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Association between Maternal Body Mass Index and Sub-therapeutic Serum Magnesium Level in Severe Preeclampsia at Maharat Nakhon Ratchasima Hospital

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ABSTRACT

Objectives: To evaluate the association between the maternal body mass index (BMI) and the subtherapeutic serum magnesium level in pregnant women with severe preeclampsia who received magnesium sulfate therapy at Maharat Nakhon Ratchasima Hospital.

Study design: Retrospective cross-sectional study.

Materials and Methods: A retrospective study from October 1, 2012 to March 31, 2015 was performed to estimate the effect of maternal BMI on serum magnesium level. 565 (2.99%) pregnant women were diagnosed with severe preeclampsia or eclampsia and received magnesium sulfate therapy at Maharat Nakhon Ratchasima Hospital. Inclusion criteria was pregnant women who delivered at gestational age ≥ 24 weeks, women who did not receive expectant management, women who received magnesium sulfate following the regimen of loading dose 4 grams, followed by a maintenance dose of 1 gram/hour intravenously, and women who had monitored serum magnesium levels. Serum magnesium level was initially monitored at 3-4 hours after loading dose, and then monitored every 4 hours during magnesium sulfate infusion. The first serum magnesium level after loading dose was used in the study. Association between maternal BMI and subtherapeutic serum magnesium level (magnesium level < 4.8 mg/dL) was evaluated.

Results: 18,923 women delivered during the study period. Intrapartum serum magnesium levels were monitored in 289 women, where 235 women (81.31%) had subtherapeutic mag-nesium level. Overweight and obese women were associated with a significantly higher risk of subtherapeutic serum magnesium level ($P < 0.05$). Renal insufficiency (creatinine > 1.1 gm/dL) and thrombocytopenia seem to have a significant correlation with a higher rate of therapeutic magnesium levels ($P < 0.05$).

Conclusion: Most cases of women with severe preeclampsia at Maharat Nakhon Ratchasima Hospital had subtherapeutic serum magnesium levels when magnesium sulfate was administered by loading dose 4 grams, followed by 1 gram per hour intravenously. Over-weightness and obesity were high risk factors contributing to subtherapeutic serum magne-sium levels.

Keywords: severe preeclampsia; eclampsia; magnesium sulfate; serum magnesium level; body mass index(BMI)

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ความสัมพันธ์ของดัชนีมวลกายของมารดา และระดับแมกนีเซียมในเลือดที่ต่ำกว่าระดับการรักษามาตรฐาน ในมารดาที่มีภาวะครรภ์เป็นพิษชนิดรุนแรง หลังได้รับการรักษาด้วยแมกนีเซียมซัลเฟตในโรงพยาบาลมหาราชนครราชสีมา

รัตนา บุญยงชัยสวัสดิ์, สิรยา กิติโยดม

วัตถุประสงค์: *เพื่อศึกษาความสัมพันธ์ของดัชนีมวลกาย และระดับแมกนีเซียมในเลือดที่ต่ำกว่าระดับการรักษามาตรฐานในหญิงตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษชนิดรุนแรงที่ได้รับการรักษาด้วยแมกนีเซียมซัลเฟตในโรงพยาบาลมหาราชนครราชสีมา*

