Comparison of the Level of Magnesium during Maintenance between 2 Gram and 1 Gram per Hour Infusion in Overweight Mothers with Preeclampsia

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Background: *Magnesium sulfate is most effective for prevention and treatment of convulsions among preeclampsia women. The therapeutic level of magnesium at 4.8 to 8.4 mg/dL and the overdose of magnesium may be fatal. In Maharat Nakhon Ratchasima Hospital, intravenous magnesium sulfate is used with the starting dose of 4 grams followed by 1 gram per hour for symptom control. However, between 2012 and 2013, in Maharat Nakhon Ratchasima Hospital, 14 cases of eclampsia developed convulsions during magnesium sulfate therapy. Additionally, all of them had serum magnesium lower than the therapeutic level and 85.7 % of them had a body weight more than the standard (Body mass index (BMI) $\geq$25 kg/m^2).*

Objective: *To compare the success rates of yielding the standard therapeutic level of magnesium among overweight mothers with preeclampsia after receiving 1 gram and 2 gram per hour of magnesium sulfate maintenance infusion.*

Material and Method: *This study was a randomized controlled trial study. The 38 overweight mothers (BMI $\geq$25 kg/m^2) who were diagnosed as having preeclampsia and administered magnesium sulfate for prevention of convulsion were recruited. The patients who had kidney impairment or were under conservative treatment were excluded. The sample size was calculated to be 19 for each group from the pilot, with five cases per group, led to type I and type II errors, 0.05 and 0.20, respectively. They were allocated with simple randomization into an experimental group that would be treated with magnesium sulfate at 2 grams per hour and a control group treated with 1 gram per hour infusion. At the fourth hour of infusion before delivery and every four hours after delivery, the magnesium levels from both groups were compared and analyzed using Chi-square.*

Results: *The body mass index of the experimental and the control groups were 33.5$\pm$6.84 and 33.7$\pm$6.09 kg/m^2, respectively. No difference in the basic characteristics between the two groups was observed. The rate of achievement of the therapeutic level of magnesium in the experimental group was higher than that of the control group both before delivery (52.6% vs. 15.8%, respectively, RR 3.3 (95% CI 1.08-10.24)) and after delivery (84.2 % vs. 42.1%, respectively, RR 2.0, 95% CI: (1.14-3.51)). Neither the overdose of magnesium nor convulsions were found in either group. The dose of magnesium in the control group was raised to 1.5 gram per hour in four patients and 2 grams per hour in seven patients to achieve the therapeutic level after delivery.*

Conclusion: *The therapeutic level of magnesium in overweight mothers with preeclampsia could be more frequently accessed before and after delivery with the dose of 2 grams per hour of magnesium sulfate infusion. No overdose of magnesium was observed. This fact would be used to improve the guideline of preeclampsia patient care.*

Keywords: *Severe preeclampsia, Magnesium sulfate, Overweight*

J Med Assoc Thai 2016; 99 (Suppl. 7): S133-S137
Full text. e-Journal: *http://www.jmatonline.com*

Preeclampsia is a complication of pregnancy due to endothelial malfunction and vasospasm leading to the new onset of hypertension in combination with proteinuria. It occurs after a 20-week pregnancy[1]. Severe preeclampsia and convulsions in severe preeclampsia are the third most common cause of maternal death worldwide[2], the second most common obstetric cause of stillbirth, and the cause of early neonatal death in developing countries[3].

So far, magnesium sulfate is the most effective medication for prevention and treatment of convulsions among preeclamptic women[4-6]. There are two standard methods of administration of magnesium sulfate[7,8], intramuscular and intravascular routes. The worldwide standard intravenous administration is started with 4 to 6 grams and maintained with 1 to 2 grams per hour. The dose is adjusted according to the kidney function to achieve the therapeutic level of magnesium at 4.8 to 8.4 mg/dL, or 4 to 7 mEQ/L, or 2.0 to 3.5 mmol/L. During administration of magnesium sulfate, precautions must

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be taken for serious signs of magnesium overdose such as cardiac arrhythmia, cardiac arrest, respiratory arrest, or fatal coma.

