

# Maternal Bodyweight and Magnesium Sulfate Levels in Preeclampsia

Metha Songthamwat MD<sup>1</sup>, Sunanthaporn Phaiphan MD<sup>1</sup>, Srisuda Songthamwat MD<sup>1</sup>

<sup>1</sup> Department of Obstetrics and Gynecology, Udonthani Hospital, Udonthani, Thailand

**Objective:** To determine the effect of maternal body weight (BW) to the serum level of Magnesium sulfate (MgSO<sub>4</sub>) in preeclampsia and define the optimum maintenance doses in different maternal weight groups.

**Materials and Methods:** A cross sectional study of preeclampsia patients who were treated by MgSO<sub>4</sub>. The percentages of subtherapeutic level of Mg in the first four hours and the optimum maintenance dosage, which achieved the therapeutic level, were compared in different BW groups.

**Results:** Four hundred seventy patients were included in this study. According to BW, 45.6% of the group with BW of less than 60 kg achieved therapeutic level in the first four hours, compared with 23.8% of the group with BW 60 to 79.9 kg, 14.9% of the group with BW 80 to 99.9 kg, and 0% of the group with BW of 100 kg or more ( $p < 0.05$ ). After adjusting the maintenance dose of MgSO<sub>4</sub>, the optimum maintenance dosages were 1.11±0.19 g/hour in BW of less than 60 kg group, 1.28±0.34 g/hour in 60 to 79.9 kg group, 1.35±0.39 g/hour in 80 to 99.9 kg group, and 1.43±0.44 g/hour in 100 kg or more group ( $p < 0.05$ ).

**Conclusion:** The higher maternal BW causes the lower serum Mg level in preeclamptic patients who were treated with MgSO<sub>4</sub>. From the present study, the optimum maintenance dose was suggested for each weight group. However, the effectiveness of this protocol needs further evaluation.

**Keywords:** Preeclampsia, Eclampsia, Pharmacology, Labor management, Magnesium sulfate

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The hypertensive disorders of pregnancy, including gestational hypertension and preeclampsia, remain leading causes of maternal and perinatal mortality and morbidity<sup>(1,2)</sup>, and affect 5% to 10% of all pregnancies<sup>(3,4)</sup>. The World Health Organization (WHO) systematically reviews maternal mortality worldwide. They reported that 16% of maternal deaths were due to hypertensive disorders<sup>(5)</sup>.

Preeclampsia is a major complication of pregnancy. It is a disorder of the placenta with multisystem involvement that leads to severe maternal morbidity and mortality from associated renal, hematological, hepatic, and cerebral impairment with oliguria, hemolysis, and eclamptic fits<sup>(3)</sup>. Eclampsia is defined as the occurrence of one or more convulsions superimposed on pre-eclampsia. In developed countries eclampsia is rare, affecting approximately one in 2,000 deliveries<sup>(6)</sup>, while in developing countries estimates vary from one in 100 to one in 1,700 deliveries<sup>(7,8)</sup>.

The risk factors associated with preeclampsia

include obesity, multifetal gestation, maternal age, hyperhomocysteinemia, and metabolic syndrome<sup>(9-11)</sup>. The maternal weight is an important and progressive risk. The risk increases from 4.3% for women with a body mass index (BMI) of less than 20 kg/m<sup>2</sup> to 13.3% in those with a BMI greater than 35 kg/m<sup>2</sup><sup>(12)</sup>. Obesity has also been linked to the development of gestational hypertensive disorder<sup>(13)</sup>.

Magnesium sulfate (MgSO<sub>4</sub>) is the agent most commonly used for prophylaxis and treatment of eclampsia in preeclamptic patients<sup>(14)</sup>. It is quite safe for the mother and fetus, used as an anticonvulsant in preeclampsia with severe feature and eclampsia reducing maternal morbidity and mortality and cost of care<sup>(15)</sup>. For eclamptic seizure prophylaxis in preeclamptic women, MgSO<sub>4</sub> is superior to phenytoin, nimodipine, diazepam, and placebo<sup>(16-20)</sup>. MgSO<sub>4</sub> reduced recurrent seizures of eclamptic women by 52% when compared to diazepam and by 67% when compared to phenytoin<sup>(21)</sup>.

