe features transferred from community hospitals: a retrospective cohort

ORIGINAL ARTICLE BY

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Accepted: January 2018
Latest revision: March 2018
Printed: April 2018

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ABSTRACT

OBJECTIVE

To compare the therapeutic level of the two routes of magnesium sulfate ($MgSO_4$) treatment; intramuscular (IM) and intravenous (IV), in the preeclamptic patients during the transfer process from community hospitals to the obstetrics care center, especially in low or high maternal weight group.

METHODS

This retrospective cohort study aimed to compare the rate of the therapeutic level achievement of serum magnesium levels in preeclamptic women with severe features with the two routes of $MgSO_4$; IM and IV, from the community hospitals before transferring to the obstetrics care center at Udonthani Hospital, Thailand. Serum magnesium level at admission and 4 hours at Udon Thani Hospital was taken. The rate of therapeutic serum Mg level achievement, sub-therapeutic, supra-therapeutic level, and adverse effects were also compared between the two routes.

RESULTS

Of these 754 preeclamptic patients with severe features, 285 in the IM group and 469 in the IV group. There were 58.3% of the women in the IM group achieved the therapeutic level compared with 22.2% in the IV group (adjusted odds ratio (AOR) 4.23; 95% confidence interval (CI) 3.01 to 5.94). For the subgroup analysis regarding body weight (BW), those with BW less than 60 kg, 79.3% of the IM group compared with 47.4% in the IV group (AOR 4.01; 95% CI 1.32 to12.2) achieved the therapeutic level; those with BW 60 to 79 kg, 66.7% in the IM group compared with 22.8% in the IV group (AOR 5.48; 95% CI 3.40 to 8.81) achieved the therapeutic level; those with BW 80 to 99 kg, 43.0% in the IM group compared with 15.6% in the IV group (adjusted OR 4.97; 95%CI 2.50 to 9.89) achieved the therapeutic level; and fort those with BW more than 100 kg, 30.0% in the IM group compared with 0% in the IV group achieved the therapeutic level.

CONCLUSION

IM route of $MgSO_4$ was associated with higher rate of therapeutic level achievement than that of the IV route in $MgSO_4$ regimen in preeclamptic women with severe features.

INTRODUCTION

Preeclampsia is a significant cause of maternal death and morbidity around the world, estimated ten million women develop preeclampsia and 76,000 women die each year worldwide.[1,2] Eclampsia is a complication which can lead to maternal death or dreadful maternal outcomes.[3] Magnesium sulfate ($MgSO_4$) is consistently recommended for eclampsia prevention by obstetrics organizations worldwide[4,5], although the $MgSO_4$ action mechanism still remains unclear.[6,7] $MgSO_4$ has been found to be more effective for convulsion prevention than other drugs such as phenytoin, diazepam or antihypertensive drug alone.[8-10] There is no consensus on the route and dosage of $MgSO_4$ administration.[11] However, two commonly used regimens are a 4-6 g of 10% $MgSO_4$ solution intravenously followed by 1-3 g/hour as a continuous infusion[12] (IV route) or 10 g of a 50% solution intramuscularly followed by 5 g intramuscularly every four hours[13] (IM route). The therapeutic drug level of $MgSO_4$ does not have a clearly established concentration threshold for ensuring convulsion prevention. However, the recommended level, based on retrospective data, is 4.8 to 8.4 mg/dL (2.0 to 3.5 mmol/L)[14] and serum Mg level monitoring has been practiced to ensure safety and to avoid toxicity.

The referral process between a community hospital and obstetrics care centers in the provincial or regional hospitals is critical for preeclamptic care. $MgSO_4$ is usually started at the community hospitals to prevent the convulsion. The route of administration is an important factor for achieving the serum therapeutic level. In general, IV route produces serum Mg level consistently, whereas the IM regimen has higher serum Mg level but inconsistently.[15] The best $MgSO_4$ administration route has not yet been clearly evaluated. The objective of this study was to compare the rate of preeclamptic women with serum therapeutic level achievement and avoiding serious side effect for $MgSO_4$ administration by two routes, IM and IV, during the referral process.

METHODS

STUDY DESIGN

A retrospective cohort study was conducted at Udonthani Hospital, Thailand. Preeclamptic patients with severe features who had been transferred from community hospitals to obstetrics care center at Udonthani Hospital from October 2011 to September 2017 were reviewed.

