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ORIGINAL ARTICLE

A retrospective review of on-admission factors on attainment of therapeutic serum concentrations of magnesium sulfate in women treated for a diagnosis of preeclampsia

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ABSTRACT

Introduction: There is little information on the effect of maternal characteristics and on-admission laboratory parameters to the therapeutic serum magnesium sulfate ($MgSO_4$) levels in women with preeclampsia (PE). We sought to identify factors that may predict timely attainment of therapeutic serum magnesium levels after intravenous administration for seizure prophylaxis.

Materials and methods: On-admission factors of 360 women with PE who received intravenous $MgSO_4$ (4-g loading and 2-g/h maintenance) for seizure prophylaxis were retrospectively reviewed. Parameters of those who attained therapeutic serum concentrations (4.8–8.4 mg/dL) within 2 h (Group A) and those who did not (Group B) were compared.

Results: There was no seizure or magnesium toxicity in this cohort. Median (min–max) level of serum magnesium was 4.3 (2.5–8.4) mg/dL. Women in Group A ($n = 105$) had lower gestational age, body mass index (BMI), and platelets count, higher blood urea nitrogen (BUN), serum creatinine, uric acid, direct bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, prothrombin, and partial thromboplastin times than those in Group B ($n = 255$) ($p < .05$). Women with mild PE were less likely to attain therapeutic serum magnesium levels compared with those with severe phenotypes (adjusted OR 23.57, 95% CI 8.20–67.76 versus adjusted OR 14.72, 95% CI 3.56–60.89, respectively; $p < .05$), which may be explained by their significantly lower serum BUN and uric acid ($p < .05$).

Conclusions: On-admission factors, especially BMI and renal clearance indices, of women with PE may affect timely attainment of therapeutic serum magnesium levels. Validation of its clinical impact requires further study focusing on women with severe PE.

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Introduction

Magnesium sulfate ($MgSO_4$) has been used to control seizure in preeclampsia (PE) [1,2]. Optimal control of convulsions is thought to be most effective with "therapeutic" serum magnesium level at 4.8–8.4 mg/dL (4–7 mEq/L) [3]. Intramuscular and intravenous regimens have comparable efficacy, but the minimum effective dose for eclampsia prevention and treatment remains elusive [4]. Subtherapeutic serum magnesium level may increase the risk for eclamptic seizures [5]. In contrast, $MgSO_4$ overdosage may have serious toxicities, including respiratory depression and arrest [6]. There is little information on the effects of clinical and laboratory parameters on serum levels of $MgSO_4$. We sought to identify factors that may predict timely (≤ 2 h) attainment of therapeutic serum magnesium levels after intravenous administration for seizure prophylaxis.

Materials and methods

Study population

The study protocol was approved by Institutional Review Board of Faculty of Medicine Siriraj Hospital (849/2557 (EC3)). This was a retrospective analysis of electronic medical records of all women with PE who presented to our institution for delivery and received intravenous $MgSO_4$ for seizure prophylaxis from January 2013 to December 2014. Our institutional protocol was a modification from the American

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College of Obstetricians and Gynecologists and the National High Blood Pressure Education Program Working Group [7,8]. The inclusion criterion was singleton pregnancy. We excluded data from multifetal pregnancies. Diagnosis of PE consisted of *de novo* hypertension after 20 weeks of gestation, with proteinuria or laboratory changes [9]. Hypertension was defined as blood pressure $\geq$140/90 mmHg measured with the automated machine (SureSigns VM4; Philips Corporation, Andover, MA). Proteinuria was described as 30 mg/dL (1 + dipstick) of protein from on-admission urine samples. PE was considered severe when there are one or more of the followings: (1) persistent severe systolic ($\geq$160 mmHg) or diastolic ($\geq$110 mm Hg) hypertension, (2) persistent severe headache, (3) visual disturbances, and (4) elevated serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels with epigastric or right upper-quadrant pain. Superimposed PE was defined as the development of PE in a patient with chronic hypertension; a rise in the systolic pressure of $\geq$30 mmHg or a rise in the diastolic pressure of $\geq$15 mmHg and the development of proteinuria, or both. Eclampsia is the seizure that cannot be attributed to other causes in women with PE [7,8,10].

