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A study of serum magnesium levels attained in intravenous magnesium sulfate therapy for preeclampsia.

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The occurence of convulsions in preeclamptic patients receiving the continuous intravenous magnesium sulfate regimen with a maintenance dose of 1 gm/hr has been reported.; There have been considerable controversy regarding the recommended regimen of magnesium used to prevent convulsions. The purpose of this study was to compare the serum magnesium levels obtained in the intravenous magnesium sulfate therapy of preeclamptic patients with a maintenance dose of 1 gm/hr and 2 gm/hr. A prospective study was conducted comparing the serum magnesium levels attained in continuous intravennous magnesium sulfate regimen with a maintenance does of 1 gm/hr (n=10) to a maintenance dose of 2 gm/hr (n=10). All group were matched regarding maternal age, height, weight, fetal gestational age, and laboratory findings. Maternal magnesium sulfate infusion associated with maternal and neonatal hypermagnesemia at birth when a maintenance dose of 1 gm/hr was compared to a maintenance dose of 2 gm/hr (2.29 $\pm$ 0.54 mEq/L to 4.52 $\pm$ 0.45 mEq/L, $p < 0.05$, and 3.10 $\pm$ 0.47 to 4.86 $\pm$ 0.43 mEq/L, $p < 0.05$, respectively) The intravenous regimen with a maintenance dose of 1 gm/hr produced serum magnesium levels much lower than that with the maintenance dose of 2 gm/hr. When maintenance doses of 1 gm/hr or 2 gm/hr were used, 6.67 and 98.33% of the respective values were in the levels considered therapeutic by several authors. Both methods were safe.

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นเรศร สุขเจริญ, ไพโรจน์ วิทูรพณิชย์. การศึกษาระดับแมกนีเซียมในน้ำเหลืองของสตรีที่เป็นโรคพิษแห่งครรภ์ ซึ่งได้รับการรักษาด้วยแมกนีเซียมซัลเฟตโดยวิธีหยดเข้าหลอดเลือดดำ. จุฬาลงกรณ์เวชสาร 2533 พฤษภาคม ; 34(5) : 349-356

จากรายงานหลาย ๆ รายงานพบว่า ผู้ป่วยโรคพิษแห่งครรภ์หลายรายมีอาการชักขณะที่ได้รับแมกนีเซียม-ซัลเฟตโดยวิธีหยดเข้าหลอดเลือดดำในขนาดต่อเนื่อง 1 กรัมต่อชั่วโมง จึงมีข้อถกเถียงกันถึงขนาดและวิธีการให้แมกนีเซียมซัลเฟตที่เหมาะสมในการป้องกันการชัก วัตถุประสงค์ของการวิจัยเพื่อเปรียบเทียบระดับแมกนีเซียมในน้ำเหลืองของผู้ป่วยที่ได้รับการรักษาด้วยแมกนีเซียมซัลเฟตโดยวิธีหยดเข้าหลอดเลือดดำในขนาดต่อเนื่อง 1 กรัมต่อชั่วโมง กับ 2 กรัมต่อชั่วโมง ได้ทำการศึกษาเปรียบเทียบระดับแมกนีเซียมในน้ำเหลืองของผู้ป่วยโรคพิษแห่งครรภ์ที่ได้รับการรักษาด้วยแมกนีเซียมซัลเฟตโดยวิธีหยดเข้าหลอดเลือดดำในขนาดต่อเนื่อง 1 กรัมต่อชั่วโมง (จำนวน 10 ราย) กับ 2 กรัมต่อชั่วโมง (จำนวน 10 ราย) ทั้งสองกลุ่มไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติใน อายุ, ส่วนสูง, น้ำหนัก, อายุครรภ์และผลการตรวจทางห้องปฏิบัติการ การให้แมกนีเซียมซัลเฟตในมารดาจะทำให้มีระดับแมกนีเซียมในน้ำเหลืองสูงขึ้นในมารดาและทารกขณะคลอดเมื่อเปรียบเทียบระหว่างขนาดต่อเนื่อง 1 กรัมต่อชั่วโมง (2.92 ± 0.45 mEq/L กับ 4.52 ± 0.54 mEq/L $p < 0.05$, และ 3.10 ± 0.47 mEq/L กับ 4.86 ± 0.43 mEq/L $p < 0.05$ ตามลำดับ) การให้แมกนีเซียมซัลเฟตขนาดต่อเนื่อง 1 กรัม และ 2 กรัมต่อชั่วโมงจะได้ระดับแมกนีเซียมในน้ำเหลืองสูงถึงระดับที่ใช้ในการรักษา 6.67% และ 98.33% ของตัวอย่างเลือดที่ส่งตรวจตามลำดับ ทั้งสองวิธีเป็นวิธีปลอดภัย

