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Shortened Postpartum Magnesium Sulfate Treatment for Severe Preeclampsia

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ABSTRACT

Objectives: To compare the benefits and risks of shortened postpartum magnesium sulfate with traditional 24 hours postpartum magnesium sulfate for treatment of severe preeclampsia and evaluate reinitiation rate of magnesium sulfate and eclamptic seizure after shortened treatment.

Materials and Methods: We recruited labouring pregnant patients in their 2nd to 3rd trimester who were diagnosed as preeclampsia (blood pressure ≥ 140/90 mmHg plus urine protein dipstick ≥ 1+) between March 1st, 2009 and February 28th, 2010. Inclusion criteria for severe preeclampsia were (1) blood pressure ≥ 160/110 mmHg, (2) urine protein dipstick ≥ 2+, (3) severe headache and blurred vision, (4) epigastric pain and willing to be enrolled in the study. Exclusion criteria were (1) platelet count <100,000 cells/mm^3 and /or evidence of microangiopathic hemolytic anemia (elevated lactic acid dehydrogenase), (2) elevated liver enzymes (ALT or AST), (3) pulmonary edema and (4) eclampsia. Criteria to stop postpartum magnesium sulfate were (1) urine output more than 100 ml/hr for 2 consecutive hours, (2) no clinical symptoms of severe headache, blurred vision and epigastric pain and (3) deep tendon reflex < 3+. The minimal time to stop magnesium sulfate was 12 hours postpartum. The period of time that magnesium sulfate was given and reinitiation rate of magnesium sulfate and eclamptic seizure were recorded. We compared the study result with the patients who were diagnosed severe preeclampsia one year earlier which was between March 1st, 2008 and February 28th, 2009 by reviewing medical and labour records. All patients in the latter group received standard dose of postpartum magnesium sulfate which was continued until 24 hours postpartum. The difference of administration time of magnesium sulfate, reinitiation rate of magnesium sulfate and effectiveness in eclamptic seizure prevention were compared between both groups.

Results: There were 76 severe preeclampsia patients who were recruited in the shortened magnesium sulfate group. There were 75 severe preeclampsia patients in the traditional 24 hours magnesium sulfate group. Shortened postpartum magnesium sulfate treatment was as effective as traditional 24 hours magnesium sulfate in seizure prevention. The period of administration time of shortened group was less than in the controlled group (14.08 ± 3.42 hours and 23.69 ± 2.65 hours, $p<0.001$). None of the patients in either groups had to reinitiate magnesium sulfate or developed seizure.

Conclusion: Clinical parameters can be used to set the criteria to stop and reinitiate postpartum magnesium sulfate regarding to patient safety. When the time and the amount of magnesium sulfate administration is reduced, it helps in reducing health personnel workload and hospital expenses.

Keywords: Severe preeclampsia, Shortened treatment of magnesium sulfate.

Severe preeclampsia is a severe complication of pregnancy and may lead to maternal and fetal morbidity and mortality[1-3] especially when complicated with eclampsia[4,5]. In 2006 and 2007, there were 73 and 96 cases of severe preclampsia out of 3,953 and 4,127 mothers, respectively in Prapokklao Hospital. Magnesium sulfate is the only medication that has been proved to prevent eclampsia in severe preeclampsia patients[6] administering prior and continuing after delivery [7] (loading dose 4-6 g slowly push then continuous dose 1-2 g/hr). Magnesium sulfate has a very narrow therapeutic range. If the level is not reached, it cannot prevent seizure, while at too high level may cause respiratory failure and finally cardiac arrest.

Nowadays, there is no specific period of time recommending how long magnesium sulfate should be given to prevent eclampsia after delivery[8]. The most common recorded eclamptic seizure incidence is during the first forty-eight hours after delivery[9]. Many hospitals including Prapokklao Hospital administer magnesium sulfate up to twenty-four hours after delivery. However, the physicians should evaluate the pros and cons of stopping magnesium sulfate concerning their overdose side effects in prolonged administrated cases or eclamptic seizure hazard in inappropriate short period.