Until December 2014 we gave $MgSO_4$ to all women with PE. For severe PE, $MgSO_4$ was given once the diagnosis is made and continued until at least 24 h after delivery. For mild PE, $MgSO_4$ was given once the patient is in active labor and continued until at least 12 h after delivery. We are aware that $MgSO_4$ has been recommended internationally as the first-line drug for treatment of severe PE and eclampsia, but not mild PE [11]. The rationale for administration of $MgSO_4$ in women with mild PE includes: (1) there is an equivocal evidence of fetal neuroprotection benefit from $MgSO_4$ administered in women with mild PE at term [12], (2) although $MgSO_4$ does not have a major impact on disease progression in women with mild PE; there is evidence from a randomized controlled trial that abbreviated postpartum $MgSO_4$ therapy (for 12 h) can prevent transformation of mild PE to severe PE [13,14], (3) $MgSO_4$ use does not seem to increase rates of cesarean delivery, infectious morbidity, obstetric hemorrhage, or neonatal depression [15,16], (4) Our 24-h availability and rapid turnaround time of automated $MgSO_4$ quantitation, and (5) although the large magpie trial showed that $MgSO_4$ reduced the risk of eclampsia in women with severe PE, but it did not address mild PE [2]. Even in the USA, the use of $MgSO_4$ in women with PE remains varied from one center to the others [17]. A recent multicountry survey showed the $MgSO_4$ was used for the treatment of mild PE in 24.3% of 147 health facilities in 15 countries across Africa, Latin America, and Asia [18].

Intravenous administration of $MgSO_4$

Our protocol for intravenous administration of $MgSO_4$ was a modification of Zuspan regimen [19]. The diagnostic criteria for PE were documented at the time of order for the infusion. A 4-g intravenous loading dose (20 mL of 20% $MgSO_4$ solution) was administered over 10 min using an infusion pump (Terufusion infusion pump TE-171; Terumo Corporation, Tokyo, Japan), followed by an infusion of 2 g/h (50 mL/h for 80 mL of 50% $MgSO_4$ solution (40 g) in 920 mL of 5% dextrose in water: robotic IV preparation). We chose this regimen because (1) it is the most commonly used regimen in the USA [20], and (2) data from Thai women showed an inadequacy 1-g/h compared with 2-g/h maintenance dose [21]. Serum magnesium levels were measured at 2 h after $MgSO_4$ administration so that the infusion rate of $MgSO_4$ could be adjusted. The intravenous infusion rate of $MgSO_4$ was then adjusted accordingly, and serum $MgSO_4$ level was measured again at 2 h after adjustment, until therapeutic serum level was achieved. Severe hypertension was promptly managed with either intravenous administration of labetalol or hydralazine [22].

Measurement of magnesium level in the serum

Four milliliters of venous blood sample was collected into serum separator tubes (Becton Dickinson, Rutherford, NJ). They were centrifuged at 3000 rpm for 5 min within 30 min of collection. We used Colorimetric Assay (Xylidyl Blue-I method) on an automated electrolyte analyzer c701/Cobas 8000 platform from Roche Diagnostics (Minneapolis, MN) to measure total magnesium, and serum magnesium concentrations of 4.8–8.4 mg/dL were considered therapeutic for seizure prophylaxis [23].

Selected on-admission maternal characteristics extracted from the electronic database for analysis included maternal age (year), parity, gestational age (weeks), body mass index (BMI; kg/m^2), risk factors, and severity of PE. Routine PE admission tests include complete blood count (with platelets count), prothrombin time (PT), partial thromboplastin time (PTT), blood urea nitrogen (BUN), creatinine, uric acid, total and direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lactate dehydrogenase (LDH). For this study, we compared the parameters from patients who did (Group A) and did not (Group B) attain therapeutic serum level magnesium within 2 h after initiation of treatment were compared. We also sought to identify comorbidities and complications of delivery that place women at risk for subtherapeutic and supratherapeutic magnesium levels.