Parenteral administation of magnesium sulfate is the most effective means of preventing convulsions in women with preeclampsia as well as arresting convulsions in eclamptic women.[1] The two most widly used regimens of magnesium sulfate administration are the intramuscular regimen popularized by Pritchard[2] and the continuous intravenous regimen recommended by Zuspan[3]. Recently Sibai et al.[4] reported the occurrence of convulsions in patients receiving the standard intravenous regimen of Zuspan. In addition, they found that the serum magnesium levels achieved with the continuous intravenous regimen were lower than the serum magnesium levels reported with the intramuscular regimen. Similar findings were reported by Cruikshank et al.[5]

At Chulalongkorn Hospital[6], magnesium sulfate ($MgSO_4.7H_2O$) is administered as follows : A loading dose od 5 gm is injected intravenously in not less than 5 minutes. This is followed immediately by a maintenance dose of 1 gm/hr. Total dose is about 10-15 gm.

Tannirandorn et al.[7] reported the occurrence of convulsions in patients receiving the intravenous regimen at Chulalongkorn Hospital. Eleven severe preeclamtic patients developed convulsions while receiving the continuous intravenous magnesium sulfate regimen with a maintenance dose of 1 gm/hr. The onset of seizures was between 3 and 28 hours (mean$\pm$SD = 11.8$\pm$7.9 hours) after starting the maintenance dose of $MgSO_4$.

The purpose of this prospective study is to compare the magnesium levels obtained in the intravenous magnesium sulfate therapy of severe preeclamptic patients with a maintenance dose of 1 gm/hr and 2gm/hr.

Material and methods

Twenty severe preeclamptic patients between 37 and 43 weeks' gestation were enrolled in this prospective study at Chulalongkron Hospital. All patients whose pregnancies had medical complications were excluded. All patients were trreated with the continuous intravenous regimen. A loading dose of 5gm (25% magnesium sulfate 20 ml) was injected intravenously in not less than 5 minutes. This was followed immediately by a maintenance dose of either 1 gm/hr (group I : n=10) or 2 gm/hr (group II : n=10). The intravenous magnesium sulfate was administered via a controlled infusion pump (IVAC Corp. Model STC-502). The infusion was continued through labour and for 24 hours after delivery.

Maternal respiratory rate, deep tendon reflexe, and fluid input and output were monitored hourly during the magnesium sulfate infusion. Maternal age, weight, height, parity, gestational age, systolic BP, diastolic BP and urine albumin were recorded for each patient at the time of admission

Evaluation of other maternal blood tests included the measurement of hematocrit, serum creatinine, uric acid, and BUN. Serum calcium and magnesium levels were every six hour until 24 hours after delivery. At the time of delivery, blood for total serum magnesium and calcium determinations was obtained from each mother. In addition, umbilical vein samples were obtained at delivery for neonatal magnesium and calcium determinations.

Specimens for magnesium determination were analyed immediately or stored frozen for up to 24 hours.

Serum magnesium determinations were performed by reacting with methylthymol blue reagent and measured by means of spectrophotometry (HITACHI Model 4020)

Total serum calcium determinations were performed by reacting with cresolphthalein complexone and measured by means of spectrophotometry (HITACHI Model 4020)

Statistical analysis was performed by means of paired and unpaired t test. A p value of < 0.05 was considered significant.

Results

Table 1. Maternal characteristics.

