Magnesium Sulfate Maintenance Infusion in Women with Preeclampsia: A Randomized Comparison between 2 Gram per Hour and 1 Gram per Hour

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Objective: *To compare the percentages of pregnant women with preeclampsia who reached the therapeutic serum magnesium levels between those who received maintenance magnesium sulfate infusion of 2 g/hour versus 1 g/hour.*
Material and Method: *Sixty women diagnosed of preeclampsia and magnesium sulfate that were considered for seizure prophylaxis were randomized into two groups. A loading dose of 5 g magnesium sulfate was given intravenously over 20 minutes to both groups. Maintenance doses of magnesium sulfate of 2 g/hour and 1 g/hour were given to the study and control groups, respectively. The maintenance dose was continued until 24 hours postpartum. Blood samples for serum magnesium were collected at 0, 1/2, 2, and 4 hours after the loading dose and at 2 and 12 hours after delivery. Clinical signs of magnesium toxicity were carefully monitored. Maternal and neonatal outcome were evaluated.*
Results: *Significantly more women in the present study group reached the therapeutic level of serum magnesium at 2 hours (70% vs. 23%, p = 0.001) and at 4 hours (80% vs. 17%, p = 0.00) after the loading dose and at 2 hours (60% vs. 20%, p = 0.003) and at 12 hours (80% vs. 37%, p = 0.001) after delivery. No clinical magnesium toxicity was observed. There were no significant differences in maternal and neonatal outcomes between the two groups.*
Conclusion: *The maintenance dose of magnesium sulfate at 2 g/hour was more likely to attain the therapeutic level of serum magnesium when compared to 1 g/hour with no detectable difference in maternal and neonatal outcomes.*

Keywords: *Serum magnesium level, Preeclampsia, Randomized controlled trial*

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Preeclampsia, which affects approximately 2% of pregnancies, is a major cause of maternal and perinatal mortality globally[1]. Eclampsia, the most severe form of preeclampsia, is associated with an estimated 50,000 maternal deaths annually worldwide[2].

Magnesium sulfate ($MgSO_4$) has been used to prevent eclamptic convulsion since 1925, its efficacy was confirmed by a large randomized controlled trial in 2002[3]. Eclampsia could be prevented in more than 50% after magnesium sulfate administration[3]. The World Health Organization (WHO) recommended magnesium sulfate as the most effective, safe, and low-cost drug for the prevention of seizure in severe preeclampsia and eclampsia[4]. The recommended dose of magnesium sulfate is 4 to 6 g intravenous loading dose, followed by maintenance intravenous drip at the rate of 1 to 2 g/hour[5].

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A previous study in Thailand[6] showed that the conventional magnesium sulfate 5 g intravenous loading followed by a maintenance infusion of 1 g/hour could not drive the magnesium level to reach the therapeutic level. The therapeutic levels of serum magnesium are between 2 to 3.5 mmol/l[7-9].

In many hospitals in Thailand, however, it is a common practice to give the 1 g/hour infusion as the maintenance dose as a precaution against magnesium toxicity. The aim of the present study was to look at the percentages of pregnant women who had the therapeutic level of serum magnesium with 2 g/hour magnesium sulfate maintenance infusion, as compared to the commonly used dosage of 1 g/hour infusion.

Material and Method

The present study was approved by the Institutional Review Board (IRB) of the Faculty of Medicine, Chulalongkorn University. Pregnant women with severe preeclampsia between July 2011 and August 2012 at King Chulalongkorn Memorial Hospital (KCMH) and magnesium sulfate was

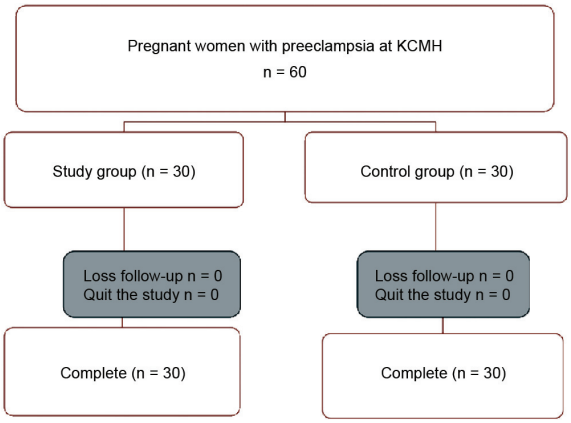

Fig. 1 This figure showed research methodology.

considered for seizure prophylaxis, were included in the present study. Sample size was calculated to give the power of 80%, $\alpha = 0.05$, which yielded the number of participants of 30 cases per group. All patients gave written informed consent.