Statistical analysis

Data were analyzed with PASW Statistics for Windows version 18.0 (SPSS Inc, Chicago, IL). On-admission factors, including maternal characteristics and laboratory parameters, were expressed as number (%), mean ± SD, or median (minimum–maximum). Independent *t*-test, one-way analysis of variance (ANOVA), and Kruskal–Wallis test were used for analysis of distributed quantitative variables, of which statistical significance was considered for p value $<.05$.

Results

Three hundred and sixty women with PE who received an intravenous infusion of $MgSO_4$ for seizure prophylaxis were identified during the study period. Among these, 38 (10.6%), 54 (15%), and 268 (74.4%) women were diagnosed with mild, superimposed, and severe PE, respectively. Approximately 68% of women with PE in this cohort had preexisting risk factors for the disease. There was no seizure or serious iatrogenic $MgSO_4$ toxicity (respiratory depression and arrest) in this cohort. Maternal characteristics, obstetric outcomes, and on-admission laboratory characteristics of women with PE in this cohort are shown in are shown in Table 1, with cutoff values provided in Appendix. There were 185 (51.4%) women who had normal serum uric acid levels, and 175 women (48.6%) who had abnormal serum uric acid levels in this cohort, as shown in Table 2.

Median (min–max) serum concentrations of $MgSO_4$ after 2 h of intravenous infusion were 4.3 (2.5–8.4) mg/dL. There were 105 (29.2%) and 255 (70.8%) women who did (Group A) and did not (Group B) attain therapeutic serum $MgSO_4$ levels, respectively. Comparison of maternal factors and on-admission laboratory parameters between patients who did and did not attain therapeutic serum $MgSO_4$ levels are shown in Table 2. The prepregnancy BMIs (mean ± SD) of women in Group A and Group B were 20.1 ± 3.1 versus 25.9 ± 6.0 kg/m^2, and the on-admission BMIs (mean ± SD) of women in Group A and Group B were 25.6 ± 3.3 versus 32.5 ± 6.3, respectively ($p < .05$). Prepregnancy and on-admission BMIs of women in Group A were significantly lower than those of women in Group B, with p value $<.05$.

Table 1. Characteristics of maternal factors ($n = 360$) and their characteristics of on-admission laboratory parameters.

Characteristics	Mean ± SD (Min–Max)
Maternal age (years)	30.0 ± 6.6 (16–48)
Gestational age (weeks)	36.6 ± 2.6 (24–41)
BMI (kg/m^2)	**Mean ± SD (Min–Max)**
Before pregnancy	24.2 ± 6.0 (14.0–49.4)
On admission	30.5 ± 6.4 (18.4–59.3)
Parity	**Number (%)**
Nulliparous	240 (66.7)
Multiparous	120 (33.3)
Gestational age (weeks)	**Number (%)**
<34	47 (13.0)
34–36	92 (25.6)
≥37	221 (61.4)
Prepregnancy BMI (kg/m^2) [24,25]	**Number (%)**
Underweight (<18.5)	44 (12.2)
Normal weight (18.5–24.9)	184 (51.1)
Over weight (25.0–29.9)	71 (19.7)
Obese (≥ 30.0)	61 (17.0)
Risk factors for PE	**Number (%)**
No	114 (31.7)
Preeclampsia symptoms (i.e. headache, visual disturbances, or epigastric pain)	26 (7.2)
Hydrops fetalis	3 (0.8)
Weight gain ≥1 kg/wk	138 (38.3)
History of preeclampsia in previous pregnancies	42 (11.7)
Chronic hypertension	59 (16.4)
History of autoimmune diseases	5 (1.4)
History of renal disorders	2 (0.6)
Gestational or overt diabetes mellitus	71 (19.7)
Diagnosis	**Number (%)**
Mild PE	38 (10.6)
Superimposed PE	54 (15.0)
Severe PE	268 (74.4)
Type of delivery	**Number (%)**
Vaginal delivery	108 (30.0)
Cesarean section	252 (70.0)
Birth weight (g) (mean ± SD) (Min–Max)	2,579.9 ± 739.0 (720–4980)
Birth weight category	**Number (%)**
Very low birth weight (<1500 g)	29 (8.0)
Low birth weight (1500–2499 g)	128 (35.6)
Normal birth weight (2500–4000 g)	202 (56.4)
High birth weight (>4000 g)	1 (0)
Laboratory parameters	**Mean ± SD**
Hemoglobin (g/dL)	12.4 ± 1.4
Hematocrit (%)	37.3 ± 3.9
Platelets count (/mL)	235,988.9 ± 78,713.8
PT (s)	11.4 ± 0.9
Partial thromboplastin time (s)	26.6 ± 2.6
BUN (mg/dL)	10.1 ± 4.3
Creatinine (mg/dL)	0.7 ± 0.2
Uric acid (mg/dL)	6.4 ± 1.7
Total bilirubin (mg/dL)	0.4 ± 0.5
Direct bilirubin (mg/dL)	0.2 ± 0.3
AST (units/L)	35.3 ± 52.7
ALT (units/L)	29.5 ± 64.5
LDH (mg/dL)	450.4 ± 187.6