	Group I		Group II		
	Mean$\pm$SD	Range	Mean$\pm$SD	Range	
Age (year)	23.1$\pm$ 2.4	19−27	22.4$\pm$ 2.7	19−25	*
Weight (kg)	64.6$\pm$ 5.0	66.0- 77.0	64.9$\pm$ 4.7	60.1-75.4	*
Height (cm)	151.3$\pm$2.8	147.5-155	151.4$\pm$ 2.2	148-155	*
Parity	0.1$\pm$ 0.3	0-1	0.1$\pm$ 0.3	0-1	*

Table 1. (Cont.)

	Group I		Group II		
	Mean ± SD	Range	Mean ± SD	Range	
Gestational age	38.2± 0.9	37-40	38.6±0.8	37 -40	*
Systolic BP	175.0±15.8	160-200	177.0±14.9	160-200	*
Diastolic BP	113.0± 4.8	110-120	113.0± 4.8	110-120	*
Deep tendon reflex		3+		3+	*
Urine albumin		+2−+3		+2−+3	*

* No statistical difference.

Table 1. summarizes the maternal characteristics for bout groups. There was no significant difference regarding maternal age, parity, height, weight, gestational age, systolic BP, diastolic BP, deep tendon reflex, and urine albumin.

Table 2. Laboratory findings.

Laboratory findings	Group I		Group II		
	Mean ± SD	Range	Mean ± SD	Range	
Hematocrit (%)	34.0 ± 3.3	30-40	34.2 ± 3.6	30-40	*
BUN (mg/dl)	8.6 ± 1.4	7.0-11.0	8.3 ± 1.7	6.0-12.0	*
Creatinine (mg/dl)	0.55 ± 0.15	0.4-0.8	0.59 ± 0.13	0.4-0.8	*
Uric acid (mg/dl)	6.6 ± 0.8	6.0-8.3	6.6 ± 0.7	5.9-8.2	*
Serum magnesium					*
mmol/L	0.84 ± 0.10	0.7-1.0	0.82 ± 0.09	0.7-1.0	*
mEq/L	1.68 ± 0.20	1.4-2.0	1.64 ± 0.18	1.4-2.0	*
Serum calcium (mg/dl)	8.213 ± 0.34	7.9-9.0	8.39 ± 0.48	7.6-9.0	*

* No statistical difference

Table 2. summarizes the laboratory findings in the two groups of patients studied. There was no significant difference regarding maternal hematocrit, BUN, creatinine, uric acid and basal serum calcium and magnesium concentration.

Table 3. Serum magnesium and calcium levels of maternal and cord blood.

	Serum magnesium (mEq/L)		Serum calcium (mg/dl)	
	Group I	**Group II**	**Group I**	**Group II**
Admission	1.68 ± 0.20	1.64 ± 0.18	8.21 ± 0.34	8.39 ± 0.48
Delivery	2.92 ± 0.54	4.52 ± 0.46	7.55 ± 0.43	7.58 ± 0.39
Change	1.24 ± 0.60	2.88 ± 0.50	0.66 ± 0.47	0.81 ± 0.59
(%)	+ 73.9%	+ 178.8%	− 8.4%	− 9.4%
Cord blood	3.10 ± 0.48	4.86 ± 0.44	9.08 ± 0.62	9.39 ± 0.53

Table 3. summarizes serum magnesium and calcium of maternal and cord blood.

At admission, there was no significant difference of maternal serum magnesium and calcium in either groups.

At delivery, serum magnesium levels increased by 73.9% in group I and by 178.8% in group II, which showed significant difference. Total serum calcium levels decreased by 8.4% in group I and by 9.4% in group II, which showed no significant difference.

There was a significant difference between the serum magnesium level from cord blood of both groups. But there was no significant difference of total serum calcium from cord blood of both groups.