รูปแบบการวิจัย: *การวิจัยเชิงวิเคราะห์ โดยการเก็บข้อมูลย้อนหลัง*

วิธีการศึกษา: *ศึกษาโดยเก็บข้อมูลจากฝ่ายเวชระเบียนย้อนหลังในหญิงตั้งครรภ์ที่ได้รับการวินิจฉัยภาวะครรภ์เป็นพิษชนิดรุนแรง และภาวะชักจากครรภ์เป็นพิษที่ได้รับยาแมกนีเซียมซัลเฟตที่มาคลอดบุตรในโรงพยาบาลมหาราชนครราชสีมา ในระหว่างวันที่ 1 ตุลาคม 2555 ถึง 31 มีนาคม 2558 ทุกราย ซึ่งมีจำนวน 565 คน โดยคัดเลือกหญิงตั้งครรภ์ที่คลอดบุตรที่อายุครรภ์ตั้งแต่ 24 สัปดาห์ขึ้นไป และต้องคลอดบุตรในระหว่างการนอนโรงพยาบาลในครั้งที่เก็บข้อมูล ได้รับยาแมกนีเซียมทางหลอดเลือดดำในรูปแบบ 4 กรัม ตามด้วย 1 กรัมต่อชั่วโมง และได้รับการเจาะเลือดเพื่อดูระดับแมกนีเซียมในเลือด ในกรณีที่ได้รับการเจาะดูระดับแมกนีเซียมในเลือด หญิงตั้งครรภ์จะได้รับการเจาะเลือดหลังได้รับยาครั้งแรก 3-4 ชั่วโมง และต่อจากนั้นอีกทุกๆ 4 ชั่วโมงระหว่างได้รับยา โดยการศึกษานี้จะนำผลเลือดครั้งแรกมาใช้ในการวิเคราะห์เพื่อหาความสัมพันธ์ของดัชนีมวลกายของมารดาและระดับแมกนีเซียมในเลือด ข้อมูลรายงานเป็นอัตราร้อยละ และ Chi-Square test โดยถือว่ามีนัยสำคัญทางสถิติ เมื่อ P-value < 0.05*

ผลการศึกษา: *ผู้ป่วยที่มีภาวะครรภ์เป็นพิษชนิดรุนแรงและภาวะชักจากครรภ์เป็นพิษ จำนวน 565 คน ได้รับการตรวจระดับแมกนีเซียมในเลือดระหว่างรอคลอด 289 คน พบมีระดับแมกนีเซียมต่ำกว่าระดับการรักษามาตรฐาน 235 คน (ร้อยละ 81.31) โดยพบว่าดัชนีมวลกายที่มากมีแนวโน้มสูงกว่าที่ระดับแมกนีเซียมในเลือดต่ำกว่าระดับการรักษามาตรฐานอย่างมีนัยสำคัญทางสถิติ ค่าการทำงานของไตที่ผิดปกติ (creatinine > 1.1 gm/dL) และค่าเกล็ดเลือดที่น้อยผิดปกติ มีแนวโน้มมากกว่าที่จะมีระดับแมกนีเซียมในเลือดอยู่ในระดับการรักษามาตรฐาน*

สรุป: *ผู้ป่วยที่มีภาวะครรภ์เป็นพิษชนิดรุนแรงและภาวะชักจากครรภ์เป็นพิษที่ได้รับยาแมกนีเซียมซัลเฟตทางหลอดเลือดดำ ในรูปแบบยา 4 กรัม ตามด้วยยาต่อเนื่อง 1 กรัมต่อชั่วโมง ส่วนมากยังมีระดับแมกนีเซียมในเลือดต่ำกว่าระดับการรักษามาตรฐาน โดยดัชนีมวลกายที่มากกว่ามีแนวโน้มมากกว่าที่ระดับแมกนีเซียมในเลือดต่ำกว่าระดับการรักษามาตรฐาน*

Introduction

One common cause of death among pregnant women is complications from pregnancy including preeclampsia, with an incidence rate of 5-11% in all pregnancies[1]. Preeclampsia is considered to be a severe condition with multiple organs involved, for example; thrombocytopenia, renal dysfunction, hepatocellular necrosis, central nervous system perturbations, pulmonary edema, or eclampsia. Fetal complications arise as a consequence of maternal complications due to preeclampsia - including placenta abruption, growth restriction, preterm birth, and death fetus in utero[1].

The basic management[1,2] for preeclampsia is a prompted diagnosis and a prompted treatment in order to decrease the incidence of eclampsia and other complications. Treatment of severe preeclampsia is hospital admission, prevention of seizure, blood pressure control, and termination of pregnancy. At present, the drug of choice to prevent convulsion in severe preeclampsia is magnesium sulfate, as this drug can reduce the risk of seizure from 1.9 to 0.8%[3].

The guideline for magnesium sulfate infusions[1] for severe preeclampsia includes the administration of the drug via intramuscular or intravenous route. For the intravenous regimen, the initial loading dose is 4-6 grams of magnesium sulfate followed by the maintenance dose of 1-2 grams per hour until 24 hours postpartum. The targeted serum magnesium level was 4.8-8.4 mg/dL. Guidelines for magnesium sulfate infusion of Maharat Nakhon Ratchasima Hospital is same as mentioned and the dose of magnesium sulfate will be adjusted according to the patient's serum magnesium level, or clinical manifestation of each patient.