SD: standard variation; BMI: body mass index; PE: preeclampsia; g/dL: gram/deciliter; mL: milliliter; PT: prothrombin time; PTT: partial thromboplastin time; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase.

Although most of the variables in Group A and Group B were in normal range; women in Group A had significantly lower gestational age, platelets count, and higher PT, PTT, BUN, serum creatinine, uric acid, direct bilirubin, AST, ALT, and LDH than women in Group B ($p < .05$). The number and percentage (%) for each variable in Group A and B are shown in Table 2.

Table 2. Comparison of parameters between patients who did and did not attain therapeutic serum $MgSO_4$ levels.

	Group A ($n = 105$)	Group B ($n = 255$)	p value
Maternal age [(years) (mean ± SD)]	29.7 ± 7.2	30.2 ± 6.4	.513
Body mass index [(kg/m^2) (mean ± SD)]			
Before pregnancy	20.1 ± 3.1	25.9 ± 6.0	.000*
On admission	25.6 ± 3.3	32.5 ± 6.3	.000*
Gestational age [(weeks) (mean ± SD)]	35.7 ± 3.3	37.0 ± 2.2	.000*
Laboratory parameters (mean ± SD)			
Hemoglobin (g/dL)	12.6 ± 1.6	12.3 ± 1.3	.177
Hematocrit (%)	37.5 ± 4.2	37.2 ± 3.8	.439
Mean corpuscular volume (fL)	82.0 ± 9.3	82.7 ± 8.5	.523
Platelet count (/mL)	219,257.1 ± 90,771.9	242,878.4 ± 72,250.3	.009*
Prothrombin time (s)	11.2 ± 1.0	11.5 ± 0.8	.002*
Partial thromboplastin time (s)	27.6 ± 2.8	26.2 ± 2.4	.000*
Blood urea nitrogen (mg/dL)	12.4 ± 4.8	9.1 ± 3.7	.000*
Creatinine (mg/dL)	0.79 ± 0.22	0.64 ± 0.15	.000*
Uric acid (mg/dL)	7.4 ± 1.7	6.0 ± 1.5	.000*
Total bilirubin (mg/dL)	0.4 ± 0.7	0.3 ± 0.4	.212
Direct bilirubin (mg/dL)	0.2 ± 0.6	0.1 ± 0.1	.018*
Aspartate aminotransferase (units/L)	53.1 ± 80.7	28.0 ± 32.8	.000*
Alanine aminotransferase (units/L)	49.6 ± 103.1	21.2 ± 35.9	.000*
Lactate dehydrogenase (mg/dL)	531.5 ± 247.5	416.9 ± 144.2	.000*
Parity [number (%)]			.806
Nulliparous	71 (29.6)	169 (70.4)	
Multiparous	34 (28.3)	86 (71.7)	
Gestational age weeks [number (%)]			.000*
<34	25 (53.2)	22 (46.8)	
34–36	29 (31.5)	63 (68.5)	
≥37	51 (23.1)	170 (76.9)	
Prepregnancy BMI [number (%)]			.000*
Underweight (<18.5 kg/m^2)	32 (72.7)	12 (27.3)	
Normal weight (18.5–24.9 kg/m^2)	66 (35.9)	118 (64.1)	
Over weight (25–29.9 kg/m^2)	6 (8.4)	65 (91.6)	
Obese (≥30 kg/m^2)	1 (1.6)	60 (98.4)	
Diagnosis [number (%)]			.000*
Mild PE	26 (68.4)	12 (31.6)	
Superimposed PE	8 (14.8)	46 (85.2)	
Severe PE	71 (26.5)	197 (73.5)	
Hemoglobin [number (%)]			.889
Normal	90 (29.0)	220 (71.0)	
High	15 (30.0)	35 (70.0)	
Hematocrit [number (%)]			.786
Normal	92 (28.9)	226 (71.1)	
High	13 (31.0)	29 (69.0)	
MCV [number (%)]			.449