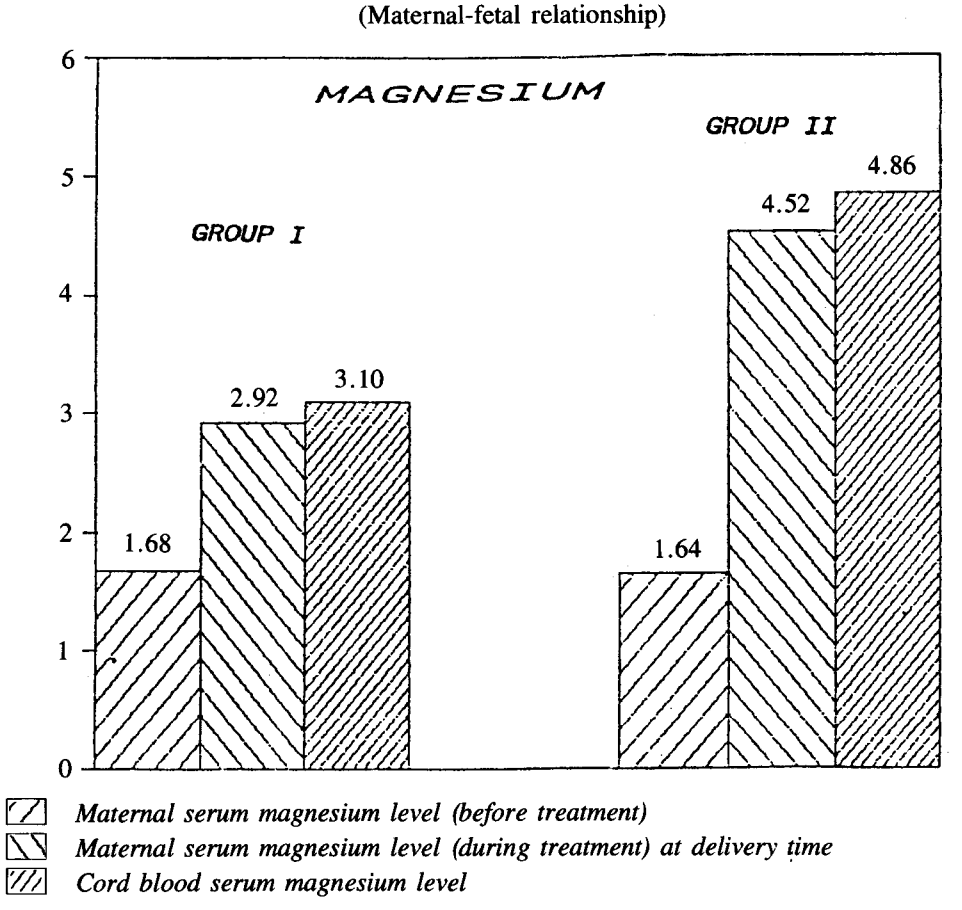

Figure 1. Maternal serum magnesium levels during intravenous $MgSO_4$ therapy.

(Maternal-fetal relationship)