To avoid MgSO<sub>4</sub> toxicity, the serum Mg level should be followed in all cases. An acceptable therapeutic level of serum Mg of between 4.8 to 8.4 mg/dl has been used<sup>(22)</sup>. The maternal body weight is also a significant factor that affects the serum Mg

**Correspondence to:**

Songthamwat M. Department of Obstetrics and Gynecology, Udonthani Hospital, Udonthani 41000, Thailand.

**Phone:** +66-81-5451499, **Fax:** +66-42-247711

**Email:** [udonhome@yahoo.com](mailto:udonhome@yahoo.com)

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level<sup>(23)</sup>. However, the recommended dosage of MgSO<sub>4</sub> in standard regimens such as Pritchard<sup>(24)</sup> or Zuspan regimen<sup>(25)</sup> are for all maternal body weight. It is not weight adjusted, thus, the proper practical dose should be studied.

Therefore, the objective of the present study was to study the effect of maternal weight to serum Mg level and the proportion of subtherapeutic level of MgSO<sub>4</sub> in different maternal weight groups. The present study used the Zuspan protocol<sup>(25)</sup> with a starting dose of 4 g of MgSO<sub>4</sub> intravenous loading, then a maintenance dose of 1 g per hour in the preeclamptic patients with severe features. The optimum maintenance dose of MgSO<sub>4</sub> that achieved serum therapeutic level in different maternal weight groups during the course of therapy was also studied.

## Materials and Methods

### Study design

The present study was a cross-sectional study. The medical records of preeclamptic patients with severe features, who delivered in Udonthani Hospital between April 2013 and April 2016, were reviewed. The preeclampsia was diagnosed using the criteria of blood pressure more than or at least 140 mmHg, or a diastolic BP of at least 90 mmHg on at least two occasions, measured at least four hours apart, plus new-onset proteinuria or a severe feature<sup>(22)</sup>.

The criteria of severe feature were defined as the patients who had one of the following: elevated blood pressure (systolic blood pressure of 160 mmHg or more, or diastolic blood pressure of 110 mmHg or more), elevated creatinine level (more than 1.1 mg per dL or two times of baseline or more), hepatic dysfunction (transaminase levels two times of upper limit or more of normal), right upper-quadrant or epigastric pain, new-onset headache or visual disturbances, platelet count of less than 100×10<sup>3</sup> per μL (100×10<sup>9</sup> per L), or pulmonary edema<sup>(26)</sup>.

The protocol of MgSO<sub>4</sub> treatment was 4 g of intravenous loading dose followed by an infusion of 1 g/hour initially. Serum MgSO<sub>4</sub> was monitored every four hours after the loading dose and the dosage of MgSO<sub>4</sub> was titrated according to maternal serum Mg until achieving the serum therapeutic levels (4.8 to 8.4 mg/dL). If a serum Mg level was less than 4.8 mg/dL, it was considered to be subtherapeutic, and if the serum Mg level was more than 8.4 mg/dL, it was considered to be suprathreshold. The dosage of MgSO<sub>4</sub> that achieved serum therapeutic level of Mg was defined as the optimum maintenance dose.

All patients were monitored for MgSO<sub>4</sub> toxicity, which was indicated by the loss of reflexes, drowsiness, poor urine output, and high serum Mg level. The treatment for toxicity was an antidote in the form of infusion of 10 ml of 10% calcium gluconate<sup>(15)</sup>. The termination of pregnancy was done according to the obstetrics indication. MgSO<sub>4</sub> was continued until 24 hours after delivery. Serum Mg was monitored until MgSO<sub>4</sub> was discontinued.

Serum Mg level was measured by the Arsenazo method and creatinine was measured by the enzymatic method, then was used to calculate the glomerular filtration rate (GFR) using the CKD-EPI GFR calculator program. Both tests were done using an ARCHITECT clinical chemistry analyzer, model C1600 (ABBOTT company).

The exclusion criteria consisted of pregnant women who delivered at gestational age less than 24 weeks, received MgSO<sub>4</sub> in other regimens, and cases without the serum Mg level recorded.