PATIENTS

Medical records of the patients with preeclampsia with severe features were retrieved and reviewed. The preeclamptic was diagnosed, according to American College of Obstetrics and Gynecology 2013 Criteria;[16] a new onset of hypertension (systolic blood pressure 140 mmHg or higher, diastolic blood pressure 90 mmHg or higher plus a new onset of proteinuria (urine protein more than 300 mg in 24 hours or urine protein creatinine ratio more than 3.0 mg/dL). The diagnosis can be made with hypertension with other symptoms such as thrombocytopenia (platelet less than 100,000/microliter), a new onset of renal insufficiency (doubling of serum creatinine or elevated serum creatinine $\geq$1.1 mg/dL in the absence of other

Table 1. Characteristics of the patients

Characteristic	Total (n = 754)	Intramuscular group (n=285)	Intravenous group (n=469)	P Value
Age-year				<0.01
Median	27	26	28	
Interquartile range	21-34	20-32	21-34	
Previous pregnancy-no. %	343 (45.5)	125 (43.9)	218 (46.5)	0.64
Gestational age-weeks				0.03
Median	37	38	37	
Interquartile range	35-39	36-39	35-39	
Body weight-kg				0.99
Median	74	74	74	
Interquartile range	65-85	65-85	65-83	
Height-cm	157.1±6.1	156.9±6.1	157.3±6.0	0.47
BMI-kg/m^2				0.42
18.5 to <25	115 (15.3)	45 (15.8)	70 (14.9)	
25 to <30	251(33.3)	85(29.8)	166(35.4)	
30 to <40	352(46.7)	139(48.7)	213(45.4)	
≥40	36(4.8)	16(5.6)	20(4.3)	
Median	30.1	30.4	30.0	0.47
Interquartile range	26.8-33.7	26.6-34.7	26.9-33.3	
MAP-mmHg				0.52
Median	126.7	126.7	126.3	
Interquartile range	120-132.3	120-132.7	(120-132)	
GFR -ml/min				<0.01
Median	157.4	139.4	169.1	
Interquartile range	122.9-203.4	109.6-191.7	134.7-208.4	

Plus minus values are means±SD; BMI: body mass index; MAP: Mean arterial pressure; GFR: Glomerular filtration rate

renal disease), hepatic dysfunction (elevated serum liver transaminases more than double of the normal concentration), pulmonary edema and a new onset of cerebral or visual disturbances.

The criteria for severe features were defined as preeclamptic patients who had one of the following; elevated blood pressure (systolic blood pressure 160 mmHg or higher or diastolic blood pressure 110 mmHg or higher), elevated creatinine level (doubling of serum creatinine or elevated serum creatinine more than 1.1 mg/dL), impaired liver function (elevated serum liver transaminases more than double of the normal concentration), severe persistent right upper

Table 2. Outcomes of treatments

Outcome	Intramuscular group	Intravenous group	Crude odds ratio	Adjusted odds ratio* (95% CI)
	no. (%)			
Achieved therapeutic level	166 (58.3)	104 (22.2)	4.9	4.23 (3.01 to 5.94)
Body weight<60 kg	23 (79.3)	27 (47.4)	4.26	4.01 (1.32-12.2)
Body weight 60-79 kg	100 (66.7)	56 (22.8)	6.77	5.48 (3.40-8.81)
Body weight 80-99 kg	37 (43.0)	21 (15.6)	4.10	4.97 (2.50-9.89)
Body weight≥100	6 (30.0)	0	NA	NA
Sub-therapeutic level	119 (41.8)	365 (77.8)		
Convulsion during transfer	0	0		

N/A not applicable

*Adjusted for age, gestational age and glomerular filtration rate

quadrant or epigastric pain without other alternative diagnosis, a new onset cerebral or visual disturbances, thrombocytopenia and pulmonary edema.[16] Eclampsia was defined as an occurrence of new onset, generalized, tonic-clonic seizure or coma in preeclampsia patient without the other causes.[16]

EXPOSURES

The protocols for $MgSO_4$ treatment; IV and IM routes were reviewed and recorded. The IV route referred to 4 g of 10% $MgSO_4$ solution IV loading dose followed by 1 g/hr initially. The IM route was 4 g of $MgSO_4$ IV and 10 gm of 50% $MgSO_4$ solution intramuscularly loading dose followed by 5 g intramuscularly every four hours. Serum $MgSO_4$ was monitored at admission and then every 4 hours after the loading dose. Serum Mg levels less than 4.8 mg/dL were considered to be sub-therapeutic and serum Mg levels more than 8.4 mg/dL were considered to be supra-therapeutic.

All patients were monitored for Mg toxicity by deep tendon reflex, respiratory rate, and urine output. The termination of pregnancy was done according to the obstetrical indication. MgSO4 was continued until 24 hours after delivery. This study's exclusion criteria were; pregnancy with myasthenia gravis, pregnant women who delivered at gestational age less than 24 weeks, received $MgSO_4$ in other regimens and cases without serum Mg level recorded.

