Associated Factors of Subtherapeutic Serum Magnesium Level for Prevention of Eclampsia in Term Pregnant Women with Severe Pre-eclampsia

Vitaya Titapant, M.D., Kingkaew Mingsuttiporn, M.D.

Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok 10700, Thailand.

ABSTRACT

Objective: To investigate the factors associated with subtherapeutic serum magnesium levels in order to prevent eclampsia in term pregnant women with severe pre-eclampsia.

Methods: This case-control study included 200 term pregnant women with severe pre-eclampsia who received magnesium sulfate for eclampsia prophylaxis. These patients were randomly allocated into case and control groups. Experimental cases included 100 women whose serum magnesium level did not reach the therapeutic level (<4.8 mg/dL) at 2 hours after initial administration, whereas the controls were 100 women whose serum magnesium levels reached therapeutic levels (4.8-8.4 mg/dL). Data from the medical records, including baseline characteristics, sign and symptoms, laboratory findings and pregnancy outcomes, were extracted for univariate and multivariate analyses.

Results: Only two factors, pre-pregnancy body mass index (BMI) and serum creatinine level, showed significant differences between the two groups. Pre-pregnancy BMI greater than 25 kg/m^2 increased the risk of subtherapeutic serum magnesium level by 56% compared with normal pre-pregnancy BMI (adjusted OR 1.56, p=0.019), whereas pre-pregnancy BMI less than 18 kg/m^2 decreased the risk by 80% (adjusted OR 0.2, p=0.02). Also, serum creatinine levels greater than 0.9 mg/dl decreased the risk by 98.7% (adjusted OR 0.013, p<0.001). No significant difference in pregnancy outcomes was noted in either group.

Conclusion: Pre-pregnancy BMI greater than 25 kg/m^2 increased the risk, whereas pre-pregnancy BMI less than 18 kg/m^2 decreased the risk of subtherapeutic serum magnesium levels. A serum creatinine level greater than 0.9 mg/dl was another factor that decreased the risk.

Keywords: Pre-eclampsia; magnesium sulfate; therapeutic level; associated factors (Siriraj Med J 2020; 72: 159-166)

INTRODUCTION

Pre-eclampsia is a common obstetric complication and one of the main causes of maternal and fetal mortality worldwide1. The incidence of pre-eclampsia varies between 3-10 percent of pregnant women and is the leading cause of maternal deaths. The causes of such deaths include intracerebral hemorrhage, congestive heart failure, acute kidney injury, and eclampsia.[1] Maternal complications and neonatal complications, such as preterm labor and respiratory distress syndrome, are also common.

Given that the etiology of eclampsia is unknown, but the condition occurs exclusively during pregnancy, the best treatment of choice is termination of pregnancy.[2] However, other supportive treatments, including prevention of eclampsia, blood pressure control and patient hydration, should also be considered.[2-4]

Corresponding author: Kingkaew Mingsuttiporn
E-mail: kingkaew.msp@gmail.com
Received 18 April 2018 Revised 6 June 2019 Accepted 13 June 2019
ORCID ID: http://orcid.org/0000-0001-5956-8109
http://dx.doi.org/10.33192/Smj.2020.21

For prevention of eclampsia, magnesium sulfate is the most appropriate treatment of choice.[5] There are two major regimens that are currently used.

1. Zuspan regimen: an intravenous regimen of 4 grams of magnesium sulfate is administered as the loading dose, followed by a maintenance infusion of magnesium sulfate solution at 2 grams/hour.[6]
2. Pritchard regimen: an intramuscular regimen of 4 grams of magnesium sulfate is administered as the loading dose, followed by 10 grams intramuscularly. Subsequently, 5 grams is administered intramuscularly every 4 hours in alternate buttocks.[7]

At Siriraj Hospital, we use the intravenous regimen because it can be easily adjusted to reach the target therapeutic level.[8]

Surprisingly, even subtherapeutic serum magnesium levels might cause serious maternal complications such as intracerebral hemorrhage and multiple organ failure. However, only one study by Tudela CM[9] reported the factors associated with subtherapeutic serum magnesium levels for the prevention of eclampsia in pre-eclamptic pregnant women. This study reported subtherapeutic serum magnesium levels in more than half of the participants. In addition, various factors associated with this condition, including body mass index (BMI), age and multipara, were reported.