In the Maharat Nakhon Ratchasima Hospital, intravenous magnesium sulfate is used with the starting dose of 4 grams followed by 1 gram per hour for symptom control. If the magnesium does not reach the therapeutic level, the dose of magnesium sulfate will be gradually increased. However, the study of eclampsia in the Maharat Nakhon Ratchasima Hospital between 2012 and 2013[9] found 14 cases that developed convulsions during magnesium sulfate therapy. Interestingly, all of them had serum magnesium lower than the standard level and 85.7% of them had a body weight greater than the standard (body mass index (BMI) >25 kg/m^2). The study of Boonyongchaisawat R et al found that the association between the excessive weight (overweight and obesity) and the occurrence of the subtherapeutic level of magnesium was statistically significant[10]. Overdose of magnesium may be fatal. This study was aimed to compare the magnesium levels between 1 gram and 2 grams an hour of magnesium sulfate infusion among preeclamptic women with overweight and to improve the guidelines for the usage of magnesium sulfate among preeclamptic women with overweight.

Material and Method

This study was a clinical experimental research. It was approved by the ethics committee of Maharat Nakhon Ratchasima Hospital. The overweight pregnant women (BMI $\geq$25 kg/m^2) who were diagnosed as having preeclampsia and treated with magnesium sulfate for prevention of convulsions in the labor room of Maharat Nakhon Ratchasima Hospital were recruited. The exclusion criteria included patients with kidney impairment or with conservative treatment.

The sample size was calculated to be 19 for each group, based on the pilot study of five cases per group. All 38 were informed and signed a consent form. They were allocated with simple randomization into the experimental group and control groups. The experimental group would receive magnesium 2 grams per hour while the control group would receive 1 gram per hour. Both groups would be initially treated with a loading dose of 4 grams and followed by the maintenance dose according to each group. The serum magnesium was checked four hours after the starting dose of magnesium sulfate but prior delivery. The maintenance dose was not adjusted before delivery. The magnesium level was repeatedly monitored every four hours for 24 hours after delivery. In the event that the serum magnesium level was lower than the standard level, the maintenance dose would be increased 0.5 gram every hour until the serum magnesium reached the therapeutic level of 4.8 to 8.4 mg/dL. In the event the serum magnesium level was higher than the therapeutic level, the maintenance dose would be stopped and a symptomatic treatment would be started. All data were described using mean, percentage, and analyzed with Chi-square for comparison of the achievement rate of the therapeutic levels of magnesium from both groups. The *p*-value <0.05 was considered statistically significant.

Results

General characteristics of patients from both groups looked similar and are shown in Table 1. The mean BMI in the experimental group (2 g/h) and control group (1 g/h) were 33.52.17$\pm$6.84 kg/m^2 (range 25.10 to 46.74) and 33.78$\pm$6.09 kg/m^2 (range 27.53 to 46.20), respectively.

The ratio of the patients with a therapeutic level of magnesium in the experimental group was higher than the control group before delivery (52.6% vs. 15.8%, respectively, RR 3.3 (95% CI: 1.08-10.24)) and after delivery (84.2% vs. 42.1%, respectively, RR 2.0 (95% CI: 1.14-3.51)), as shown in the Table 2. No overdose of magnesium was seen in either group from this study. In the 1 gram per hour group, the dose of magnesium after delivery was increased to 1.5 grams per hour in four patients, and to 2 grams per hour in seven patients.

As shown in Table 3, there was no difference in the pregnancy outcomes of either group; they included the postpartum hemorrhage and eclampsia.

Discussion

This study included 38 preeclamptic women with overweight who were diagnosed, and treated with magnesium sulfate at Maharat Nakhon Ratchasima Hospital. They were randomly allocated into two groups equally, 19 cases in each group, and the basic characteristics of both groups were similar.

The serum magnesium in the group of 2 grams per hour maintenance infusion was higher than that of the 1 gram per hour group, both before and after delivery. It was consistent with a former study[11] that compared the dose of magnesium sulfate between 2 grams per hour and 1 gram per hour. However, that former study showed the magnesium level four hours after magnesium sulfate therapy but before delivery of

Table 1. General characteristics of the patients from 2 groups

Characteristics	Mg 2 g/h (n = 19)	Mg 1 g/h (n = 19)
Mean age, year: mean ± SD	26±7.6	28±6.6
BMI: mean ± SD	33.5±6.8	33.8±6.1
Gravida		
Primigravida: n (%)	7 (36.8)	12 (63.2)
Multigravida: n (%)	9 (47.4)	10 (52.6)
Gestational diabetes: n (%)	1 (5.3)	4 (21.1)
Preterm (gestational age <37 weeks): n (%)	8 (42.1)	6 (31.6)

Table 2. Magnesium level from both groups

Mg level	Mg 2 g/hNo (%)	Mg 1 g/hNo (%)	RR (95 % CI)	*p*-value
Intrapartum Mg level,				
Therapeutic	10 (52.6)	3 (15.8)	3.3 (1.08-10.24)*	0.017
Sub therapeutic	9 (47.4)	16 (84.2)	1	
Postpartum Mg level				
Therapeutic	16 (84.2)	8 (42.1)	2.0 (1.14-3.51)*	0.007
Sub therapeutic	3 (15.8)	11 (57.9)	1	

* *p*-value <0.0: statistics significant.

