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Effect of Maternal Body Mass Index on Serum Magnesium Level in Pregnant Women with Preeclampsia at Maharat Nakhon Ratchasima Hospital

Pemika Jaisamut, M.D.*,
Siraya Kitiyodom, M.D.*.

** Department of Obstetrics and Gynaecology, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima 30000, Thailand*

ABSTRACT

Objectives: To compare serum magnesium level in pregnant women with severe preeclampsia between normal body mass index (BMI) and high BMI after receiving magnesium sulfate at Maharat Nakhon Ratchasima Hospital.

Materials and Methods: The prospective study of 52 pregnant women with severe preeclampsia who received magnesium sulfate for preventing seizure at Maharat Nakhon Ratchasima Hospital during May 2015 to November 2015. The patients were pregnant women with severe preeclampsia who were given 4 grams and then a 1 gram per hour as a maintenance dose. Serum magnesium level was monitored every 4 hours during magnesium sulfate infusion and level was considered subtherapeutic if it was less than 4.8 mg/dL, therapeutic from 4.8 – 8.4 mg/dL and supratherapeutic at 8.5 mg/dL or more. The magnesium sulfate infusion was adjusted after delivery to maintain therapeutic serum magnesium level. The first serum magnesium level and the first one after delivery were collected to compare between two groups of patients divided by the body mass index (BMI): normal BMI (BMI < 25 kg/m^2), and high BMI (BMI ≥ 25 kg/m^2).

Results: A total of 119 patients were diagnosed with severe preeclampsia during the period of study. There were 52 women who met the inclusion criteria. Normal BMI group was proved to have a higher chance of therapeutic serum magnesium level by both records significantly (RR 10.0, 95%CI 1.38-72.61 and 4.33, 95%CI 1.39 – 13.44) (P = 0.005, 0.0027 respectively). After delivery, the high BMI group tends to have higher dose of magnesium sulfate infusion to maintain therapeutic serum magnesium level.

Conclusion: Body weight of the pregnant woman has effected serum magnesium level. The BMI of more than 25 kg/m^2 tends to get subtherapeutic serum magnesium level. However the study has been found no seizure in patients with subtherapeutic serum magnesium level in both groups. No case of supratherapeutic serum magnesium level was found during magnesium sulfate infusion 1 gram per hour.

Keywords: severe preeclampsia, maternal body mass index (BMI), overweight, serum magnesium level.

Correspondence to: *Pemika Jaisamut, M.D., Department of Obstetrics and Gynaecology, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima 30000, Thailand, E-mail: oceanheart.pemika@gmail.com*

ผลของดัชนีมวลกายสตรีตั้งครรภ์ต่อระดับแมกนีเซียมในเลือดของสตรีภาวะครรภ์เป็นพิษชนิดรุนแรงหลังได้รับการรักษาด้วยแมกนีเซียมซัลเฟตในโรงพยาบาลมหาราชนครราชสีมา

เปมิกา ใจสมุทร, สิรยา กิติโยดม

บทคัดย่อ

วัตถุประสงค์: *เพื่อเปรียบเทียบระดับแมกนีเซียมในเลือดของสตรีภาวะครรภ์เป็นพิษชนิดรุนแรง ในกลุ่มดัชนีมวลกายปกติและดัชนีมวลกายมากกว่าปกติ หลังได้รับการรักษาด้วยแมกนีเซียมซัลเฟต ในโรงพยาบาลมหาราชนครราชสีมา*