The purpose of the study is to compare the benefits and risks of shortened postpartum magnesium sulfate with traditional twenty-four hours postpartum magnesium sulfate in terms of seizure prevention, and also their reinitiation rate.

Materials and Methods

The sample size was calculated according to earlier research that the percentages of severe preeclampsia patients needed reinitiating of treatment after receiving 24 hours magnesium sulfate and shortened magnesium sulfate group were 2.27[10] and 20[11], respectively. A total of 59 patients were needed in each group, calculated by Epi Info version 6.0 program ($\alpha = 0.05$, $\beta = 0.2$).

A Quasi experimental study was performed at Prapokklao Hospital under the approval of the Institutional Ethic Committee. The study was conducted from March 1st, 2009 to February 28th, 2010. We recruited the labouring pregnant patients who were diagnosed preeclampsia (blood pressure ≥ 140/90 mmHg plus urine protein dipstick ≥ 1+) in their second to third trimesters. Inclusion criteria for severe preeclampsia were (1) blood pressure ≥ 160/110 mmHg, (2) urine protein dipstick ≥2+, (3) severe headache and blurred vision, (4) epigastric pain and willing to be enrolled in the study. Exclusion criteria were (1) platelet count <100,000 cells/mm^3 and/or evidence of microangiopathic hemolytic anemia (elevated lactic acid dehydrogenase), (2) elevated liver enzymes (ALT or AST), (3) pulmonary edema and (4) eclampsia. All patients were given the information about advantages and disadvantages of each line of the treatment before signing the informed consent. Their names and data were kept confidentially.

Severe preclampsia patients who participated in the study received standard intrapartum care which included blood sample for CBC, BUN, Cr, electrolytes, coagulogram, uric acid, liver function test, urine sample for urine analysis and 10% magnesium sulfate 5 g iv slowly pushed over 5 minutes, following by 50% magnesium sulfate 10 g in 5% dextrose water 1,000 ml iv rate 100 ml/hr (1 g/hr). 10%
calcium gluconate 10 ml was prepared in case of magnesium sulfate intoxication. The vital signs, urine output and the clinical symptoms were closely observed and recorded every hour. The delivery methods were judged by the physicians according to the obstetric indications.

The standard postpartum care was given, including 50% magnesium sulfate 20g in 5% dextrose water 1,000 ml iv drip with rate 50 ml/hr (1 g/hr) and syntocinon 10 U in RLS 1,000 ml iv rate 60 ml/hr (overall rate 110 ml/hr). The vital signs, urine output and the

clinical symptoms were monitored hourly until twelve hours postpartum period. After twelve hours post delivery, if (1) the urine output was more than 100 ml/hr for 2 consecutive hours, (2) no clinical symptoms of severe headache, blurred vision and epigastric pain and (3) deep tendon reflex < 3+, magnesium sulfate was stopped. On the contrary, magnesium sulfate was maintained if the mentioned criteria were not met.

After magnesium sulfate was taken off, vital signs, urine output and clinical symptoms observation were continued hourly until 24 hours postpartum. If there was any one of the following evidence such as severe headache, blurred vision, epigastric pain or deep tendon reflex ≥3+, magnesium sulfate was promptly reinitiated (magnesium sulfate 20 g in 50 % dextrose water 1,000 ml iv rate 50 ml/hr (1 g/hr)) for only 24 hours no matter whether the criteria was met. The patients were further closely observed for eclampsia, if occurred, magnesium sulfate was then administered
and blood sample was taken for magnesium level.