DATA COLLECTIONS

The demographic data such as age, gestational age (GA), gravity (G), parity (P), blood pressure (BP), mean arterial pressure (MAP), body weight (BW),

height (Ht) , body mass index (BMI), glomerular filtration rate (GFR) were verified and reviewed. The BMI was calculated from the BW and Ht on the delivery day (BW in kilograms divided by the square of Ht in meters). Maternal body weight was classified into four groups; (i) 60 kg or less, (ii) 60 to 79 kg, (iii) 80 to 99 kg, and (iv) 100 kg or more. This classification is made for easy practical use in routine practice.

STATISTICAL ANALYSIS

The patients' demographic data were presented as number and percentage for all categorical variables. The continuous variables were presented by the mean, standard deviation, median, and interquartile range. The data were collected for all participants and categorized for the IV and IM group. The rate for the patients achieving therapeutic level was presented as number and percentage.

A crude analysis was used to determine the effective administration route and other clinical characteristics had on the $MgSO_4$ therapeutic level. Binomial regression and logistic regression analysis were performed to estimate the crude odds ratios and their 95% confidence intervals (CI). The multiple logistic regression analysis and their 95% CI were performed to adjust the effect of other covariate factors with $MgSO_4$ therapeutic level achievement. The magnitudes of effect were presented in terms of adjusted odds ratio (AOR). All analyses were done using Stata 13 (Stata Corp). The significance level was set at $P<0.05$ and all statistical tests were two-sided.

RESULTS

From October 2011 to September 2017, a total of 754 pregnant women composed of 733 preeclamptic patients with severe features and 19 eclamptic patients were transferred from community hospitals to Udonthani Hospital. The distance between hospitals ranged from 30 to 120 kilometers. The time between starting of $MgSO_4$ to serum Mg testing ranged from 50 to 120 minutes. Of these patients, 469 were in the IV group and 285 were in the IM group. The patients' baseline characteristics in each group are presented in Table 1.

The percentages of patients with therapeutic level achievement, at the obstetrics care center, were compared between the IM and IV routes, our study found that 58.3% of IM regimen patients achieved therapeutic level compared with only 22.2% of IV regimen patients. No subject with supra-therapeutic serum Mg was found in either regimen and no convulsion occurred during the referral process in both regimens The covariate factors were adjusted by multiple logistic regression analysis. The IM regimen was found to have the AOR 4.23 times greater than the IV regimen for therapeutic level achievement. The detail is shown in Table 2.

Factors that influenced the therapeutic level for both groups were analyzed. The route and maternal weight were shown to be the factors that affected $MgSO_4$ therapeutic level achievement, as shown in Table 2. The data for patients who achieved the $MgSO_4$ therapeutic level was

classified into four groups according to their maternal BW. The data demonstrated that in all weight groups the IM regimen had a higher rate of therapeutic level achievement. However, in those with BW 80 kg or more, the rate of therapeutic level achievement was less than 50% in both regimens.

DISCUSSION

$MgSO_4$ remains the drug of choice for eclampsia prevention. There is strong evidence proving its effectiveness,[17] However, the proper route and dose in seizure prophylaxis are still controversy.[11] From the current study, the IM route was found to be more effective than the IV regimen during the referral process with 58.2% achieving a therapeutic level at the Obstetrics care center compared with only 22.2% in the IV route. However, the IV loading dose was 4 g, which is commonly used in general practice. A higher loading dose for the IV regimen would still need further evaluation. The IM route also has some advantage in the avoidance of drug administration problem during the patient's transfer. The IV route needs an infusion machine to control the rate of infusion during transfer. It also has to disconnect and reconnect to the IV line during transfer which may cause serious cardiopulmonary problems if the rate of infusion is wrong. However, the IM route cause more pain at the injection site and has a less constant blood level of $MgSO_4$.[15]

Maternal weight is also an important factor. A problem was found in obese women who had a thick layer of fat tissue at the injection site. The recommendation is the use of a longer needle for IM injection. However from this study, even in the higher maternal weight group, the IM regimen was still better than the IV regimen regarding the therapeutic level achievement of $MgSO_4$.

According to maternal weight, the higher maternal weight had a lower proportion of the therapeutic level achievement. Therefore, we advise the adjustment of dosage of $MgSO_4$ according to maternal weight. Women with higher maternal weight should receive a higher dose of $MgSO_4$. The recommended dosage of $MgSO_4$ should be weight adjusted, not to be a single dose for all women. The strength of this study is its large sample size with the focus at the referral time which is the most critical point for the patients. However, the limitation is the retrospective data collection and the use of serum Mg as the measurement outcome. The most appropriate outcome should be seizure avoidance which a very larger sample size is needed to see the differences between these two routes of $MgSO_4$ on this clinical outcome. Moreover, the other confounders such as time between needle to lab might be affected the result.