Table 3. Pregnancy outcomes from both groups

Pregnancy outcomes	Mg 2 g/hNo (%)	Mg 1 g/hNo (%)	*p*-value
Route of delivery			
Cesarean section	18 (94.7)	16 (84.2)	0.290
Vacuum	1 (5.3)	3 (15.8)	0.290
Low birth weight	11 (57.9)	9 (47.4)	0.516
Birth asphyxia	3 (15.8)	2 (10.5)	0.631

**p*-value <0.05

the maintenance dose of 2 grams per hour reached the therapeutic level more than the 1 gram per hour group, 80% vs. 17%, respectively. It was higher than this study at four hours after magnesium administration because the loading dose was 5 grams, which was higher than the 4 grams of this study. Furthermore, this study recruited only the overweight, which was demonstrated by Boonyongchaisawat et al[10] that it could result in the subtherapeutic level of magnesium with statistical significance, $p<0.001$. In a different study[11], serum magnesium was found over the therapeutic level without clinical magnesium toxicity in four cases in group of 2 grams per hour of magnesium sulfate, which was different from this study in which no overdose was found.

From systemic review in 2015[8], the regimen of magnesium sulfate of 4 grams loading dose and 1 gram per hour continuous maintenance infusion (Zuspan regimen) could give the mean serum concentration between 1.64 and 1.70 mmol/l, which is not the therapeutic level. However, a regimen of magnesium sulfate of 4 grams loading dose and 2 grams per hour continuous maintenance infusion could keep the mean serum concentration higher than the therapeutic level in the majority and at a constant level after four hours of administration[12].

In this study, neither the overdose of magnesium nor convulsions were found. There was no

difference in the pregnancy outcomes in the two groups. However, because of the small sample size, it may not be enough to signify the efficacy and safety of the aforementioned method. If the sample size is large enough in further study, the efficacy and safety may be confidently documented and would be further implemented into clinical practice.

Conclusion

Magnesium sulfate 2 grams per hour infusion can offer overweight preeclamptic women the medicament to reach therapeutic level, both before and after delivery better than 1 gram per hour regimen, without overdose. The pregnancy outcomes are not different between both groups.

What is already known on this topic?

In former studies, the therapeutic level of magnesium in mothers with preeclampsia may be more frequently reached before and after delivery with a dose of 2 grams per hour of magnesium sulfate infusion than 1 gram per hour. The former studies found an association between the maternal body mass index and the subtherapeutic serum magnesium level in severe preeclampsia.

What this study adds?

This study showed the therapeutic level of magnesium in mothers with preeclampsia between magnesium sulfate infusion 2 grams per hour and 1 gram per hour in overweight mother (special group).

Potential conflicts of interest

None.

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การศึกษาเปรียบเทียบระหว่างการให้แมกนีเซียมซัลเฟตขนาด 2 กรัมต่อชั่วโมงกับ 1 กรัม ต่อชั่วโมงในสตรีภาวะครรภ์เป็นพิษชนิดรุนแรงที่มีภาวะน้ำหนักเกินมาตรฐาน

สิรยา กิติโยดม

ภูมิหลัง: *การให้แมกนีเซียมซัลเฟตเป็นวิธีการที่ได้รับการยอมรับว่ามีประสิทธิภาพในการป้องกันและรักษาภาวะชักจากครรภ์เป็นพิษ โดยระดับแมกนีเซียมที่ได้ระดับการรักษาคือ 4.8-8.4 มิลลิกรัมต่อเดซิลิตร โดยการให้แมกนีเซียม ทำให้เกิดอันตรายถึงชีวิตได้ในกรณีภาวะแมกนีเซียมเกินระดับการรักษา ในโรงพยาบาลมหาราชนนรราชสีมา การให้แมกนีเซียมซัลเฟตเริ่มให้ยาขนาด 4 กรัม ตามด้วยขนาดยาเพื่อควบคุมอาการขนาด 1 กรัมต่อชั่วโมงในปี พ.ศ. 2555-2556 พบผู้ป่วย 14 รายเกิดภาวะชักขณะให้ยาแมกนีเซียมซัลเฟตอยู่ ซึ่งทุกรายพบว่าระดับแมกนีเซียม ไม่ได้ระดับการรักษาทั้งหมด และร้อยละ 85.7 มีภาวะน้ำหนักเกินมาตรฐาน*