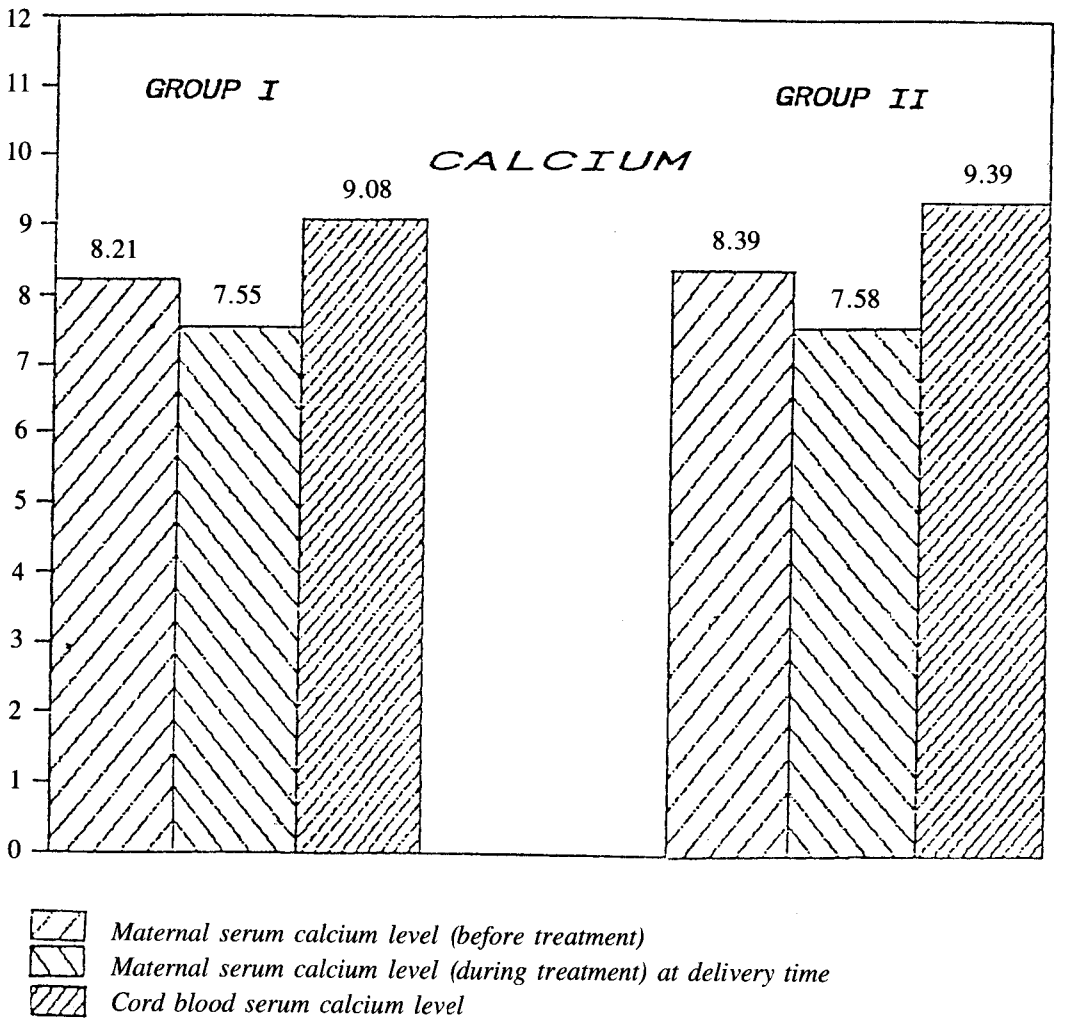

Figure 2. Changes of serum calcium level during intravenous $MgSO_4$ therapy.

Table 4. Maternal serum magnesium levels during intravenous $MgSO_4$ therapy.

Time (hours)	Serum magnesium levels (mEq/L)		
	Group I	Group II	
6	3.04 ± 0.46	4.66 ± 0.30	*
12	3.20 ± 0.40	4.72 ± 0.38	*
18	3.30 ± 0.38	4.76 ± 0.34	*
24	3.42 ± 0.38	4.90 ± 0.28	*
30	3.52 ± 0.44	5.04 ± 0.28	*
36	3.50 ± 0.30	4.80 ± 0.20	*

* Statistical difference

Table 4. shows the marked difference in serum magnesium levels achieved with the intravenous regimen with a maintenance dose of 2 gm/hr compared to the much lower level achieved with a maintenance dose of 1 gm/hr.