Until now, no such study has been conducted in Thailand. We seek to determine the factors associated with subtherapeutic serum magnesium levels and whether these factors differ between our country and the Western countries.

The primary aim of this study was to identify the factors associated with subtherapeutic serum magnesium levels for the prevention of eclampsia in term pregnant women with severe pre-eclampsia. The secondary aim was to compare the pregnancy outcomes, including delivery outcomes, maternal outcomes and neonatal outcomes, as well as the use of antihypertensive drugs in these pregnant women.

MATERIALS AND METHODS

Study design

This was a case-control study with a retrospective chart review.

Sample size calculation

The test of difference between two independent proportions was chosen to calculate the sample size in this study, based on the study of Tudela CM[9] that reported associated factors related with subtherapeutic serum magnesium level in pre-eclampsia pregnant women. From this study, obesity (BMI >25 kg/m^2) and multipara were two factors that were strongly related to subtherapeutic serum magnesium levels. Obese and multipara pregnant women accounted for 83% and 59%, respectively, of the 2,698 women in the subtherapeutic serum magnesium level group and approximately 54% and 41%, respectively, of the 2,600 women in the therapeutic serum magnesium level group.

Given that multipara was the factor which accounted for a small percentage, we chose it as the factor for calculation of sample size. Using this factor for the calculations, the sample size would be sufficiently large to identify a significant difference in our study.

After calculation, 200 participants, i.e., 100 participants in each group were required for this study.

Intervention

After approval by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University (Si 580/2014), all medical records of term pregnant women with severe pre-eclampsia who delivered their babies in Siriraj Hospital from January 2006 to December 2013 were reviewed and extracted for further study. The exclusion criterion included pregnant women who developed eclampsia before magnesium sulfate administration.

Two hundred medical records that met the inclusion criteria were randomly allocated into two groups as follows:

1. Case group: 100 pregnant women with subtherapeutic serum magnesium levels (<4.8 mg/dl).
2. Control group: 100 pregnant women with therapeutic serum magnesium levels (4.8-8.4 mg/dl).

Measurement of serum magnesium level in Siriraj Hospital

Serum magnesium levels were assessed using the standard Roche/Hitachi Cobas c systems.[10-12]

All the basic characteristics, signs and symptoms of pre-eclampsia, laboratory findings, antihypertensive drug use and pregnancy outcomes were carefully extracted from the patients' medical records and compared between the case and control groups.

Statistical analysis

Quantitative data, such as age, pre-pregnancy BMI, and total weight gain, were analyzed with the help of a two-sample t-test.

Qualitative data, such as pregnancy outcomes and antihypertensive drug use, were analyzed using the Chi-square test.

A logistic regression model was used for the multivariate analysis. The outcomes were quantified as percentage and odds ratio with a 95% confidence interval. A P-value < 0.05 was considered significant. All analyses were performed with the SPSS version 20 statistical package.

RESULTS

We started with univariate analysis to compare the basic characteristics between the case and control groups. The case group had a significantly higher number of pregnant women with a pre-pregnancy BMI greater than 25 kg/m^2 than the control group, whereas the number of pregnant women with a pre-pregnancy BMI less than 18 kg/m^2 was lower in the case group than in the control group. All the findings are presented in Table 1.

The laboratory results, including the renal function test (creatinine, uric acid), the liver function test (AST, LDH) and hematology (platelet), exhibited significant differences between groups. The details are provided in Table 2.

All of the signs and symptoms of pre-eclampsia, including headache, blurred vision, epigastric pain, leg edema and pulmonary edema, were not significantly different as shown in Table 3.

TABLE 1. Basic characteristics of the subjects.

	Subtherapeutic level n*=100	Therapeutic level n*=100	*P*-value
Age (year)	28.24 ± 6.36#	28.64 ± 6.61#	0.633
Prepregnancy BMI (kg/m^2)			
<18.5	6 (6%)	32 (32%)	<0.001
18.5-24.9	55 (55%)	61 (61%)	
≥25	39 (39%)	7 (7%)	
Total weight gain (kg)			<0.001
Underweight gain	23 (23%)	37 (37%)	
Normal weight gain	19 (19%)	41 (41%)	
Overweight gain	58 (58%)	22 (22%)	
Nullipara	59 (59%)	69 (69%)	0.226
Associated condition and diseases			
DM			0.688
GDMA1	10 (10%)	8 (8%)	
GDMA2	3 (3%)	1 (1%)	
Overt DM	3 (3%)	2 (2%)	
Chronic HT	19 (19%)	10 (10%)	0.071
Other	7 (7%)	8 (8%)	0.788
Smoking	2 (2%)	2 (2%)	1.00
Alcohol	3 (3%)	1 (1%)	0.621
Drug abuse	3 (3%)	1 (1%)	0.621

*n = number, Data was presented as Mean ± SD or n (%)

TABLE 2. Laboratory findings.