In conclusion, IM route of $MgSO_4$ was associated with higher rate of therapeutic level achievement than that of the IV route in $MgSO_4$ regimen in preeclamptic women with severe features. However, the strong policy recommendation and implication of the findings of this retrospective cohort should be, however, confirmed with a further prospective randomized controlled trial regarding the effectiveness and the safety of both routes of the preeclamptic patients.

ACKNOWLEDGMENTS & DECLARATION

The authors would like to acknowledge Dr.Thammanoon Wisittanawat director of Udonthani Hospital for permission and support. Thanks for Dr.Sunanthaporn Phaiphan and Orathai Jaikwang, Udonthani Hospital staff who participated in this study.

COMPETING INTERESTS: The authors declare no conflict of interest relative to this work.

FUNDING: This study has been supported by Udonthani Hospital

REFERENCES

1.Cunningham FG LK, Bloom SL, Spong CY, Dashe JS, Hoffman BL, Casey BM, Sheffield JS. Williams obstetrics 24th ed. New York McGraw-Hill; 2014.

2.Preeclampsia and Maternal Mortality: a Global Burden. (Accessed 15 Nov, 2016, at http://www.preeclampsia.org/health-information/149-advocacy-awareness/332-preeclampsia-and-maternal-mortality-a-global-burden.)

3.Mazhar SB, Batool A, Emanuel A, Khan AT, Bhutta S. Severe maternal outcomes and their predictors among Pakistani women in the WHO Multicountry Survey on Maternal and Newborn Health. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics 2015;129:30-3.

4.American College of Obstetricians and Gynecologists ;Task Force on Hypertension in Pregnancy. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstetrics and gynecology 2013;122:1122.

5.Magee LA, Pels A, Helewa M, Rey E, von Dadelszen P ; Canadian Hypertensive Disorders of Pregnancy Working Group Diagnosis, evaluation, and management of the hypertensive disorders of pregnancy: executive summary. Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC 2014;36:416-41.

6.Hallak M. Effect of parenteral magnesium sulfate administration on excitatory amino acid receptors in the rat brain. Magnesium research : official organ of the International Society for the Development of Research on Magnesium 1998;11:117-31.

7.Cotton DB, Hallak M, Janusz C, Irtenkauf SM, Berman RF. Central anticonvulsant effects of magnesium sulfate on N-methyl-D-aspartate-induced seizures. American journal of obstetrics and gynecology 1993;168:974-8.

8.Duley L, Henderson-Smart D. Magnesium sulphate versus diazepam for eclampsia. The Cochrane database of systematic reviews 2003:CD000127.

9.Duley L, Henderson-Smart D. Magnesium sulphate versus phenytoin for eclampsia. The Cochrane database of systematic reviews 2003:CD000128.

10.Duley L, Gulmezoglu AM, Henderson-Smart DJ. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. The Cochrane database of systematic reviews 2003:CD000025.

11.Duley L, Matar HE, Almerie MQ, Hall DR. Alternative magnesium sulphate regimens for women with pre-eclampsia and eclampsia. The Cochrane database of systematic reviews 2010:CD007388.

12.Zuspan FP. Problems encountered in the treatment of pregnancy-induced hypertension. A point of view. American journal of obstetrics and gynecology 1978;131:591-7.

13.Pritchard JA, Cunningham FG, Pritchard SA. The Parkland Memorial Hospital protocol for treatment of eclampsia: evaluation of 245 cases. American journal of obstetrics and gynecology 1984;148:951-63.

14.Sibai BM, Lipshitz J, Anderson GD, Dilts PV, Jr. Reassessment of intravenous $MgSO_4$ therapy in preeclampsia-eclampsia. Obstetrics and gynecology 1981;57:199-202.

15.Okusanya BO, Oladapo OT, Long Q, et al. Clinical pharmacokinetic properties of magnesium sulphate in women with pre-eclampsia and eclampsia. BJOG : an international journal of obstetrics and gynaecology 2016;123:356-66.

16.American College of Obstetricians and Gynecologists. Hypertension in pregnancy. In: Task force on hypertension in pregnancy, ed. Washington DC2013.

17.Duley L, Gulmezoglu AM, Henderson-Smart DJ, Chou D. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. The Cochrane database of systematic reviews 2010:CD000025.