All patients received 5 g intravenous loading dose of magnesium sulfate over 20 minutes, then were randomized into two groups. The study group received a maintenance dose of magnesium sulfate at 2 g/hour and the control group received 1 g/hour. Serum magnesium was collected before magnesium loading, at 30 minutes, 2 hours, and 4 hours after loading magnesium sulfate. Postpartum serum magnesium was collected at 2 hours and 12 hours after delivery as shown in Fig. 1. The samples were kept in collection tubes (clot blood) and sent to laboratory then analyzed by magnesium kit (Cobas®). The therapeutic levels of serum magnesium are defined as the level between 2 and 3.5 mmol/l[5,7,13]. Clinical magnesium toxicity was closely monitored by recording of the urine output, deep tendon reflexes, and respiratory rate. Calcium gluconate at 10% was made readily available in case of clinical magnesium toxicity. Apgar score was measured to determine neonatal outcome. Numerical values were expressed as mean. Categorical data was expressed as proportion. Statistical analysis was performed by means of Student's t-test and Chi-square test, a p-value of less than 0.05 was considered statistically significant. Statistical data was analyzed by SPSS for Windows version 17.

Results

Sixty patients were recruited and completed the study. There was no case of loss to follow-up. The demographic data is shown in Table 1. There was no statistically significant difference in the demographic data between the two groups. The number and percentage of patients who had serum magnesium reaching the therapeutic level between the two groups are shown in Table 2.

It is shown that the percentage of patients who had serum magnesium reaching the therapeutic level were significantly higher in the study group than in the control the group. Apgar score was similar between two groups ($p>0.05$). In the study group, four cases had serum magnesium higher than 3.5 mmol/l (Table 3), none of the recruited cases had symptoms and signs of magnesium toxicities or hypocalcemia during the study period. No patient had convulsions while receiving intravenous magnesium sulfate infusion.

Discussion

The present study clearly demonstrated that pregnant women with preeclampsia who received a 5 g intravenous loading dose of magnesium sulfate followed by a maintenance infusion of 2 g/hour (the study group) had a higher likelihood of attaining the designated therapeutic serum magnesium level, as compared to the group with a maintenance infusion of 1g/hour (the control group). In the present study, the authors did not find any single case of clinical magnesium toxicity. On the contrary, none of the patients had seizures despite some obviously had serum magnesium sulfate below the therapeutic level.

Nevertheless, some patients in the study group did not have serum magnesium reaching the therapeutic level. This is probably due to the difference in pharmacokinetic of magnesium sulfate distribution and metabolism in obese patients, or in patients with different phases of diuresis. In the four cases with serum magnesium above therapeutic level, all were

Table 1. Demographic data

	Study group (n = 30)	Control group (n = 30)	p-value
Age (years)	31.63	31.57	0.969
Parity			0.789
Nulliparous	20	18	
Multiparous	10	12	
Gestational age (weeks)	36.17	36.27	0.881
Body weight (kg)	74.99	71.64	0.456
Height (cm)	158.80	156.27	0.041
Fetal weight (grams)	2,485.20	2,468.70	0.938

Table 2. Number of patients whose serum magnesium reached the therapeutic level

Time of sample collection	Number (percentage) of patients who had serum magnesium reaching therapeutic level		p-value
	Dose 2 g/h	Dose 1 g/h	
30 min after loading dose	21 (70)	14 (46.7)	0.115
2 hours after loading dose	21 (70)	7 (23.3)	0.001
4 hours after loading dose	24 (80)	5 (16.7)	0.000
2 hours after delivery	18 (60)	6 (20.0)	0.003
12 hours after delivery	24 (80)	11 (36.7)	0.001

Table 3. Details of 4 cases with serum magnesium level above therapeutic level

Patient	Body weight (kg)	Urine output (ml/h)	Serum magnesium level (mmol/l)				
			30 min after loading dose	2 h after loading dose	4 h after loading dose	2 h after delivery	12 h after delivery
1	72.8	20-100	2.13	4.01	3.68	2.80	2.77
2	81.0	10-120	4.98	2.10	2.35	2.19	1.70
3	90.0	20-200	2.37	2.45	4.17	2.43	2.54
4	82.0	15-70	2.02	2.38	2.72	3.00	3.90

found to have intermittent oliguria during the course of magnesium infusion. The lowered rate of magnesium excretion by the kidney may partly explain the periodic higher levels of serum magnesium.

In the present study, the authors did not find clinical toxicities of magnesium sulfate or eclamptic convulsion in all cases. Neonatal outcomes were satisfactory in both groups. Due to the small sample size, it is inappropriate to generalize or over-emphasize its therapeutic efficacy and safety. Further studies with a larger sample size to yield enough power in order to elucidate the safety aspects are required before establishing its use in clinical practice.