Normal	44 (27.2)	118 (72.8)	
High	61 (30.8)	137 (69.2)	
Platelets count [number (%)]			.007*
Normal	96 (27.8)	249 (72.2)	
High	9 (60.0)	6 (40.0)	
PT [number (%)]			.600
Normal	102 (29.0)	250 (71.0)	
High	3 (37.5)	5 (62.5)	
PTT [number (%)]			.035*
Normal	97 (28.1)	248 (71.9)	
High	8 (53.3)	7 (46.7)	
BUN [number (%)]			.000*
Normal	42 (17.8)	194 (82.2)	
High	63 (50.8)	61 (49.2)	
Creatinine [number (%)]			.000*
Normal	79 (25.0)	237 (75.0)	
High	26 (59.1)	18 (40.9)	
Uric acid [number (%)]			.000*
Normal	29 (15.7)	156 (84.3)	
High	76 (45.0)	99 (55.0)	
Total bilirubin [number (%)]			.421
Normal	102 (28.9)	251 (71.1)	
High	3 (42.9)	4 (57.1)	
Direct bilirubin [number (%)]			.448
Normal	33 (32.0)	70 (68.0)	
High	72 (28.0)	185 (72.0)	

(*continued*)

Table 2. Continued.

	Group A ($n = 105$)	Group B ($n = 255$)	p value
AST [number (%)]			.000*
Normal	88 (26.5)	244 (73.5)	
High	17 (60.7)	11 (39.3)	
ALT [number (%)]			.001*
Normal	92 (27.1)	247 (72.9)	
High	13 (61.9)	8 (38.1)	
LDH			.000*
Normal	78 (25.2)	231 (74.8)	
High	27 (52.9)	24 (47.1)	

Group A serum $MgSO_4$ level $\geq$4.8 mg/dL, Group B serum $MgSO_4$ level <4.8 mg/ dL.
SD: standard deviation; BMI: body mass index; PE: preeclampsia; PT: prothrombin time; PTT: partial thromboplastin time; BUN: blood urea nitrogen; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase.
*Statistically significant at $p < .05$.

Logistic regression analyses showed a tendency for subtherapeutic levels in women with prepregnancy overweight and obesity (adjusted OR 7.22, 95% CI 2.34–22.31, and adjusted OR 115.75, 95% CI 7.67–1747.25, respectively), as shown in Table 3. There was also a tendency for subtherapeutic levels women with mild PE compared to those with severe phenotypes (adjusted OR 23.57, 95% CI 8.20–67.76 versus adjusted OR 14.72, 95% CI 3.56–60.89, respectively; $p < .05$). Women with elevated BUN and uric acid levels were less likely to have subtherapeutic serum $MgSO_4$ levels. We were not able to perform logistic regression analysis for a tendency for supratherapeutic levels as no women in our cohort had supratherapeutic levels. Renal function parameters in mild, superimposed, and severe PE were analyzed, as shown in Table 4. Although most values were in normal range; serum concentrations of BUN and uric acid, but not creatinine, were significantly higher in women with severe PE, compared women with mild and superimposed PE ($p < .05$). It is important to note that 316 (87.8%) women had normal, and only 44 women (12.2%) had abnormal serum creatinine levels (Table 1).