วัตถุประสงค์: *เพื่อเปรียบเทียบสัดส่วนของผู้ที่มีระดับแมกนีเซียมได้มาตรฐานการรักษาหลังให้แมกนีเซียมซัลเฟตในสตรีครรภ์เป็นพิษที่มีภาวะน้ำหนักเกินมาตรฐานในการให้ขนาดยาที่ควบคุมอาการระหว่าง 1 กรัมต่อชั่วโมง และ 2 กรัมต่อชั่วโมง*

วัสดุและวิธีการ: *การวิจัยเชิงทดลองทางคลินิกแบบสุ่มและมีกลุ่มควบคุม ได้รับอนุญาตจากคณะกรรมการพิจารณาการวิจัยในคน รพ. มหาราชนครราชสีมา ศึกษาสตรีตั้งครรภ์ที่มีภาวะน้ำหนักเกินมาตรฐานได้รับการวินิจฉัยภาวะครรภ์ เป็นพิษและต้องได้รับยาแมกนีเซียมซัลเฟตเพื่อป้องกันภาวะชัก เกณฑ์การคัดออกคือการทำงานไตผิดปกติ หรือทำการรักษาด้วยวิธี conservative กลุ่มตัวอย่างทั้งหมด 38 รายคำนวนจากการศึกษานำร่อง แบ่งผู้ป่วยเป็นสองกลุ่มโดย simple randomization กลุ่มทดลองได้รับขนาดยาที่ควบคุมอาการ 2 กรัมต่อชั่วโมง และกลุ่มควบคุมได้รับยา 1 กรัมต่อชั่วโมง ทำการเจาะตรวจค่าแมกนีเซียมก่อนคลอดหลังให้ยา 4 ชั่วโมง และหลังคลอดทุก 4 ชั่วโมงในผู้ป่วยทั้งสองกลุ่ม ทำการวิเคราะห์ข้อมูลเชิงสถิติโดยใช้ percentage และ Chi-square*

ผลการศึกษา: *Body Mass Index ในกลุ่มทดลองและกลุ่มควบคุมคือ 33.5±6.84 และ 33.7±6.09 ตามลำดับ ทั้งสองกลุ่มไม่พบความแตกต่างกันของลักษณะพื้นฐานพบกลุ่มทดลองมีสัดส่วนของผู้ที่มีระดับแมกนีเซียม ก่อนคลอดได้ระดับการรักษาสูงกว่ากลุ่มควบคุม (ร้อยละ 52.6 และ 15.8 ตามลำดับ ค่าความเสี่ยงสัมพันธ์ RR 3.3 (95% CI: 1.08-10.24)) และหลังคลอด (ร้อยละ 84.2 และ 42.1 ตามลำดับ ค่าความเสี่ยงสัมพันธ์ RR 2.0 (95% CI: 1.14-3.51)) ในการศึกษานี้ไม่พบภาวะแมกนีเซียมเกินระดับมาตรฐานและภาวะชักในทั้งสองกลุ่มการศึกษา พบว่ากลุ่มให้แมกนีเซียมขนาด1กรัมต่อชั่วโมงหลังคลอดได้เพิ่มขนาดยาควบคุมอาการเพื่อให้แมกนีเซียมได้ระดับการรักษา โดยต้องเพิ่มเป็นขนาด 1.5 กรัมต่อชั่วโมง 4 รายและขนาด 2 กรัมต่อชั่วโมง 7 ราย*

สรุป: *การให้แมกนีเซียมซัลเฟตขนาด 2 กรัมต่อชั่วโมง ในสตรีครรภ์เป็นพิษที่มีน้ำหนักเกินมาตรฐานทำให้แมกนีเซียมได้ระดับการรักษาสูงกว่าทั้งก่อนและหลังคลอดโดยไม่พบระดับแมกนีเซียมเกินมาตรฐาน ซึ่งจะได้นำผลไปพัฒนาแนวทางการดูแลสตรีครรภ์เป็นพิษต่อไป*