Whether or not the difference in therapeutic level of magnesium sulfate will translate into clinical difference in eclamptic episode may need a larger study.

Conclusion

The maintenance dose of magnesium sulfate at 2 g/hour was more likely to attain the therapeutic level of serum magnesium when compared to 1 g/hour with no difference in maternal and neonatal outcomes.

Potential conflicts of interest

None.

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การให้แมกนีเซียมซัลเฟตในผู้ป่วยที่มีภาวะครรภ์เป็นพิษโดยเปรียบเทียบระหว่างการให้ต่อเนื่องในขนาด 2 กรัม/ชั่วโมง กับ 1 กรัม/ชั่วโมง

ธีระภัทร เจริญวิทย์, ศักนัน มะโนทัย

วัตถุประสงค์: *เพื่อเปรียบเทียบเปอร์เซนต์ของผู้หญิงที่ได้รับยาแมกนีเซียมซัลเฟต ที่มีระดับซีรัมแมกนีเซียมถึงระดับที่ใช้ในการรักษา ระหว่างหญิงตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษที่ได้แมกนีเซียมซัลเฟตทางหลอดเลือดดำแบบต่อเนื่องในขนาด 2 กรัม/ชั่วโมง หรือ 1 กรัม/ชั่วโมง*

วัสดุและวิธีการ: *หญิงตั้งครรภ์ที่มีภาวะครรภ์เป็นพิษและได้รับแมกนีเซียมซัลเฟต เพื่อป้องกันภาวะชักจำนวน 60 ราย จะถูกแบ่งโดยการสุ่มเป็น 2 กลุ่ม ทั้ง 2 กลุ่มจะได้รับแมกนีเซียมซัลเฟต ขนาด 5 กรัม ผ่านทางหลอดเลือดดำช้า ๆ ในเวลา 20 นาที ในกลุ่มทดลองจะได้รับยาแมกนีเซียมซัลเฟต แบบต่อเนื่องทางหลอดเลือดดำในขนาด 2 กรัม/ชั่วโมง ส่วนในกลุ่มควบคุมได้รับยาแมกนีเซียมซัลเฟต ทางหลอดเลือดดำแบบต่อเนื่องในขนาด 1 กรัม/ชั่วโมง การให้ยาแมกนีเซียมซัลเฟตนี้จะต่อจนหลังคลอดบุตรครบ 24 ชั่วโมง จากนั้นตรวจระดับซีรัมแมกนีเซียม ที่ 0 นาที, 30 นาที, 2 ชั่วโมง และ 4 ชั่วโมง ภายหลังให้ยา และที่ 2 ชั่วโมง และ 12 ชั่วโมงหลังคลอด ภาวะระดับยาที่เป็นพิษจะถูกตรวจและเฝ้าระมัดระวังอย่างใกล้ชิดตรวจประเมินภาวะแทรกซ้อนในมารดาและทารกแรกเกิด*

ผลการศึกษา: *ผู้ป่วยในกลุ่มทดลองมีระดับของซีรัมแมกนีเซียมที่ถึงระดับการรักษามากกว่ากลุ่มควบคุมอย่างมีนัยสำคัญที่ 2 ชั่วโมงหลังให้ยา (70% เทียบกับ 23%, p = 0.001) ที่ 4 ชั่งโมงหลังให้ยา (80% เทียบกับ 17%, p = 0.00), ที่ 2 ชั่วโมงหลังคลอด (60% เทียบกับ 20%, p = 0.003) และที่ 12 ชั่วโมงหลังคลอด (80% เทียบกับ 37%, p = 0.001) ในการศึกษานี้ไม่พบว่ามีผู้ป่วยคนใดมีภาวะระดับยาเป็นพิษ และพบว่าภาวะแทรกซ้อนในมารดาและทารกแรกเกิดไม่แตกต่างกันระหว่าง 2 กลุ่ม*

สรุป: *ในกลุ่มทดลองซึ่งได้รับแมกนีเซียมซัลเฟต ผ่านทางหลอดเลือดดำแบบต่อเนื่องในขนาด 2 กรัม/ชั่วโมง จะมีจำนวนของผู้ป่วยที่มีระดับซีรัมแมกนีเซียมถึงระดับการรักษามากกว่ากลุ่มที่ได้ยาแมกนีเซียมซัลเฟต ผ่านทางหลอดเลือดดำแบบต่อเนื่องในขนาด 1 กรัม/ชั่วโมง อย่างมีนัยสำคัญ โดยภาวะแทรกซ้อนในมารดาและทารกแรกเกิดไม่แตกต่างกัน*