วัสดุและวิธีการ: *การศึกษาเชิงวิเคราะห์โดยการเก็บข้อมูลไปข้างหน้า ศึกษาในสตรีตั้งครรภ์ที่ได้รับการวินิจฉัยภาวะครรภ์เป็นพิษชนิดรุนแรง ที่ได้รับยาแมกนีเซียมซัลเฟตเพื่อป้องกันภาวะชักในโรงพยาบาลมหาราชนครราชสีมา ระหว่างเดือนพฤษภาคม พ.ศ. 2558 ถึงเดือนพฤศจิกายน พ.ศ. 2558 จำนวน 52 คน โดยคัดเลือกสตรีภาวะครรภ์เป็นพิษชนิดรุนแรง ที่ไม่ได้รับการรักษาแบบประคับประคอง และได้รับยาแมกนีเซียมซัลเฟตทางหลอดเลือดดำ เริ่มต้น 4 กรัม ตามด้วยขนาดคงที่ 1 กรัมต่อชั่วโมง ทำการตรวจระดับแมกนีเซียมในเลือด หลังเริ่มให้ยาทุก 4 ชั่วโมง และเริ่มปรับขนาดยาหลังคลอดบุตร หากระดับแมกนีเซียมน้อยกว่าระดับมาตรฐานการรักษา คือ น้อยกว่า 4.8 mg/dL เพื่อให้ระดับแมกนีเซียมได้ระดับการรักษาที่ 4.8 – 8.4 mg/dL และพิจารณาว่าระดับแมกนีเซียมเกินขนาดการรักษาที่มากกว่า 8.5 mg/dL การศึกษานี้จะนำผลเลือดครั้งแรกและหลังคลอดก่อนทำการปรับยามาใช้ในการวิเคราะห์เพื่อเปรียบเทียบระดับแมกนีเซียมในเลือดระหว่างกลุ่มดัชนีมวลกายปกติ (ดัชนีมวลกายน้อยกว่า 25 kg/m^2) และดัชนีมวลกายมากกว่าปกติ (ดัชนีมวลกายมากกว่า 25 kg/m^2 ขึ้นไป)*

ผลการศึกษา: *ในช่วงที่ทำการศึกษามีสตรีตั้งครรภ์ที่ได้รับการวินิจฉัยภาวะครรภ์เป็นพิษชนิดรุนแรงทั้งหมด 119 คน จากการศึกษาในสตรีตั้งครรภ์ที่เข้าตามเกณฑ์การศึกษา 52 คน พบว่าสตรีตั้งครรภ์กลุ่มดัชนีมวลกายปกติมีระดับแมกนีเซียมในเลือดได้ระดับการรักษามากกว่าดัชนีมวลกายมากกว่าปกติอย่างมีนัยสำคัญ ทั้งจากผลเลือดครั้งแรก ค่า relative risk เท่ากับ 10 (ช่วงความเชื่อมั่น ร้อยละ 95 เท่ากับ 1.38-72.61) และหลังคลอดเท่ากับ 4.33 (ช่วงความเชื่อมั่น ร้อยละ 95 เท่ากับ 1.39-13.44) (P = 0.005, 0.0027 ตามลำดับ) ในช่วงหลังคลอดพบว่า กลุ่มดัชนีมวลกายมากกว่าปกติต้องปรับเพิ่มขนาดยาแมกนีเซียมมากกว่าเพื่อให้ได้ระดับการรักษา*

สรุป: *น้ำหนักของสตรีตั้งครรภ์มีผลต่อระดับแมกนีเซียมในเลือด โดยสตรีที่มีดัชนีมวลกายมากกว่าปกติมีแนวโน้มที่ระดับแมกนีเซียมไม่ถึงระดับการรักษามากกว่า แต่ไม่พบภาวะชักในสตรีตั้งครรภ์ที่ระดับแมกนีเซียมในเลือดไม่ถึงระดับการรักษา และไม่พบภาวะแมกนีเซียมเกินขนาดจากการให้ขนาดคงที่ 1 กรัมต่อชั่วโมง*

คำสำคัญ: *ครรภ์เป็นพิษชนิดรุนแรง, ดัชนีมวลกาย, ระดับแมกนีเซียม*

Introduction

Hypertensive disorder is the third major cause of death among pregnant women worldwide[1] with the incidence of 5 to 10 percent of all pregnancies[2]. Evidence of multiorgan involvement in preeclampsia may include renal dysfunction, liver dysfunction, coagulopathy, thrombocytopenia, central nervous system perturbations, placental abruption, or pulmonary edema. The consequences from preeclampsia are also fetal complications[2] such as preterm birth, fetal growth restriction, stillbirth and neonatal deaths.