During fiscal year 2012-2013[4], 734 women presented with complications due to severe preeclampsia, out of which 31 women developed eclampsia and 1 womandied due to intracranial hemorrhage from eclampsia in Maharat Nakhon Ratchasima Hospital. 14 patients (45.16%) experienced seizures during magnesium sulfate infusion and all of them had subtherapeutic levels of serum magnesium. 12 women (85.7%) were overweight (BMI ≥ 25 kg/m^2) or higher.

There is no current data of the correlation between BMI and serum magnesium level in pregnancies complicated with severe preeclampsia after receiving magnesium therapy in Thailand. The objective of this study is to estimate the effect of maternal BMI on serum magnesium levels in severe preeclampsia presented at Maharat Nakhon Ratchasima Hospital during October 1, 2012 to March 31, 2015.

Materials and Methods

This retrospective study was approved by the Maharat Nakhon Ratchasima Hospital In-stitutional Review Board. Data was collected from medical records of all women diagnosed with severe preeclampsia who delivered in Maharat Nakhon Ratchasima hospital from October 1, 2012 to March 31, 2015.

The criteria used to diagnose severe preeclampsia[5] includes recent onset hyperten-sion (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg) with pro-teinuria 2$^+$ or more by urine protein dipstick, and 24 hours urine protein ≥ 2 grams. Eclamp-sia was defined as the occurrence of seizures in women with preeclampsia which could not be from other possible causes. Data was collected from all women diagnosed with severe preeclampsia and eclampsia that delivered in Maharat Nakhon Ratchasima Hospital and re-ceived magnesium sulfate by intravenous loading dose of 4 grams followed by 1 gram per hour. Serum magnesium level was recorded initially at 3-4 hours after the loading dose, and then recorded every 4 hours along treatment. This study used the initial record of serum magnesium level after loading dose. The exclusion criteria consisted of pregnant women who delivered at gestational age < 24 weeks, received magnesium sulfate in other regimens (not loading dose of 4 grams, followed by 1 gram per hour intravenously), severe preeclampsia cases managed by expectant management (not delivered), and cases where serum magnesium sulfate level were not monitored.

At the time of study, the Maharat Nakhon Ratchasima Hospital team developed a treatment

protocol for intravenous administration of magnesium sulfate to prevent seizure, which was 4-6 grams of intravenous loading dose administered over 20 minutes, followed by an infusion of 1-2 grams/hour until 24 hours postpartum. However, no routine serum magnesium levels were monitored. In monitored cases, serum magnesium levels were obtained 3-4 hours after the infusion to achieve a therapeutic range of 4.8 to 8.4 mg/dL. Women whose serum magnesium level was less than 4.8 mg/dL were considered to be sub-therapeutic, and had the infusion increased up to 1.5-2 grams per hour. Women who had a serum magnesium level of more than 8.4 mg/dL were considered to be supratherapeutic. These patients would be monitored for magnesium toxicity, magnesium sulfate infusions would be withheld, and serum magnesium levels would be drawn at 1 to 2 hour intervals until therapeutic range levels were achieved. The BMI was calculated from the weight and height on the delivery day (weight in kilograms divided by the square of the height in meters). Patients were classified into 4 groups according to this index[6]. BMI of 18.4 kg/m^2 or less, 18.5–24.9 kg/m^2, 25–29.9 kg/m^2, and 30 kg/m^2 or more are defined as underweight, normal weight, overweight and obese respectively. In this study, serum magnesium levels were compared among women classified by BMI categories. The data was collected and then analyzed by program Stata/SE 11.1. Statistical analysis was performed by Chi-Square test and statistical signifi-cance was considered if the P-value was less than 0.05.