Table 3. Logistic regression analyses to determine independent associated factors of subtherapeutic serum magnesium level.

	Adjusted OR	95% CI	p value
Prepregnancy BMI (kg/m^2)			
Underweight	0.15	0.06–0.37	.000*
Overweight	7.22	2.34–22.31	.001*
Obesity	115.75	7.67–1747.25	.001*
Diagnosis			
Mild PE	23.57	8.20–67.76	.000*
Severe PE	14.72	3.56–60.89	.000*
BUN ($\geq$11 mg/dL)	0.29	0.14–0.62	.001*
Uric acid ($\geq$6.3 mg/dL)	0.34	0.16–0.70	.003*

BMI: body mass index; PE: preeclampsia; OR: odd ratio; CI: confidence interval.
*Statistically significant at $p < .05$.

Discussion

With our intravenous $MgSO_4$ infusion regimen (4 g loading and 2-g/h maintenance), no women in this cohort had supratherapeutic serum concentrations, and approximately one-third of them attained therapeutic serum concentrations. Wide ranges of postinfusion serum $MgSO_4$ concentration (min–max =2.5–8.4 mg/dL) suggests a significant impact from maternal characteristics and renal clearance indices. Timely attainment of therapeutic serum $MgSO_4$ concentrations was associated with lower gestational age, BMIs, and platelets count, and higher BUN, serum creatinine, uric acid, direct bilirubin, AST, ALT, LDH, PT, and PTT. Prepregnancy BMI, BUN, and serum uric acid are a major determination of attainment of therapeutic serum $MgSO_4$ concentration.

Our previous publication did not show an association between BMI and severity of PE or requirement of $MgSO_4$ prophylaxis [26]. Pharmacodynamics of $MgSO_4$ in women with PE may not be identical to its use for other purposes [27]. A previous report showed that BMI of >30 was associated with subtherapeutic $MgSO_4$ serum concentrations, but without significant clinical impact [28,29]. From our cohort, over 90% of women with prepregnancy BMI of $\geq$25 had a subtherapeutic $MgSO_4$ level when measured at 2 h. The association between overweight/obesity and subtherapeutic $MgSO_4$ level from our logistic regression model is consistent with $MgSO_4$ pharmacokinetics. Bone, muscle, and soft tissue buffer $MgSO_4$ to the extent that only 1% of $MgSO_4$ is in the extracellular space. High BMI could affect $MgSO_4$ distribution by: (1) increased ability to buffer intravenously infused $MgSO_4$ (more soft tissue, muscle, bone, and a larger extracellular space), (2) increased blood volume, and (3) higher physiologic volume expansion of pregnancy in overweight/obese women (38.3 and 19.7% of women in our cohort had excessive weight gain and diabetes mellitus, respectively). As BMI is also correlated with gestational age;

Table 4. Serum levels of BUN, creatinine, and uric acids in mild, superimposed, and severe PE.

	Mild PE ($n = 38$)	Superimposed PE ($n = 54$)	Severe PE ($n = 268$)	p value
Median BUN (min–max) (mg/dL)	9.3 (4.5–13.7)	8.4 (3.3–40.3)	9.45 (0.6–43)	<.02*
Median creatinine (min–max) (mg/dL)	0.65 (0.33–1.03)	0.57 (0.39–1.42)	0.66 (0.38–1.82)	.30
Median uric acid (min–max) (mg/dL)	5.85 (3.8–10.6)	5.45 (2.2–10)	6.35 (3.4–13.4)	<.02*

BUN: blood urea nitrogen; PE: preeclampsia.
*Statistical significance between mild PE compared with severe PE ($p < .05$).

the effects from these two parameters to serum $MgSO_4$ levels cannot be clearly differentiated.