The treatment of severe preeclampsia[3] is hospitalization, prevention of seizure, blood pressure control and termination of pregnancy. Current effective drug to prevent seizure for severe preeclampsia[2-4] is magnesium sulfate through administered via intravenous or intramuscular route[2,3].

Standard guideline for magnesium sulfate infusion[2-4] for severe preeclampsia includes administration of the drug via intravenous route. The initial loading dose is 4 to 6 grams of magnesium sulfate followed by the maintenance dose of 1 to 2 grams per hour. Magnesium sulfate is discontinued 24 hours after delivery. Serum magnesium level was monitored every 4 to 6 hours especially in patients with renal dysfunction. The target of therapeutic serum magnesium level is 4.8-8.4 mg/dL. Guideline for magnesium sulfate infusion at Maharat Nakhon Ratchasima Hospital is 4 gram loading dose followed by the maintenance dose 1 gram per hour. Serum magnesium level was monitored every 4 hours, then adjust dose of magnesium sulfate infused according to the patient's serum magnesium level. During magnesium sulfate infusion, the signs of magnesium toxicity must be observed.

During fiscal year 2012 to 2013 at Maharat Nakhon Ratchasima Hospital, 734 pregnant women were diagnosed with severe preeclampsia and 31 women with eclampsia[5]. One eclamptic patient died from intracranial hemorrhage. There were 14 out of 31 pregnant women found to have eclamptic seizure during magnesium sulfate infusion. All of them had subtherapeutic level of serum magnesium, 12 women (85.7%) were high BMI (BMI ≥ 25 kg/m^2).

Magnesium sulfate is buffered in the bone, muscle, and soft tissue. Almost one half of it is intracellular. Magnesium concentration in extracellular fluid is relatively low. High BMI may affect both the ability to buffer administered magnesium sulfate in soft tissue, muscle, bone, as well as in a larger extracellular fluid[6]. Blood volume of women with obese BMI is more pronounced. Pregnant women with higher BMI may have larger volume of distribution, which may be reflected to lower magnesium level.

Thus, the researchers are interested in comparing of serum magnesium level in pregnant women with severe preeclampsia between normal BMI (BMI < 25 kg/m^2) and high BMI (BMI ≥ 25 kg/m^2) after receiving magnesium sulfate at Maharat Nakhon Ratchasima Hospital including the maternal and perinatal outcomes in both groups.

Materials and Methods

This prospective cohort study was approved by Maharat Nakhon Ratchasima Hospital Institutional Review Board. The data was collected from medical records of pregnant women diagnosed with severe preeclampsia who delivered at Maharat Nakhon Ratchasima Hospital from May 2015 to November 2015. The patients had received magnesium sulfate to prevent seizure. The exclusion criteria were pregnant women who were diagnosed with severe preeclampsia, including no intrapartum serum magnesium level monitoring, administration of magnesium sulfate in other regimen (not loading dose 4 grams, followed by 1 gram per hour intravenously), severe preeclampsia cases managed by expectant management (not delivered), and factors that affect the serum magnesium level such as renal dysfunction. In this study, renal dysfunction defined as serum creatinine > 1.1 mg/dL.

The criteria for diagnosis of severe preeclampsia[4] includes new onset hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 110 mmHg) with cerebral symptoms such as persistent headache, visual disturbances, upper abdominal pain, serum creatinine > 1.1 mg/dL or doubling of serum creatinine concentration in the absence of other renal disease, platelets < 100,000/ µL, impaired liver function (serum transaminase levels more than twice normal),

pulmonary edema. Eclampsia was defined as occurrence of seizures in women with preeclampsia without attribution to other causes.

Sample size from pilot study is at least 26 patients per group, the patients were divided into 2 groups by body mass index, 26 with normal BMI (BMI < 25 kg/m^2) and 26 with high BMI (BMI ≥ 25 kg/m^2). Both groups received 4-gram loading dose and the maintenance dose 1-gram per hour. Serum magnesium level was monitored initially at 4 hours after loading dose, and then monitored every 4 hours during magnesium sulfate infusion until magnesium sulfate was discontinued 24 hours after delivery. Pregnant women whose serum magnesium level less than 4.8 mg/dL were considered to be subtherapeutic, and would get more magnesium sulfate infused by 0.5 gram per hour (up to 2 grams per hour). Magnesium sulfate infusion was adjusted after delivery (after the first record after delivery) to achieve a therapeutic range of 4.8 to 8.4 mg/dL. The signs of magnesium toxicity were monitored, magnesium sulfate infusion would be withheld and serum magnesium level was drawn until therapeutic range level was achieved.