We compared our experimental study with the medical and labour records of severe preeclampsia patients who delivered during March 1st, 2008 and February 28th, 2009. Before this research was conducted (March 1st, 2009), standard treatment of severe preeclampsia in Prapokklao Hospital included magnesium sulfate loading dose of 5 g and maintained with the rate of 1 g/hr until 24 hours postpartum. The inclusion and exclusion criterion and intrapartum care were the same as in the experimental group. After delivery, they received magnesium sulfate intravenous rate 1 g/hr together with syntocinon until 24 hours postpartum regarding of their urine output or their clinical symptoms. Our main outcome is to compare the difference of administration time of magnesium sulfate, reinitiation rate of magnesium sulfate and effectiveness in eclamptic seizure prevention in both groups.

Statistical analysis was performed using SPSS for window version 11.5. A p-value of less than 0.05 was considered statistically significant. Chi-square or Fisher's exact test was used to compare categorical differences. Student T-test was used to compare continuous variables.

Results

There were 76 severe preeclampsia patients who were recruited in the shortened magnesium sulfate group and 75 cases in the traditional 24 hours magnesium sulfate group. There was no statistically difference in their baseline characteristics between two groups. The data was demonstrated in Table 1.

The maternal age and gestational age were not different between two groups. Since the data in the traditional magnesium sulfate group had to be reviewed from the medical records, the total weight gain during pregnancy was the missing.

The maternal treatment and delivery data are showed in Table 2.

Table 1. Demograghic data and details in diagnosis of severe preeclampsia

	Traditional 24 hours magnesium sulfate (n=75)	Shortened treatment magnesium sulfate (n=76)	p-value
Age (year ± SD)	28.57 ± 9.08	26.32 ± 7.73	0.102
GA (week ± SD)	37.07 ± 2.73	37.47 ± 2.71	0.360
Primigravid (%)	36(48.0)	35(46.1)	0.811
Previous HT (%)	4(5.3)	3(3.9)	0.719
Body weight (kg)	77.28 ± 15.77	78.14 ± 19.04	0.766
Total weight gain (kg)	Not available	13.01 ± 5.33	
Criteria in diagnosis of severe preeclampsia			
- Severe HT (%)	67(89.3)	75(98.7)	0.018
- Urine protein dipstick ≥ 2+ (%)	43(57.3)	49(64.5)	0.369
- Severe headache and blurred vision (%)	20(26.7)	16(21.1)	0.418
- Epigastric pain (%)	10(13.3)	12(15.8)	0.669

GA = gestational age, HT = hypertension, CNS = central nervous system

Table 2. Maternal treatment and delivery data

	Traditional 24 hours magnesium sulfate (n=75)	Shortened treatment magnesium sulfate (n=76)	p-value
Normal labor (%)	16(21.3)	22(28.9)	0.281
Vaccuum extraction (%)	2(2.7)	3(3.9)	0.660
Forceps extraction (%)	10(13.3)	13(17.1)	0.519
Cesarean delivery (%)	46(61.3)	36(47.4)	0.119
Breech assisting (%)	0(0)	1(1.3)	0.319
Birth before arrival (%)	1(1.3)	1(1.3)	0.992
Singleton (%)	73(97.3)	71(93.4)	0.45
Twins (%)	2(2.7)	5(6.6)	0.45
Antepartum $MgSO_4$ duration (hr ± SD)	5.61 ± 5.93	4.82 ± 3.97	0.333
Postpartum $MgSO_4$ duration(hr ± SD)	23.69 ± 2.66	14.08 ± 3.42	<0.001
$MgSO_4$ reinitiation (%)	0(0)	0(0)	
Seizure incidence (%)	0(0)	0(0)	
Antihypertensive medication at discharge (yes %)	22(29.3)	11(14.5)	0.027
Hospital stay (day ± SD)	7.71±3.36	8.12±1.83	0.353
Birth weight (gram ± SD)	2,696.93 ± 742.35	2,708.82 ± 732.26	0.921

There were five pairs of twins in the shortened magnesium sulfate group while there were two in the traditional magnesium sulfate group. The period of time magnesium sulfate given prior to delivery did not vary statistically between two groups. The period of postpartum magnesium sulfate was statistically different (14.08 ± 3.424 hours and 23.69 ± 2.656 hours, p<0.001). The length of hospital stay did not differ between two groups. There was no patient in either groups who developed the clinical symptoms of severe headache, blurred vision, epigastric pain, hyperreflexia or seizure and had to reinitiate magnesium sulfate.