The elimination of $MgSO_4$ occurs primarily in the kidneys, and PE-associated renal damages can result in increased serum $MgSO_4$ levels [30,31]. Creatinine is a product of muscle metabolism and the most specific indicator of renal function because it is freely filtered through the glomerulus; whereas urea nitrogen is a less specific indicator of kidney function and is a reflection of ingested protein and muscle catabolism. Levels of urea nitrogen in the blood fluctuate with a number of conditions such as increased protein intake, intestinal bleeding, infection, fever, dehydration, medications, and burns. Our study found an effect of the severity of PE to BUN and serum uric acid on $MgSO_4$ levels; with the reversed association between abnormal BUN/uric acid and subtherapeutic levels. Women with mild disease may have less PE-related blood volume contraction and less renal damages (Table 4), which may explain the inability of women with mild PE to achieve therapeutic serum levels. Our study did not have adequate power to confirm an association between elevated serum creatinine level and supratherapeutic $MgSO_4$ levels; because (1) 87.8% of women in our cohort had normal serum creatinine levels, and (2) there was no supratherapeutic $MgSO_4$ level in our cohort [32]. Serum concentrations of liver enzymes could be confounded by the disease's severity and renal function, and may not directly affect the serum $MgSO_4$ levels.

Since the establishment of intramuscular $MgSO_4$ therapy for PE in 1955, data from many randomized trials could not reach an agreement regarding optimal indication (mild or severe PE), route of administration (intramuscular or intravenous), dosage (loading and maintenance), and duration of $MgSO_4$ therapy [2,15,16,33–44]. The variation of $MgSO_4$ therapy regimens from different trials explains the differences in the rates of seizures and side effects among those assigned to $MgSO_4$. Intravenous regimens, which vary slightly from institution to institution both in the initial load (4 or 6 g) and the infusion rate (1–3 g/h), are titrated to achieve the therapeutic levels of 3.5–7 mEq/L (4.8–8.4 mg/dL) [41]. Although these "therapeutic" levels are widely accepted in practice, they have not been extensively validated in terms of efficacy. Historically, the total dose of $MgSO_4$ used for treating PE was gradually increased from 2 to 54 g/24 h with the belief that this would increase clinical efficacy [36,45,46]. For 4 g loading and 2-g/h infusion protocol, the total dose from our institutional protocol will be 52 g/24 h. The maintenance dose of $MgSO_4$ at 2 g/h was chosen at our institute because it has been repetitively shown to better attain the therapeutic level of serum $MgSO_4$ compared with 1 g/h with no detectable difference in maternal and neonatal outcomes [5,21].

We chose to monitor serum concentrations of $MgSO_4$ at 2 h after the infusion. This time interval is based on a pharmacodynamics study showing that, with our intravenous 4 g loading and 2-g/h maintenance, serum $MgSO_4$ concentration rose rapidly to double the baseline values within 30 min, and reached plateau level at 2–4 h with minimum fluctuation [35,36,39]. At 2 h after administration of this intravenous regimen, serum $MgSO_4$ ranged broadly from 2.5 to 8.4 mg/dL. The absence of seizure even two third of women with PE in our cohort did not attain therapeutic serum $MgSO_4$ levels at 2 h was in agreement with previous studies [47]. Our "seizure-free" dataset may also be from (1) the adjustment of intravenous infusion rate of $MgSO_4$ when initial serum magnesium level was suboptimal, (2) most of the women who could not attain therapeutic level were mild PE, (3) prompt control of blood pressure, (4) commercially available assays do not quantify ionized magnesium, and (5) the mechanism of $MgSO_4$ action in preventing eclamptic seizure remains poorly understood. The widely adopted therapeutic serum $MgSO_4$ levels of 4.8–8.4 mg/dL derived from clinical and laboratory observations in earlier studies rather than standard exposure-response studies [41,45]. Serum concentrations of ionized (free, active) and total magnesium may not be highly correlated. At baseline, the ionized fraction was between 50–64.9% of the total serum magnesium but these fractions appeared to decrease as the serum level approached steady-state levels [38,39,48,49]. We are not able to conclude that the conventional "therapeutic" serum $MgSO_4$ level is not valid, but we suggest that the lower limit for effective prevention and control of eclamptic fits may need to be revisited with a standardized laboratory assay.