The demographic data, including age, gestational age (GA), gravity (G), parity (P), body weight (BW), blood pressure (BP), mean arterial pressure (MAP), height (Ht), body mass index (BMI), and glomerular filtration rate (GFR), were reviewed. The BMI was calculated from the BW and Ht (BW in kg divided by the square of the Ht in m<sup>2</sup>).

Patients were classified into four groups according to their maternal BW: less than 60 kg, 60 kg to less than 79.9 kg, 80 kg to less than 99.9 kg, and equal to or greater than 100 kg.

The sample size calculation used the estimated proportion of achieved therapeutic level from a previous study<sup>(27)</sup>, which was 0.45, with an acceptable error of 0.045. An alpha error is 0.05 and power is 80%. Therefore, the number of subjects by calculation was 470 subjects.

### Statistical analysis

The patients' demographic data were presented as number and percentage for all categorical variables. Continuous variables were summarized by the mean, standard deviation, and range (minimum and maximum).

A crude analysis was performed to determine the effect of maternal weight and other clinical characteristics on subtherapeutic level of MgSO<sub>4</sub>. Binary logistic regression analysis was used to estimate the crude odds ratios (OR<sub>crude</sub>) with their 95% confidence intervals (CIs). Multivariable logistic regression analysis was performed to adjust the

effect of other covariate factors with subtherapeutic level of MgSO<sub>4</sub>. All analyses were performed using the statistical program Stata (version 13, StataCorp, College Station, Texas). The significant level was set as *p*-value smaller than 0.05 and all statistical tests were two-sided.

### Ethical consideration

The present study was conducted according to the principles of the Good Clinical Practice (Chapter 2 of the International Conference of Harmonized Tripartite Guideline for Good Clinical Practice), the declaration of Helsinki, and national laws and regulations about clinical studies. The study protocol was approved by the Udonthani Hospital Ethics Committee.

### Results

Between April 2013 and April 2016, 470 pregnant women composed of 458 patients with preeclampsia with severe features and 12 eclamptic patients were included in the present study. After MgSO<sub>4</sub> treatment, two patients (0.4%) with subtherapeutic serum Mg level had eclampsia during treatment.

The mean maternal age was 27.8±7.7 years, mean BMI was 30.4±5.2 kg/m<sup>2</sup>, and mean GA was 36.4±3.0 weeks. The mean serum Mg level at four hours was

4.2±0.8 mg/dL, at eight hours was 4.4±0.8 mg/dL, and at 12 hours was 4.7±0.7 mg/dL.

Using the intravenous MgSO<sub>4</sub> protocol, the present study found that 365 pregnant women (77.6%) had a subtherapeutic level of serum Mg at four hours after treatment. The baseline characteristics of subtherapeutic and therapeutic groups are presented in Table 1.

The factors that might affect the subtherapeutic serum magnesium level are shown in Table 2. The binary logistic regression analysis showed maternal BW was statistically significant correlated with subtherapeutic level of MgSO<sub>4</sub>. Age, gravida, parity, gestation age, Ht, and GFR had no significant correlation. Because BMI is the ratio of BW/Ht<sup>2</sup> and Ht had no significant correlation with the subtherapeutic level of MgSO<sub>4</sub>, the authors used only the maternal BW without BMI in multiple logistic regression analysis to avoid the multicollinearity problem. The analysis result showed that maternal weight was the only factor that correlated with subtherapeutic level of MgSO<sub>4</sub>. The adjusted odd ratio was 1.05 (95% CI 1.03 to 1.07) for each 1 kg of increasing maternal BW and the risk of subtherapeutic level of MgSO<sub>4</sub> increased by 64.1% for each 10 kg of increase in maternal BW (adjusted OR 1.64, 95% CI 1.36 to 1.98).