One patient in the traditional 24 hours magnesium sulfate group became drowsiness and breathed slowly after one hour of postpartum magnesium sulfate administration. The deep tendon reflex was 1+. The intravenous magnesium sulfate was stopped and 10% calcium gluconate 10 cc was given. The symptom was improved rapidly. Her magnesium level was 5.92 mg/dl (1.7-2.8 mg/dl). Since then she did not need any more magnesium sulfate.

We recorded the postpartum eclampsia incidence after discharge but after going through many medical records, only few patients came back for postpartum care. The physicians routinely appointed postpartum follow up at 2 weeks after delivery. There were only 8 out of 76 patients in the shortened magnesium sulfate group and 22 out of 75 patients in the 24 hours magnesium sulfate group returned to postpartum clinic. None of them developed seizure. The rest were interviewed by telephone and none of them developed seizure.

Discussion

Many experimental and randomized controlled trial studies tried to find the perfect timing to discontinue magnesium sulfate after delivery. Some of them used clinical and laboratory parameters to determine the point of time to avoid side effect of drug as well as to prevent eclamptic seizure. The parameters such as low blood pressure, no clinical evidence of severe headache, blurred vision, epigastric pain, catheterized urine protein dipstick ≤100 mg/dl, urine output ≥100 ml per hour for 2 consecutive hours (without fluid challenge or furosemide stimulation).

We have chosen the appropriate minimal time of 12 hours postpartum magnesium sulfate according to the study of Ascarelli MH et al [10]. After that he used many clinical and laboratory parameters to decide when to stop magnesium sulfate. None of the participants in his study had postpartum eclampsia. The most common symptom leading to eclampsia was central nervous system symptom[7]. The more urine output meant the better improvement the disease has become. It was the reason why we used these parameters for the criteria to stop and reinitiate magnesium sulfate.

The result showed that we can rely on clinical parameters as the criteria to stop and reinitiate postpartum magnesium sulfate regarding to patient safety. These parameters are simple and practical. The eclamptic rate and the rate of reinitiation of magnesium sulfate was zero in both groups. When the time and the amount of magnesium sulfate administration is decreased, it can reduce health personnel workload and hospital expense.

The randomized controlled trial would be more appropriate and valid. Since postpartum eclampsia is a very rare event, we cannot simply make conclusion out of only 76 subjects. More severe preeclampsia patients are needed in the study to meet the significant conclusion or even a bigger multicenter trial study should be considered.

Eclampsia is one of the most feared condition in obstetric care. The end point of postpartum magnesium sulfate administration is considered appropriate if eclampsia does not occur after magnesium sulfate cessation. However, the standard traditional 24 hours postpartum magnesium sulfate is not based on patients' individualization.

Conclusion

The study was to encourage the use of clinical parameter to individualize time of therapy. The minimal postpartum magnesium sulfate of 12 hours together with clinical parameters (the urine output more than 100 ml/hr for 2consecutive hours, no clinical symptoms of

severe headache, blurred vision, epigastric pain and deep tendon reflex <3+) could assure that eclamptic seizure would not occur after that. However, a larger randomized controlled trial is strongly encouraged.