BMI of the patients was calculated from the documented weight and height (weight in kilograms divided by the square of the height in meters) on the date of admission. Patients were classified according to BMI. Normal weight was defined as 18.5–24.9 kg/m^2 (normal BMI), overweight was defined as 25–29.9 kg/m^2, and obese was defined as 30 or greater kg/m^2 [7]. In this study, the overweight and obese patients were in high BMI group.

In this study, serum magnesium level was analyzed to compare therapeutic serum magnesium level between the group of normal BMI and the high BMI pregnant women, including complications during admission. The data were analyzed by program Stata/SE 11.1. Statistical analysis was performed by Chi-Square test and Fisher's exact test when the expected values are small. $P < 0.05$ was considered statistically significance. Magnesium sulfate infusion rate to maintain therapeutic serum magnesium level was collected in both groups.

Results

There were 3,903 pregnant women who delivered at Maharat Nakhon Ratchasima Hospital during the time of study, 119 women (3.05%) were diagnosed with severe preeclampsia. Their weight and height on the day of admission were recorded as BMI calculation. All of them received magnesium sulfate to prevent seizure. From the calculated BMI, there are 26 normal BMI women (21.85%) and 93 high BMI women (78.15%). The 52 pregnant women who received 4-gram loading dose and the maintenance dose of 1-gram per hour. All of them agreed to participate in the study (Fig. 1). Serum magnesium level was drawn at 4-hours after the loading dose.

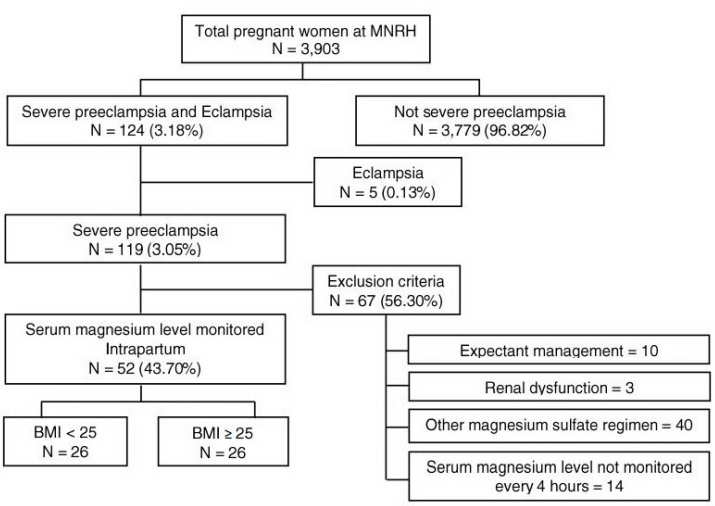

Fig. 1. Flow chart

Baseline characteristics of both groups is shown in Table 1. The most common age was 20-35 years old. Majority of them were less than 34 weeks (early preterm), while the pregnancy of high BMI women was more than 37 weeks (term). The difference had no statistical significance (p = 0.344). Diagnosis was based on blood pressure, headache, visual symptoms, epigastric pain, thrombocytopenia, liver and renal dysfunction that were similar in both groups. Furthermore, other factors including proteinuria, oliguria, comorbid diseases such as gestational diabetes mellitus, chronic hypertension and autoimmune disease were similar in both groups.

Table 1. Baseline characteristics.