**Table 1.** Baseline characteristics

Characteristics	Total	Subtherapeutic group (n = 365) Mean ± SD	Therapeutic group (n = 105) Mean ± SD	<i>p</i> -value
Age (year)	470	28.0±7.7	27.1±7.8	0.26
Gravida	470	2.0±1.1	1.9±1.1	0.49
Parity	470	0.7±0.9	0.7±0.9	0.65
Gestation age (weeks)	470	36.5±2.9	35.9±3.4	0.06
Body weight (kg)	470	77.4±15.1	68.7±10.9	<0.01
Height (cm)	470	157.4±6.1	156.8±5.7	0.37
MAP	470	126.5±9.3	126.6±11.1	0.93
GFR	470	123.6±17.1	120.5±22.2	0.12

SD = standard deviation; MAP = mean arterial pressure; GFR = glomerular filtration rate

**Table 2.** Factors which might influences subtherapeutic level of MgSO<sub>4</sub>

Factors	Subtherapeutic group Mean ± SD	Therapeutic group Mean ± SD	OR (95% CI)	Adjusted OR (95% CI)	<i>p</i> -value
Bodyweight (kg)	77.4±15.1	68.7±10.9	1.05 (1.03 to 1.07)	1.06 (1.04 to 1.08)	<0.01
Age (year)	28.0±7.7	27.1±7.8	1.02 (0.99 to 1.05)	1.01 (0.97 to 1.06)	0.52
Gravida	2.0±1.12	1.9±1.1	1.07 (0.88 to 1.31)	1.02 (0.65 to 1.60)	0.93
Parity	0.7±0.9	0.7±0.9	1.06 (0.83 to 1.34)	0.93 (0.56 to 1.56)	0.79
GA (weeks)	36.5±2.9	35.9±3.4	1.07 (1.00 to 1.14)	1.03 (0.96 to 1.11)	0.45
Height (cm)	157.4±6.1	156.8±5.7	1.01 (0.98 to 1.05)	0.96 (0.92 to 1.00)	0.06
MAP	126.5±9.3	126.6±11.1	1.00 (0.98 to 1.02)	1.01 (0.98 to 1.03)	0.67
GFR	123.6±17	120.5±22.2	1.01 (1.00 to 1.02)	1.01 (1.00 to 1.02)	0.25

SD = standard deviation; OR = odds ratio; CI = confidence interval; GA = gestational age; MAP = mean arterial pressure; GFR = glomerular filtration rate

**Table 3.** Percentage of achieved therapeutic level in different BW group

BW group	Total	Subtherapeutic group (n = 365) n (%)	Therapeutic group (n = 105) n (%)	p-value
<60 kg	57	31 (54.4)	26 (45.6)	-
60 to ≤79.9 kg	248	189 (76.2)	59 (23.8)	<0.01
80 to ≤99.9 kg	134	114 (85.1)	20 (14.9)	<0.01
≥100 kg	31	31 (100)	0 (0.0)	NA

BW = body weight

Based on the maternal BW, the authors found 45.6% of BW of less than 60 kg group achieved therapeutic level in first four hours compared with 23.8% of BW 60 to 79.9 kg group, 14.9% of BW 80 to 99.9 kg group, and 0% of BW of 100 kg or more group ( $p<0.01$ ) (Table 3).

The dosage of MgSO<sub>4</sub> was adjusted according to the serum Mg level. The authors found that the optimum maintenance dosages of MgSO<sub>4</sub> that achieved the therapeutic level (4.8 to 8.4 mg/dl) were 1.11±0.19 g/hour in the BW of less than 60 kg group, 1.28±0.34 g/hour in the BW 60 to 79.9 kg group, 1.35±0.39 g/hour in the BW 80 to 99.9 kg group, and 1.43±0.44 g/hour in the BW of 100 kg or more group ( $p<0.05$ ). The regression analysis showed that the optimum maintenance dose increased 0.07 g/hour for every ten kg of increasing maternal weight.

## Discussion

MgSO<sub>4</sub> is an effective treatment option for the prevention of eclampsia<sup>(28)</sup>. It can reduce the risk of eclampsia from 1.9% to 0.8%<sup>(20)</sup>. The therapeutic level of MgSO<sub>4</sub> is still questionable<sup>(29)</sup>, however the range of 4.8 to 8.4 mg/dL has been accepted by many centers for the monitoring of this drug. The data showed that the intravenous regimen of MgSO<sub>4</sub>, using 4g loading dose and a maintenance dose starting at 1g per hour, achieved serum therapeutic level at the first four hours in only 22.4% of the patients. This incidence was less than the previous studies<sup>(23,30)</sup>.