	Subtherapeutic level n*=100 n (%)	Therapeutic level n*=100 n (%)	*P*-value
Renal function test			
Creatinine (mg/dl) >0.9	6 (6%)	81 (81%)	< 0.001
Uric acid (mg/dl) >8	7 (7%)	36 (36%)	< 0.001
Hematology			
Platelet (x10^3/µl) < 100,000	1 (1%)	4 (4%)	0.001
Liver function test			
AST (U/L) >70	1 (1%)	9 (9%)	0.009
ALT (U/L) >70	1 (1%)	6 (6%)	0.059
LDH (U/L) >600	5 (5%)	17 (17%)	0.006

*n = number

TABLE 3. Signs and symptoms of preeclampsia.

	Subtherapeutic level n*=100 n (%)	Therapeutic level n*=100 n (%)	*P*-value
Headache	10 (10%)	17 (17%)	0.147
Blur vision	9 (9%)	7 (7%)	0.602
Epigastric pain	8 (8%)	8 (8%)	1.00
Leg edema	61 (61%)	52 (52%)	0.199
Pulmonary edema	1 (1)	0 (0)	1.000

*n = number

The number of pregnant women who used antihypertensive drugs was significantly increased in the case group compared with the control group. The details of antihypertensive drug use are reported in Table 4. Overall pregnancy outcome exhibited no significant differences for any of the variables as shown in Table 5. After the univariate analysis was performed, the multivariate analysis was performed to eliminate the confounding factors by reanalyzing all of the significant factors associated with subtherapeutic serum magnesium levels. The odds ratio was used for the prediction of subtherapeutic magnesium levels. The multivariate analysis results identified two factors that exhibited a significant association with subtherapeutic serum magnesium levels, which included pre-pregnancy BMI and serum creatinine levels. Pregnant women with a pre-pregnancy BMI greater than 25 kg/m^2 exhibited a 56% increased risk of having subtherapeutic levels compared with women with a normal pre-pregnancy BMI (18-24.9 kg/m^2). In contrast, pregnant women with a pre-pregnancy BMI less than 18 kg/m^2 exhibited an 80% decreased risk. In addition, serum creatinine levels greater than 0.9 mg/dl also decreased the risk of subtherapeutic serum magnesium levels by 98.7%. The details of the multivariate analysis are presented in Table 6.

TABLE 4. Antihypertensive drug use after magnesium administration.

	Subtherapeutic level n*=100 n (%)	Therapeutic level n*=100 n (%)	*P*-value
Amlodipine	1 (1%)	0 (0%)	
Hydralazine	18 (18%)	14 (14%)	
Labetalol	20 (20%)	6 (6%)	
Total	39 (39%)	20 (20%)	0.003

*n = number

TABLE 5. Pregnancy outcomes.

	Subtherapeutic level n*=100 n (%)	Therapeutic level n*=100 n (%)	*P*-value
Delivery outcome			
Spontaneous vertex delivery	28 (28%)	37 (37%)	0.235
Vacuum extraction	7 (7%)	10 (10%)	
Forceps extraction	0 (0%)	1 (1%)	
Cesarean section	64 (64%)	52 (52%)	
Others	1 (1%)	0 (0%)	
Maternal outcomes			
Eclampsia	0 (0%)	0 (0%)	-
Post-partum hemorrhage	3 (3%)	5 (5%)	0.498
Intracerebral hemorrhage	0 (0%)	1 (1%)	0.497
Sepsis	1 (1%)	1 (1%)	1.000
Intensive unit care admission	0 (0%)	2 (2%)	0.246
Blood transfusion	1 (1%)	3 (3%)	0.369
Death	0 (0%)	0 (0%)	-
Neonatal outcomes			
Apgar score <7			
At 1 minute	7 (7%)	9 (9%)	0.431
At 5 minutes	4 (4%)	1 (1%)	0.184

*n = number

TABLE 6. Multivariate analysis of associated factors of subtherapeutic serum magnesium level.