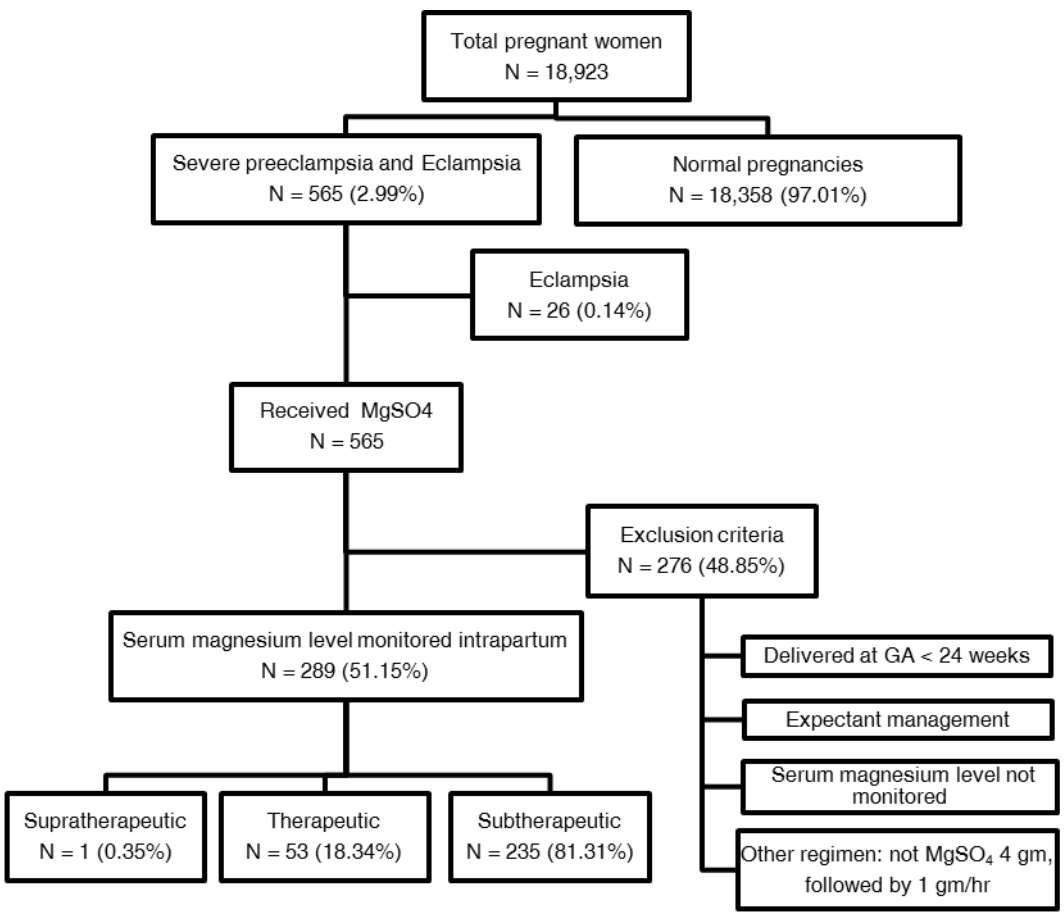

Diagram 1.

Results

A total of 18,923 women delivered in Maharat Nakhon Ratchasima Hospital during the study period. Among the cases of severe preeclampsia, magnesium sulfate was administered for seizure prophylaxis in 565 women (2.99%); where 26 cases (0.14%) were diagnosed with eclampsia. The BMI was calculated from the weight and height on delivery day. Intra-partum magnesium levels were recorded after magnesium sulfate loading dose for 3-4 hours. Among patients who received magnesium sulfate, 289 patients (51.15%) were included in the study and 276 patients were excluded. 235 (81.31%) women were found to have subtherapeutic magnesium levels, 53 (18.34%) women had therapeutic magnesium levels, and 1 woman had a supratherapeutic magnesium level, as shown in diagram 1.

Baseline characteristics of both subtherapeutic and therapeutic groups of magnesium levels were compared as shown in Table 1. The most common age in both groups was twenty to less than thirty-five years old. The most common gestational age in the subtherapeutic group was thirty-seven weeks (term pregnancy) or more, but the most common gestational age in the therapeutic group was less than thirty-four weeks (early preterm pregnancy). The difference in gestational age of subtherapeutic and therapeutic levels were statistically significant (P = 0.018). Severe preeclampsia was diagnosed commonly at Maharat Nakhon Ratchasima Hospital in both the subtharapeutic and therapeutic group. Systolic and diastolic blood pressure at the time of diagnosis of severe preeclampsia was similar in both groups. The most common route of delivery of both groups was cesarean section. Additional symp-toms, such as headaches, visual symptoms, and epigastrium pain were similar in both groups.