The strength of our study was the homogeneity of the data from adherence to the institutional protocol. However, its retrospective nature precluded the best assessment methodology, as suggested by a recent systematic review of the pharmacokinetic profile of $MgSO_4$ published by Okusanya and colleagues [35]. We want to emphasize that our sample size of 360 women with PE enrolled for retrospective analysis of their seizure outcomes is not sufficient to demonstrate clinical impact of $MgSO_4$ on PE. The number needed to treat (NNT) for the magpie trial was 91, so there would be too few cases in this series [6]. With appropriate monitoring, administration of $MgSO_4$ in selected cases of mild PE does not seem to majorly increase maternal or neonatal morbidities [15,50]. Of noted, we did not seek to evaluate neonatal outcomes in this study. The neonatal outcomes from a cohort of women with severe PE from our center in the last decade (which overlapped this cohort) have recently been published, and it showed that neonatal morbidities were more related to the PE and anesthetic methods, and not to the administration of $MgSO_4$ [51]. Because the majority of women in our cohort had on-admission BMI $\leq 25.6\,kg/m^2$, a generalization of the data in other subpopulation may be limited.

Our data suggested for the effect of BMI and renal clearance for the timely attainment of therapeutic serum magnesium levels in women with PE, although the real clinical impact may require a different study design and sample size. Protocol-based management for PE-eclampsia is proven to reduce adverse perinatal outcomes from the disease, and knowledge from our study can be used to personalize the institutional protocol of $MgSO_4$ administration for prevention and control of seizure in women with PE [52]. Routine evaluation of levels is a recommended practice, especially in overweight women who are at significant risk of being subtherapeutic. Considering that only one-third of women in our cohort attained therapeutic levels; we may consider increasing the loading dose (probably to 6 g) in our institutional protocol, especially in overweight and obese women. Considering the toxicities associated supratherapeutic $MgSO_4$ levels, we feel that more studies are needed before recommending larger initial dose (e.g. 8 g) in our population; of which most women have on-admission BMI $\leq 25.6\,kg/m^2$. Close observation for signs of toxicity in women with severe PE, especially if their laboratory parameters suggest for delayed renal clearance of $MgSO_4$, and there should be a low threshold for obtaining a $MgSO_4$ level in these women. Future studies can be targeted in standard pharmacokinetic–pharmacodynamic (PK/PD) modeling and simulation studies to determine the minimum effective dosage of $MgSO_4$ for prophylaxis and treatment of eclampsia. Validation of its clinical, and not just statistical, impact requires further study focusing on women with severe PE.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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Appendix. Cutoff values for on-admission laboratory parameters.

Laboratory parameters	Cutoff values [References]
Hemoglobin (g/dL)	$<$11 g/dL (or $\leq$10.9 g/dL) at $\geq$32 weeks' [53]
Hematocrit (%)	$<$33% (or $\leq$32.9 g/dL) at $\geq$32 weeks' [53]
Platelets count (/mL)	$<$100,000/mL (or $\leq$99,999 /mL) [9]
PT (s)	$>$13 s (or $\geq$14 s) [9]
Partial thromboplastin time (s)	$>$30 s (or $\geq$14 s) [9]
BUN (mg/dL)	$\geq$11 mg/dL in the third trimester [54]
Creatinine (mg/dL)	$\geq$0.9 mg/dL in the third trimester [54]
Uric acid (mg/dL)	$\geq$6.3 mg/dL [54]
Total bilirubin (mg/dL)	$\geq$1.2 mg/dL in the third trimester [54–56]
Direct bilirubin (mg/dL)	$\geq$0.1 mg/dL in the third trimester [54–56]
AST (units/L)	$\geq$70 IU/L [9]
ALT (units/L)	$\geq$70 IU/L [9]
LDH (mg/dL)	$\geq$600 IU/L [9]