	Adjusted OR (95% CI)	*P*-value
BMI (kg/m^2)		0.002
< 18	0.20 (0.05,0.77)	0.020
18-24.9	1.00	
≥ 25	1.56 (1.32,23.41)	0.019
Weight gain (kg)		0.066
Under weight gain	0.79 (0.23,2.77)	0.720
Normal weight gain	1.00	
Over weight gain	2.92 (0.88,9.75)	0.081
Creatinine (mg/dl)		<0.001
≤ 0.9	1.00	
> 0.9	0.013 (0.004,0.047)	
Uric acid (mg/dl)		0.616
≤ 8	1.00	
> 8	1.45 (0.34,6.08)	
Platelet count (µl)		0.247
≥ 100,000	1.00	
< 100,000	0.21 (0.01,2.92)	
AST (U/L)		0.958
≤ 70	1.00	
> 70	1.07 (0.08,14.54)	
LDH (U/L)		0.091
≤ 600	1.00	
> 600	0.24 (0.05,1.26)	

DISCUSSION

The association of subtherapeutic serum magnesium levels with the prevention of eclampsia in pre-eclamptic pregnant women was first proposed by Tudela CM.[9] In that study, more than half of the participants exhibited subtherapeutic serum magnesium levels. That study also reported factors associated with subtherapeutic serum magnesium levels in pre-eclamptic pregnant women, including BMI, age and multipara status.

According to our multivariate analysis, the only two factors that exhibited significant association with subtherapeutic serum magnesium levels were pre-pregnancy BMI and serum creatinine level.

Similar to the study of Tudela CM.[9], the outcome of pre-pregnancy BMI indicated that pregnant women with a BMI greater than 25 kg/m^2 exhibited a 56% increased risk of subtherapeutic serum magnesium levels compared with pregnant women with a normal BMI (18-24.9 kg/m^2).

In addition, those with a BMI less than 18 kg/m^2 exhibited an 80% decreased risk of subtherapeutic serum magnesium levels.

Based on the magnesium metabolism theory, the constant proportions of magnesium distribution in the human body under normal conditions are as follows: soft tissue, 19.3%; muscle, 27%; bone, 52.9%; serum, 0.3%; and red blood cell, 0.5%. Obese women have more fat, bone and muscle mass than women with normal BMI, potentially explaining the relationship of BMI and serum magnesium levels. Pregnant women with increased BMI exhibit an increased distribution of magnesium to fat, bones and muscle, which would reduce the magnesium distribution in the serum. In addition, women with an increased BMI had more blood volume, which might dilute the serum magnesium level. Based on this mechanism, women with increased BMI have a tendency to have subtherapeutic serum magnesium levels.[13-16]

The kidneys are the crucial organs for controlling magnesium homeostasis. A serum creatinine level greater than 0.9 mg/dl reflects the reduced efficacy of the kidney in magnesium excretion. This physiology supported our finding that the subtherapeutic serum magnesium level decreases the risk by up to 98.7%.

The number of pregnant women who needed antihypertension drugs in our study increased in the subtherapeutic serum magnesium level group compared with the therapeutic serum magnesium level group. The finding can be explained by the effect of magnesium sulfate, which can also decrease the blood pressure by modulating vascular tone. Therefore, the pregnant women with lower serum magnesium levels in the subtherapeutic group might require more antihypertensive drugs.

With regard to the comparison of pregnancy outcomes, there were no statistically significant differences in terms of delivery outcomes, maternal outcomes and neonatal outcomes in either group. The explanation for these findings is that not only the serum magnesium level, but also many other confounding factors can influence the outcomes.

The use of a case-control study design for this study is useful for determining the significant outcomes for multiple risk factors. The criteria for selecting subjects were carefully considered to control the heterogeneity and selection bias affecting the similarity of the basic characteristics of both groups.

At Siriraj Hospital, we manage pregnant women with severe pre-eclampsia according to our institutional guidelines. The same practice of history taking, physical examination, and laboratory investigation and the same protocol for intravenous regimens of magnesium sulfate were used for each patient. Therefore, most of the retrospective data were completely recorded, and the minimal deviation of data collection increased the reliability of this study.

However, the retrospective nature of the study presented some limitations. Patient data from our medical records were documented by many physicians. Many subjective data, such as the signs and symptoms of pre-eclampsia, may vary.