Factors that might affect the subtherapeutic serum magnesium level are shown in Table 2. BMI, platelet count, aspartate transferase level, albuminuria dipstick ≥ 2^+, renal insufficiency (creatinine > 1.1 mg/dL), oliguria (urine output < 0.5 ml/kg/hour), and gestational diabetes mellitus between subtherapeutic and therapeutic groups were compared. Multiple logistic regression had shown that pregnant women with higher body mass index was significantly associated with the subtherapeutic level of magnesium (P < 0.001). Thrombocytopenia and renal insufficiency were associated with therapeutic level rather than subtherapeutic, significantly. The other factors including aspartate transferase, albuminuria ≥ 2^+, oliguria, and gestational diabetes mellitus had no significant association.

Supratherapeutic magnesium level in this study was only present in one case. She had underlying diasease of chronic hypertension and chronic renal failure. Her baseline serum creatinine was 2.29 mg/dL.

Table 1. Baseline characteristics.

Characteristic	Subtherapeutic N = 235	Therapeutic N = 53	P
Age (years)			0.715
< 20	54 (23.0%)	15 (28.3%)	
20 – less than 35	135 (57.5%)	28 (52.8%)	
≥ 35	46 (19.6%)	10 (18.9%)	
Gestational age (weeks)			0.018*
< 34	48 (20.4%)	21 (39.6%)	
34 – less than 37	72 (30.6%)	13 (24.5%)	
≥ 37	115 (48.9%)	19 (35.9%)	

Table 1. Baseline characteristics. (Cont.)

Characteristic	Subtherapeutic N = 235	Therapeutic N = 53	P
Diagnostic place			0.185
Referred case	43 (18.3%)	14 (26.4%)	
MNRH	192 (81.7%)	39 (73.6%)	
SBP ≥ 160 mmHg	206 (87.7%)	47 (88.7%)	1.000
DBP ≥ 110 mmHg	118 (50.2%)	30 (56.6%)	0.448
Route of delivery			0.186
Vaginal delivery	34 (14.5%)	10 (18.9%)	1.000
Vacuum extraction	10 (4.3%)	5 (9.4%)	0.448
Cesarean section	191 (81.3%)	38 (71.7%)	
Headache	62 (26.4%)	15 (28.3%)	0.864
Visual symptom	19 (8.1%)	5 (9.4%)	0.783
Epigastrium pain	37 (15.7%)	10 (18.9%)	0.544

MNRH = Maharat Nakhon Ratchasima Hospital
SBP = Systolic blood pressure
DBP = Diastolic blood pressure
* Statistical significance

Table 2. Association between clinical factors and serum magnesium levels.

Factors	Subtherapeutic N = 235	Therapeutic N = 53	P
Body mass index(kg/m2)			< 0.001*
≤ 18.4 (N = 47)	25 (53.2%)	22 (46.8%)	< 0.001*
18.5 – 24.9 (N = 88)	74 (84.1%)	14 (15.9%)	0.448
25 – 29.9 (N = 125)	111 (88.8%)	14 (11.2%)	
≥ 30 (N = 27)	25 (92.6%)	2 (7.4%)	
Platelet < 100000/μL	6 (2.6%)	6 (11.3%)	0.011*
AST ≥ 90 U/L	12 (5.1%)	7 (13.5%)	0.056
Urine albumin dipstick ≥ 2^+	114 (48.5%)	31 (59.6%)	0.169
Creatinine > 1.1 mg/dl	11 (4.7%)	13 (25.0%)	< 0.001*
Oliguria	86 (36.6%)	18 (34.0%)	0.754
GDM	23 (9.8%)	5 (9.4%)	1.000

AST = Aspartate transferase
Oliguria = Urine output < 0.5 ml/kg/hour
GDM = Gestational diabetes mellitus
* Statistical significance

Discussion

At present, magnesium sulfate is considered to be the standard treatment to prevent eclampsia. The target therapeutic serum magnesium level is 4.8-8.4 mg/dL[1]. At the time of study, Maharat Nakhon Ratchasima Hospital's standard treatment for seizure prophylaxis in severe preeclampsia was a magnesium sulfate loading dose of 4-6 grams, followed by maintenance doses of 1-2 grams/hour. However, serum magnesium level monitoring was not performed in all cases. In some cases, we monitored patients' symptoms instead of serum magnesium level. Therefore, these cases were excluded from the study.