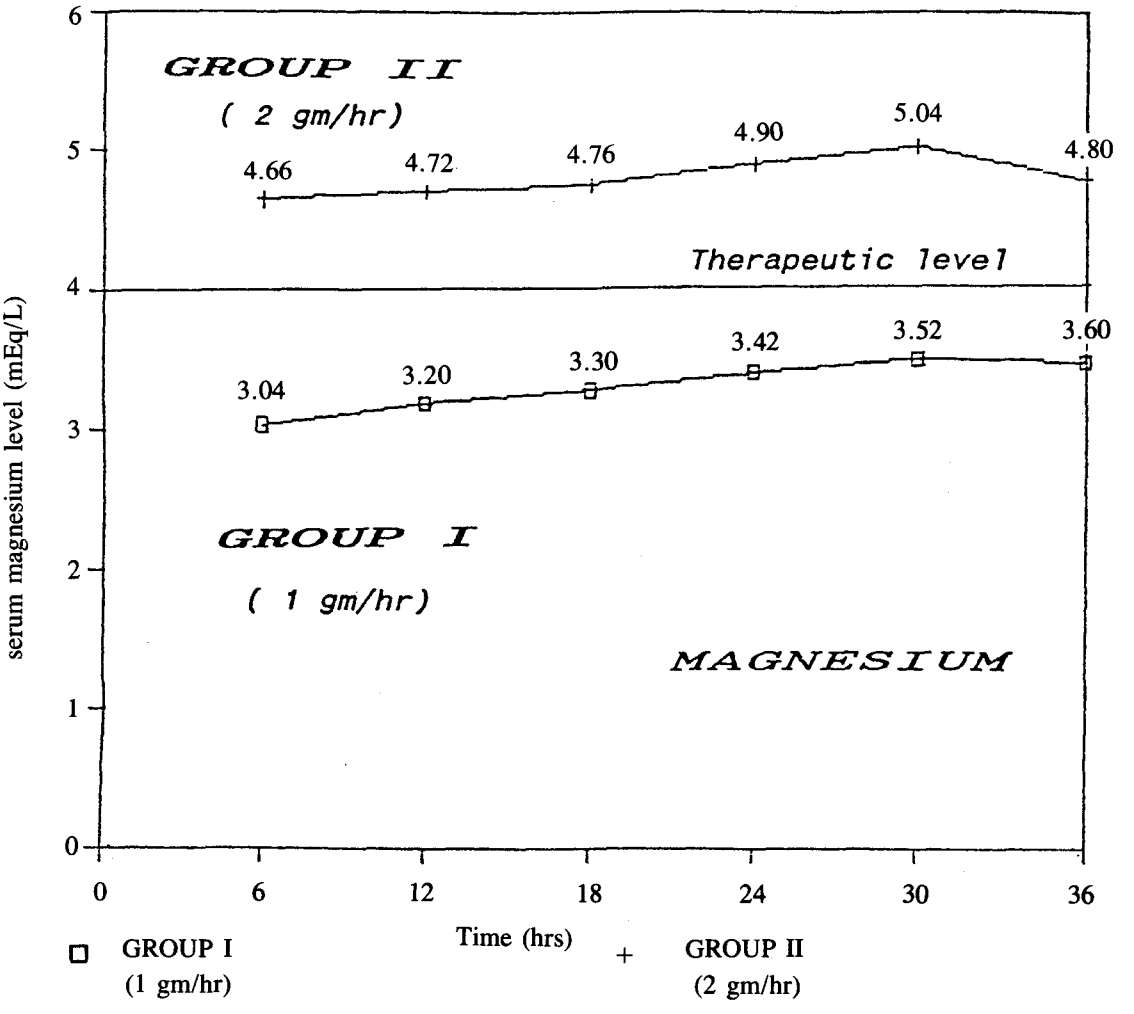

Figure 3. Changes of serum magnesium level during intravenous $MgSO_4$ therapy.

Figure 3. Comparison of the mean magnesium levels in the patients receiving the continuous intravenous regimen with a maintenance dose of 1 gm/hr and 2 gm/hr.

One hundred and twenty serum Mg levels were measured in 20 patients treated with intravenous $MgSO_4$ with a maintenance dose of 1 gm/hr. Only 4 of 60 (6.67%) Mg samples were in the therapeutic range (4-7 mEq/L).[1] A maintenance dose of 2 gm/hr resulted in values in the therapeutic range in 59 of 60 (98.33%).

Table 5. Neonatal characteristics.

	Group I	Group II	
Birth weight (gm)	2,778 ± 375	2,905 ± 282	*
Apgar score			
1-minute	8.7 ± 0.5	8.6 ± 0.5	*
5-minute	10	10	*
Route of delivery			
F/E	6 cases	7 cases	
LT C/S	4 cases	3 cases	

* No statistical difference.

Neonatal characteristics are shown in Table V. No differences were found between the birth weights, Apgar scores of the group I and group II.

None of the patients and their newborns demonstrated either symptomatic hypermagnesemia or hypocalcemia during the study period. No patient had convulsions while receiving either regimen of magnesium sulfate.