This study found that the factors associated with subtherapeutic serum magnesium levels included pre-pregnancy BMI and serum creatinine levels. This result could be applied to daily medical practice by increasing the dosage of magnesium sulfate in pregnant women of the subtherapeutic serum magnesium level group, including women with a pre-pregnancy BMI greater than 25 kg/m^2. In addition, physicians should be cautious when administering magnesium sulfate to those with a pre-pregnancy BMI less than 18 kg/m^2 or those with greater than 0.9 mg/dl serum creatinine.

However, because there are only a few studies available on this subject, further studies should be performed, especially prospective studies, and a risk scoring model for subtherapeutic serum magnesium levels should be developed. We hope that the future guidelines for the management of pre-eclamptic women will include more evidence-based data, which in turn can improve the outcomes of management for these patients.

CONCLUSION

The factors associated with subtherapeutic serum magnesium levels were pre-pregnancy BMI and serum creatinine levels. A pre-pregnancy BMI greater than 25 kg/m^2 increased the risk of subtherapeutic serum magnesium levels in severe pre-eclamptic women, whereas pre-pregnancy BMI less than 18 kg/m^2 decreased the risk. Serum creatinine levels greater than 0.9 mg/dl also decreased the risk of subtherapeutic magnesium levels in these women.

REFERENCES

1. Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rose DJ, Spong CY, editor. Williams's Obstetrics. 23rd ed. New York: McGraw Hill; 2012.p.706.
2. Taweesul P, Tannirandorn Y. Clinical and laboratory parameters associated with eclampsia in Thai Pregnant Women. J Med Assoc Thai 2014;97:139-46.
3. Sibai BM, Lipshitz J, Anderson GD, Dilts PV Jr. Reassessment of intravenous MgSO4 therapy in preeclampsia-eclampsia. Obstel Gynecol 1981;57:199-202.
4. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol 2003;102:181-2.

5. JamiluTukur. The use of magnesium sulphate for the treatment of severe pre-eclampsia and eclampsia. Ann Afr Med 2009;8: 76-80.
6. Zuspan FP. Problems encountered in the treatment of pregnancy-induced hypertension. A point of review. Am J Obstet Gynecol 1978;131:591-7.
7. Pritchard JA, Cunningham FG, Pritchard SA. The Parkland memorial hospital protocol for treatment of eclampsia: evaluation of 245 cases. Am J Obstet Gynecol 1984;148:951-63.
8. Smith JM, Lowe RF, Fullerton J, Currie SM, Harris L, Felker-Kantor E. An integrative review of the side effects related to the use of magnesium sulfate for pre-eclampsia and eclampsia management. BMC Pregnancy Childbirth 2013;13:34.
9. Tudela CM, McIntire DD, Alexander JM. Effect of maternal body mass index on serum magnesium levels given for seizure prophylaxis. Obstet Gynecol 2013;121:314-20.
10. Yu AS. Evolving concepts in epithelial magnesium transport. Curr Opin Nephrol Hypertens 2001;10:649-53.
11. Mann CK, Yoe JH. Spectrophotometric determination of magnesium with sodium 1-azo-2-hydroxy-3-(2, 4-dimethyl-carboxanilido)-napthalene-1'-(2-hydroxybenzene-5-sulfonate) Anal Chem 1956;28:202-5.
12. Kanagal DV, Rajesh A, Rao K, Devi UH, Shetty H, Kumari S, et al. Levels of serum calcium and magnesium in pre-eclamptic and normal pregnancy: a study from coastal India. J Clin Diagn Res 2014;8:OC01-4.
13. Swaminathan R. Magnesium metabolism and its disorders. Clin Biochem Rev 2003;24:47-66.
14. Saris NE, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A. Magnesium.an update on physiological, clinical and analytical aspects. Clin Chim Acta 2000;294:1-26.
15. Kroll MH, Elin RJ. Relationships between magnesium and protein concentrations in serum. Clin Chem 1985;31:244-6.
16. Ephraim RK, Osakunor DN, Denkyira SW, Eshun H, Amoah S, Anto EO. Serum calcium and magnesium levels in women presenting with pre-eclampsia and pregnancy-induced hypertension: a case-control study in the Cape Coast metropolis, Ghana. BMC Pregnancy Childbirth 2014;14:390.