Half of the underweight group had therapeutic magnesium levels. A higher BMI showed correlation with more chance of having subtherapeutic magnesium levels. It can be concluded that overweight and obese patients have more incidence of subthrapeutic serum magnesium levels than underweight and normal weight patients. Serum magnesium itself is buffered in the bone, muscle, soft tissue and extracellular space[7]. Metabolism of serum magnesium is unchanged in pregnant women[1]. The BMI affects the ability to buffer magnesium sulfate since it tends to distribute more in patient's soft tissue, muscle, bone, as well as in a larger extracellular space. Severe preeclampsia patients with higher BMI are more likely to have subtherapeutic level of serum magnesium compared to patients who have normal BMI. According to previous studies, Tudela[8] and Dayicioglu[9] stated that overweight and obese cases with preeclampsia had more chance of subtherapeutic serum magnesium levels than normal BMI patients, if they recieved the same regimen of magnesium sulfate. However, most women in this study had subtherapeutic magnesium levels when they received magnesium sulfate by regimen of a loading dose of 4 grams, followed by maintenance doses of 1 gram per hour.

Forty two percent of women in the subtherapeutic group were classified in the underweight and normal weight group. This suggests that overall cases seem to be for more loading and maintenance dose of magnesium sulfate for target therapeutic level. If we had given a higher dose of magnesium sulfate, magnesium levels were monitored to avoid magnesium toxocity.

Magnesium sulfate is mostly eliminated via renal excretion[7]. Therefore, renal insufficiency patients tend to have higher incidence of therapeutic level.

Other factor that can contribute to subtherapeutic magnesium level is gestational diabetes mellitus[10,11]. However, in this study GDM was not correlated to subtherapeutic serum magnesium level.

In this study, the limitations were retrospective data collection and small sample size. The strength of this study is that there was no selection and collection bias, because all women who were diagnosed severe preeclampsia were selected to the study. From this study, overweight and obese pregnancy groups may be adjusted to higher doses of magnesium sulfate infusion for seizure prophylaxis in the future.

Conclusion

Almost 80% of severe preeclampsia cases were presented with subtherapeutic serum magnesium level when they received magnesium sulfate by regimen of loading dose 4 grams, followed by 1 gram/hour intravenously, causing a higher risk for development of eclampsia. In this study, it was found that overweight and obese cases with higher BMI have higher risk for developing subtherapeutic serum magnesium levels. Renal insufficiency and thrombocytopenia patients had higher rate of therapeutic serum magnesium level. If renal insufficiency and thrombocytopenia cases are present, serum magnesium levels should be closely monitored for magnesium toxicity.

References

1. Cunningham FG, Leveno KJ, Bloom LS, Spong CY, Dashe JS, Hoffman BL, et al. Hypertensive disorders. Williams Obstetrics 24thed. New York: McGraw-Hill, 2014:728-79.
2. Sibai BM. Diagnosis and management of gestational hypertension and preeclampsia. Obstet Gynecol 2003; 102:181-92.
3. Altman D, Carroli G, Duley L, Farrell B, Moodley J, Neilson J, et al. Do women with pre-eclampsia, and their babies, benefit from magnesium sulfate?. Lancet 2002

level in severe preeclampsia and eclampsia undergoing magnesium sulfate therapy at Chonburi hos-pital. Thai J Obstet Gynecol 2009;17:190-95.
11. Borella P, Szilagyi A, Than G, Csaba I, GiardinoA, Facchinetti F. Maternal plasma concentrations of magnesium, calcium, zinc and copper in normal and patho-logical pregnancies. Sci Total Environ 1990;99: 67-76.