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การให้ยาแมกนีเซียมซัลเฟตระยะสั้นเพื่อป้องกันการชักในผู้ป่วยครรภ์เป็นพิษ (severe preeclampsia) ในระยะหลังคลอด

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วัตถุประสงค์ *: (1) เพื่อศึกษาข้อดีและข้อเสียของการให้แมกนีเซียมซัลเฟตระยะสั้นในผู้ป่วย severe preeclampsia เปรียบเทียบกับการให้แมกนีเซียมซัลเฟตหลังคลอดครบ 24 ชั่วโมง และศึกษาอัตราการให้แมกนีเซียมซัลเฟตซ้ำและอุบัติการณ์การชักหลังการให้แมกนีเซียมซัลเฟตระยะสั้น*

วัสดุและวิธีการ *: ประชากรที่ใช้ศึกษาเป็นผู้ป่วย severe preeclampsia ที่เจ็บครรภ์คลอดที่โรงพยาบาลพระปกเกล้าและได้รับแมกนีเซียมซัลเฟตระยะสั้นเป็นเวลา 1 ปีระหว่างวันที่ 1 มีนาคม 2552 ถึงวันที่ 28 กุมภาพันธ์ 2553 เปรียบเทียบกับกลุ่มที่ให้แมกนีเซียมซัลเฟตหลังคลอดครบ 24 ชั่วโมงโดยเก็บข้อมูลในช่วงเวลาก่อนหน้านี้เป็นเวลา 1 ปี ผู้ป่วย severe preeclampsia คือผู้ป่วยที่มีเกณฑ์ข้อใดข้อหนึ่งต่อไปนี้ (1) ความดันโลหิตมากกว่าหรือเท่ากับ 160/110 มิลลิเมตรปรอท (2) urine protein dipstick มากกว่าหรือเท่ากับ 2+ (3) มีอาการปวดหัว ตามัว (4) จุกแน่นลิ้นปี่ ที่ยินยอมเข้าร่วมการวิจัย เกณฑ์การคัดออกคือ (1) เกร็ดเลือดน้อยกว่า 100,000 เซลล์ต่อลูกบาศก์มิลลิเมตร (2) เอ็นไซม์ตับค่าขึ้นสูง (3) น้ำท่วมปอดและ (4) มีภาวะชัก เกณฑ์ในการหยุดให้แมกนีเซียมซัลเฟตหลังคลอดระยะสั้น คือ ไม่มีอาการปวดหัว ตามัว จุกแน่นลิ้นปี่ และปัสสาวะออกมากกว่า 100 มิลลิลิตรต่อชั่วโมงเป็นเวลา 2 ชั่วโมงติดต่อกัน และ deep tendon reflex น้อยกว่า 3+ โดยจะต้องได้รับแมกนีเซียมซัลเฟตอย่างน้อย 12 ชั่วโมงหลังคลอด*

ผลการศึกษา *: ผู้ป่วยในกลุ่มได้แมกนีเซียมซัลเฟตระยะสั้นที่เข้าร่วมการวิจัยมี 76 คน ผู้ป่วยในกลุ่มได้แมกนีเซียมซัลเฟตแบบ 24 ชั่วโมงหลังคลอดที่เก็บข้อมูลย้อนหลังเป็นเวลา 1 ปีมี 75 คน พบว่าการให้ แมกนีเซียมซัลเฟตระยะสั้นสามารถป้องกันการชักในช่วงที่นอนโรงพยาบาลได้เท่ากับในกลุ่มที่ให้ 24 ชั่วโมง และจำนวนชั่วโมงที่ให้น้อยกว่าในกลุ่ม 24 ชั่วโมงอย่างมีนัยสำคัญ (14.8$\pm$3.42 ชั่วโมง และ 23.69$\pm$2.65 ชั่วโมง, ตามลำดับ) ไม่มีผู้ป่วยในกลุ่มใดได้รับแมกนีเซียมซัลเฟตซ้ำและเกิดภาวะชักหลังคลอด*

สรุป *: การใช้ clinical parameter เป็นตัวกำหนดระยะเวลาการให้แมกนีเซียมซัลเฟตในช่วงหลังคลอดสามารถทำได้โดยคำนึงถึงความปลอดภัยของผู้ป่วยและผลข้างเคียงของแมกนีเซียมซัลเฟตเป็นหลัก นอกจากนั้นยังช่วยลดภาระงานและค่าใช้จ่ายของของผู้ป่วยและโรงพยาบาลได้อีกด้วย*