Characteristics	BMI < 25 kg/m^2 (n=26)	BMI ≥ 25 kg/m^2 (n=26)	p value
Age (years)			0.700
< 20	6 (23.1%)	4 (15.4%)	
20 - less than 35	15 (57.7%)	16 (61.5%)	
≥ 35	5 (19.2%)	6 (23.1%)	
Gestational age (weeks)			0.344
< 34	10 (38.5%)	10 (38.5%)	
34 – less than 37	9 (34.6%)	5 (19.2%)	
≥ 37	7 (26.9%)	11 (42.3%)	
Multifetal gestation	1 (3.8%)	2 (7.7%)	1.000
Diagnostic place			1.000
Referred case	14 (53.8%)	14 (53.8%)	
MNRH	12 (46.2%)	12 (46.2%)	
SBP ≥ 160 mmHg	25 (96.2%)	24 (92.3%)	1.000
DBP ≥ 110 mmHg	18 (69.2%)	17 (65.4%)	1.000
Headache	13 (50.0%)	14 (53.8%)	1.000
Visual symptom	6 (23.1%)	6 (23.1%)	1.000
Epigastric pain	3 (11.5%)	5 (19.2%)	0.703
Platelet < 100000 /μL	2 (7.7%)	1 (3.8%)	1.000
AST ≥ 80 U/L	1 (3.8%)	2 (7.7%)	1.000
Hematuria	5 (19.2%)	5 (19.2%)	1.000
Urine albumin dipstick ≥ 2$^+$	19 (73.1%)	14 (53.8%)	0.249
Oliguria	2 (7.7%)	3 (11.5%)	1.000
Gestational diabetes mellitus	2 (7.7%)	5 (19.2%)	0.419
Chronic hypertension	1 (3.8%)	4 (15.4%)	0.350
Autoimmune disease	1 (3.8%)	2 (7.7%)	1.000

* Chi square test statistical analyses were applied, Data are presented as n (%)
MNRH = Maharat Nakhon Ratchasima Hospital, SBP = Systolic blood pressure, DBP = Diastolic blood pressure, AST = Aspartate transferase

Serum magnesium level was measured at 4 hours after the loading dose. Ten pregnant wome with normal BMI women (38.5%) and one pregnant woman with high BMI (3.8%) had therapeutic serum magnesium levels.

Normal BMI women had serum magnesium level by the initial record more than women with high BMI group (RR 10, 95% CI 1.38-72.61) (Table 2). Normal BMI women had serum magnesium level after delivery at therapeutic magnesium level more often than high BMI women (RR 4.33, 95%CI 1.39-13.44). The magnesium sulfate infusion was adjusted according to the serum magnesium level after delivery. None of the women had supra-therapeutic serum magnesium level. No seizure was found during treatment in both groups.

After adjusting the dose of magnesium sulfate to maintain therapeutic serum magnesium level during postpartum, it was found that 12 cases (46.2%) of normal BMI women had received a maintenance dose 1 gram per hour, 10 cases (38.5%) had received dose 1.5 grams per hour and 4 cases (15.4%) had received dose 2 grams per hour. In high BMI group, there were 3 cases (11.5%) that received magnesium at 1 gram per hour, 10 cases (38.5%) receiving 1.5 grams per hour and 13 cases (50.0%) getting 2 grams per hour. There was only one case in normal BMI group whose serum magnesium level was still not up to the therapeutic level after adjusting the maintenance dose, while four high BMI women had subtherapeutic level.

The pregnancy outcomes show that women with severe preeclampsia in both groups had no statistical difference in the route of delivery, maternal and perinatal complications. (Table 3)

Table 2. The distribution of serum magnesium level of patients receiving magnesium sulfate with different BMI classification.

Factors	BMI < 25 kg/m^2 (n=26)	BMI ≥ 25 kg/m^2 (n=26)	p value	RR (95%CI)
Intrapartum (1st)				
Therapeutic	10 (38.5%)	1 (3.8%)	0.005*	10(1.38-72.61)
Subtherapeutic	16 (61.5%)	25 (96.2%)		
Postpartum				
Therapeutic	13 (50.0%)	3 (11.5%)	0.0027*	4.33 (1.39-13.44)
Subtherapeutic	13 (50.0%)	23 (88.5%)		

Data are presented as n (%), * Statistic significance, $p < 0.05$

Table 3. Pregnancy outcomes in different BMI classification.