From the present study, the effect of maternal BW with the subtherapeutic level of MgSO<sub>4</sub> was demonstrated. Overweight patients have more prevalence of subtherapeutic serum magnesium levels than underweight and normal weight patients. These are the same finding as in other studies<sup>(20,31)</sup>, which studied the association of BMI with the serum MgSO<sub>4</sub> level. The present study used the maternal BW instead of BMI, because the implementation of BMI in the adjustment of dosage of drug is unpractical. Most drugs' adjustment is based on bodyweight such as mg per kg or g per kg. Some drugs (i.e., chemotherapy)

are based on body surface area. Therefore, the authors expected that MgSO<sub>4</sub> dosage should be weight-adjusted or body surface area-adjusted. In the present study, the authors found that the height was not associated with the serum MgSO<sub>4</sub> level, so the association of BMI with the serum MgSO<sub>4</sub> might be from the effect of BW and the adjustment of dosage of MgSO<sub>4</sub> should be weight-adjusted.

After adjusting the dosage of MgSO<sub>4</sub>, the authors determined the mean optimum maintenance dose that achieved the serum therapeutic level. The multivariable logistic regression analysis showed the optimum maintenance was increased by 0.07 g per hour for every 10 kg of increasing maternal weight. For practical use, the authors classified the maternal bodyweight into four groups and the mean optimum maintenance doses in each group were: 1.11 g per hour for maternal BW of less than 60 kg, 1.28 g per hour for maternal BW 60 to 79.9 kg, 1.35 g per hour for maternal BW 80 to 99.9 kg and 1.43 g per hour for maternal BW of 100 kg or more. The authors recommend this dosage for the initial maintenance dose after loading of MgSO<sub>4</sub>. However, the serum Mg should be monitored and the dosage of MgSO<sub>4</sub> should be adjusted until the serum therapeutic level is reached.

The limitation of the present study is the use of serum therapeutic level of MgSO<sub>4</sub> as the primary outcome. The objective of MgSO<sub>4</sub> treatment is the prevention of convulsion, however the incidence of convulsion after treatment is small<sup>(20)</sup>. In the present study, only two cases had convulsion after treatment. A larger sample size is needed to demonstrate the effect of weight related of therapeutic result of MgSO<sub>4</sub> treatment. Additionally, the effect of weight-adjusted maintenance dose of MgSO<sub>4</sub> in the prevention of convulsion still needs further evaluation.

## Conclusion

The higher maternal BW causes the lower serum Mg level in preeclamptic patients treated by MgSO<sub>4</sub>. From the present study, the optimum maintenance dose was suggested for each weight group. However,

the effectiveness of this protocol needs further evaluation.

### What is already known on this topic?

MgSO<sub>4</sub> is an anticonvulsant in preeclampsia with severe feature and eclampsia. A commonly used protocol of MgSO<sub>4</sub> treatment was 4 g of intravenous loading dose followed by an infusion of 1 g/hour initially and the dosage of MgSO<sub>4</sub> was titrated according to maternal serum Mg until achieving the serum therapeutic levels (4.8 to 8.4 mg/dL).

### What this study adds?

This research studied the prevalence of subtherapeutic serum Mg level in preeclamptic women and suggested the weight-adjusted maintenance dose in different weight groups. The 4 g of intravenous loading dose followed by maintenance dose of 1 g/hour protocol had high proportion of subtherapeutic level of MgSO<sub>4</sub>, especially for overweight patients.

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### Author contribution

All authors had been involved in the intellectual content, design, analysis and interpretation of the data, as well as the writing of the manuscript.

### Disclosure

No author has any potential conflict of interest. However, this paper was presented at the 25th Asian and Oceanic Congress of Obstetrics and Gynaecology (AOCOG) held at the Hong Kong Convention and Exhibition Centre on 15 to 18 June 2017 as an oral presentation. The abstract was published in "Oral presentation abstracts" in the Journal of Obstetrics and Gynaecology Research, Volume 43, Issue Supplement S1, June 2017 (J. Obstet. Gynaecol. Res. Vol. 43, No. S1: 56 to 82, June 2017).

### Potential conflicts of interest

The authors declare no conflict of interest.

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