Comment

Magnesium sulfate is the drug of choice in Thailand for the prevention and treatment of convolsions in severe preeclampsia and eclampsia. There is considerable controversy regarding the recommended regimen of magnesium sulfate used and the therapeutic level of magnesium needed to prevent convulsions. [4] Although there is no single accepted therapeutic level of magnesium, Pritchard[1] suggests a level of 4.8 to 8.4 mg/dl (4-7 mEq/L) and 4.2 to 7.2 mg/dl to be sattisfactory for patients with severe and mild preeclampsia, reapectively. On the other hand, Cruikshank et al.[5] suggest that the therapeutic levels of magnesium may be lower than those recommended by Pritchard.

There are several reports describing the kinetics of parenteral magnesium sulfate and serum mahnesium levels achieved with use of the intravenous mode[4,5,8,9] of administration. However, there is little to no information comparing the serum magnesium levels achieved by using the intravenous mode of administration with a maintenance dose of 1 gm/hr and 2 gm/hr in Thailand. This study compares the two regimens of intravenous magnesium sulfate admimistration.

The intravenous regimen with a maintenance dose of 1 gm/hr produced serum magnesium levels that were much lower than those acheived with the maintenance dose of 2 gm/hr. When a maintenance dose 1 gm/hr or 2 gm/hr was used, 6.67% and 98.33% of the respective values were in the therapeutic levels as considered by several authors. In considering the maternal serum magnesium levels achieved using the intravenous regimen with a maintenance dose of 1 gm/hr, it seems that such a regimen is not adequate for therapeutic purposes.

The significance of this study can only be appreciated if other clinical factors are considered. Sibai et al.[4] measured magnesium levels in 13 patients who developed convulsions while receiving continuous intravenous magnesium sulfate. Eleven of the 13 patients had serum magnesium levels of (4.8 mg/dl and most of them were receiving a maintenance dose of 1 gm/hr. Similar experience was reported by Goodlin et al.[10] However, occasionally a patient might develop convulsions with serum magnesium levels in therapeutic range (4.8 to 8.4 mg/dl or 4 to 7 mEq/L).[4] Another clinical factor to consider is magnesium toxicity. Winkler et al.[11] observed that the loss of patellar reflexes occured at magnesium levels of 8.4 to 12 mg/dl (7 to 10 mEq/L) and respiratory depression began at levels of 12 to 14.4 mg/dl (10 to 12 meq/L). All the serum magnesium levels obtained in this study were less than 8.4 mg/dl.

The ideal magnesium level would be one that avoids low levels at which convulsions are more prevalent and avoids very high levels that may place both mother and fetus at risk for magnesium toxicity. This ideal level

is obtained with the intravenous regimen of 2 mg/hr as maintenance dose.

Magnesium ions cross the placenta readily and are known to cause hypermagnesemia in the neonate.[12] Although some investigators have found that fetal/ newborn levels exceed maternal levels,[13] others have shown that neonatal magnesium levels are proportionate to the increase in maternal magnesium levels.[14-15] This study has found that cord blood levels exceed maternal levels.

Magnesium is intimately involved with calcium homeostasis. Hypermagnesemia depresses serum calcim levels, and some have suggested that this is due to interference with the synthesis or release of parathyroid hormone.[17] Maternal hypocalcemia following therapy with magnesium sulfate has ben described.[18]

Magnesium ions cross the placenta[12] and an apparent depression in serum calcium has been reported in fetuses of mothers treated with magnesium sulfate.[19] While some adverse effects on the offspring of these patients have been reported,[20] their occurence is quite rare.[21]

This study fails to demonstrate and deleterious effect of magnesium on the newborn infant when maintenance infusions of 1 and 2 gm/hr follow a 5 gm loading dose.

Finally, our findings reveal that the intravenous regimen with a maintenance dose of 1 gm/hr produces serum magnesiumm levels much lower than those acheived with the maintenance dose of 2 gm/hr. When maintenance doses of 1 gm/hr or 2 gm/hr were used, 6.67 and 98.33% of the respective values were in the therapeutic levels considered by several authors. Both methods are safe. Larger randomized therapeutic trials are required to compare the efficacy of both regimens.

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