Factors	BMI < 25 kg/m^2 (n=26)	BMI ≥ 25 kg/m^2 (n=26)	p value
Maternal complication			
Abruptio placentae	1 (3.8%)	1 (3.8%)	1.000
Postpartum hemorrhage	2 (7.7%)	3 (11.5%)	1.000
Route of delivery			
Vaginal delivery	5 (19.2%)	3 (11.5%)	0.703
Cesarean section	21 (80.8%)	23 (88.5%)	
Perinatal complication			
Fetal growth restriction	12 (46.1%)	8 (30.7%)	0.250
Birth weight < 2,500 g	21 (80.8%)	16 (61.5%)	0.220
Apgar score at 5 min < 7	2 (7.7%)	1 (3.8%)	1.000
NICU admission	2 (7.7%)	1 (3.8%)	1.000
Perinatal death	1 (3.8%)	1 (3.8%)	1.000

Data are presented as n (%)

Discussion

Currently, magnesium sulfate is the first line drug to prevent eclamptic seizure in severe preeclampsia. Maharat Nakhon Ratchasima Hospital has standard regimen for preventing seizure by giving magnesium sulfate intravenous infusion with 4 grams and maintenance dose of 1 gram per hour during labor and for 24 hours postpartum. Serum magnesium level is monitored in all cases, then adjust the dose of magnesium sulfate infusion rate according to the patient's serum magnesium level to be aware of magnesium overdose. The target serum magnesium level for preventing convulsion is 4.8-8.4 mg/dL. Renal dysfunction may affect serum magnesium level because magnesium sulfate is excreted by the kidneys, and the patients who received magnesium sulfate in other regimen were eliminated from the study.

Our results showed that the normal BMI pregnant women tend to get therapeutic serum magnesium level more often than the high BMI group. This may be caused by weight of the pregnant women which affects the distribution and buffer serum magnesium. The overweight patients who have more muscle volume, bone, soft tissue, fats and extracellular space as well as severe preeclampsia with greater BMI are more likely to have subtherapeutic serum magnesium level. Tudela[8]'s study included 5,304 women who received intravenous magnesium sulfate 6 gram loading dose, followed by infused of 2 gram per hour. Magnesium level among pregnant women classified by BMI categories was compared. According to the study of Tudela, the patients with BMI over 30 kg/m^2 tend to have subtherapeutic serum magnesium level. Furthermore, Dayicioglu[9] examined the effect of BMI on the efficacy of magnesium sulfate preventing eclampsia in 194 pregnant women. They used the infusion protocol as loading dose of 4.5 gram of magnesium sulfate followed by a maintenance infusion of 1.8 gram per hour. They discovered that serum magnesium level was inversely related to BMI both during the ante- and postpartum periods. Level was lowest in patients with high BMI. They were able to demonstrate that BMI of more than 30 mg/m^2 was related with subtherapeutic serum magnesium level and suggested increasing maintenance infusion rates.

In addition, the results from this study show that the 1 gram maintenance infusion rate produced therapeutic serum magnesium level at less than 50% in both groups. However this study has found no seizure in patients with therapeutic serum magnesium level in both groups that differ from the study of Dayicioglu[9]. They reported eclamptic seizures occurred in four women with low BMI and three of these had therapeutic serum magnesium level. However, the study was underpowered to determine this outcome. Intrapartum serum magnesium level monitoring was shown no supratherapeutic serum magnesium level (>8.4 mg/dL) in both groups.

This study is limited by small sample size, excluding the severe preeclampsia with renal dysfunction. The strength of study is prospective study which can be used to collect the data completely.

Conclusion

The institute standard regimen is a loading bolus dose of 4 grams and a maintenance dose of 1 gram per hour, which can produce only one third of patients with therapeutic serum magnesium level. However, the study has been found no seizure in patients with subtherapeutic serum magnesium level in both groups. Weight of the pregnant women may affects the serum magnesium level. Normal BMI women tend to have a higher chance of therapeutic serum magnesium level significantly. Whereas the high BMI pregnant women had only 11.5% for therapeutic serum magnesium level before adjust maintenance dose of magnesium sulfate infusion. More research is required to determine appropriate magnesium sulfate infusion protocol.

Potential conflicts of interest

The authors declare no conflict of interest.

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