# Alternative Magnesium Sulfate Dosing Regimens for Women With Preeclampsia: A Population Pharmacokinetic Exposure-Response Modeling and Simulation Study

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## Abstract

Magnesium sulfate is the anticonvulsant of choice for eclampsia prophylaxis and treatment; however, the recommended dosing regimens are costly and cumbersome and can be administered only by skilled health professionals. The objectives of this study were to develop a robust exposure-response model for the relationship between serum magnesium exposure and eclampsia using data from large studies of women with preeclampsia who received magnesium sulfate, and to predict eclampsia probabilities for standard and alternative (shorter treatment duration and/or fewer intramuscular injections) regimens. Exposure-response modeling and simulation were applied to existing data. A total of 10 280 women with preeclampsia who received magnesium sulfate or placebo were evaluated. An existing population pharmacokinetic model was used to estimate individual serum magnesium exposure. Logistic regression was applied to quantify the serum magnesium area under the curve-eclampsia rate relationship. Our exposure-response model-estimated eclampsia rates were comparable to observed rates. Several alternative regimens predicted magnesium peak concentration < 3.5 mmol/L (empiric safety threshold) and eclampsia rate ≤ 0.7% (observed response threshold), including 4 g intravenously plus 10 g intramuscularly followed by either 8 g intramuscularly every 6 hours × 3 doses or 10 g intramuscularly every 8 hours × 2 doses and 10 g intramuscularly every 8 hours × 3 doses. Several alternative magnesium sulfate regimens with comparable model-predicted efficacy and safety were identified that merit evaluation in confirmatory clinical trials.

## Keywords

eclampsia, exposure-response, magnesium sulfate, population modeling, preeclampsia

Magnesium sulfate (MgSO₄) is the anticonvulsant of choice for eclampsia prophylaxis and treatment.[1] International guidelines recommend 2 MgSO₄ regimens as standard therapy for prevention and treatment of eclampsia: the intravenous Zuspan regimen and the predominantly intramuscular Pritchard regimen.[2,3] Despite the wide acceptance of MgSO₄ as the first-line treatment for women with preeclampsia and eclampsia,

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coverage in resource-limited settings remains suboptimal, partly because the recommended dosing regimens are costly and cumbersome and can be administered only by skilled health professionals.

Since 2013, the World Health Organization (WHO) has embarked on an initiative to determine whether simpler alternative dosing regimens of $MgSO_4$ can be identified, with the goal of optimizing access for women in resource-limited countries.

The objective of this study was to support the initiative via a population-modeling approach by establishing a relationship between estimated magnesium exposure and eclampsia occurrence using a previously developed population pharmacokinetic model,[4] then to simulate the probability of eclampsia for various dosing regimens. The optimal alternative dosing regimen(s) were then evaluated in terms of simulated eclampsia probability and magnesium exposures.

## Methods

This modeling and simulation study was based on existing data sets, and specific informed consent from individual women was not required because of the retrospective study design.

Ethics approval was secured for each of the individual studies that were included in this analysis.

This was a 2-part research project that used data sets for women with preeclampsia from Stanford University Hospital, Stanford, California ("Stanford study")[5]; Siriraj and Khon Kaen Hospitals, Thailand ("Thai study," Lumbiganon et al, unpublished); and a multicenter randomized trial in 33 countries (Magpie Trial).[6] The first part of this project focused on the development of a population pharmacokinetic model based on serial pharmacokinetic data from the Stanford study for 92 pregnant women from a preeclampsia cohort who received intravenous $MgSO_4$ treatment. A 2-compartment population pharmacokinetic model was developed, and body weight and serum creatinine concentrations were identified to have a significant impact on magnesium pharmacokinetics (PK). Model estimated clearance was 3.72 L/h, and distribution volume was 32.4 L/85 kg. The final model structure and simulated magnesium profiles for standard and alternative intravenous and intramuscular regimens are provided in Supplemental Table 1 and Supplemental Figures 1 and 2 (additional details can be found in the previous publication).[4] The second part (presented in the current article) consisted of exposure-response (E-R) modeling using pooled clinical outcome data from the Thai study and the Magpie Trial[6] to predict magnesium exposure and the probability of eclampsia for various $MgSO_4$ dosing regimens.

For the Magpie Trial, women provided informed consent prior to participation. Each hospital in the trial secured appropriate local ethics or research committee approval before opening to recruitment. In the UK, the trial was approved by the Northwest Multicentre Research Ethics Committee. It was also approved by the WHO Scientific and Ethical Review Group, Geneva, Switzerland. All women provided written informed consent.

The Thai study was approved by the Ethics Committees of (1) Khon Kaen University, February 9, 2015, reference no. HE581035, (2) Faculty of Medicine, Siriraj Hospital, Mahidol University, July 3, 2015, reference no. Si350/2015, and (3) Khon Kaen Hospital, July 15, 2015, reference no. KE57047.

### Characteristics of the Studies

Supplemental Table S2 presents a summary of the characteristics of the 3 studies used to develop the population PK model[4] and the E-R model (current analysis).

### Outline of Analysis

No serum magnesium samples were collected in the Magpie Trial, and only sparse postdose samples were collected in the Thai study. Therefore, serum magnesium pharmacokinetic exposure, expressed as area under the curve (AUC) for change from baseline in serum magnesium concentration, was estimated using the pharmacokinetic model.[4] Subsequently, the relationship between the projected AUC and the observed eclampsia outcome was quantified using a logistic regression approach. Using the developed E-R model, the probability of eclampsia occurrence was predicted for different types of "typical" women who received the standard Zuspan and Pritchard regimens and a series of simplified alternative intravenous and intramuscular dosing regimens that were considered more practical and/or convenient compared with the standard regimens, by virtue of fewer injections, shorter treatment duration, or lower doses.

### Eclampsia Response

Observed eclampsia outcomes from the Magpie Trial and the Thai study were pooled and included in the analysis. Of the women included in the analysis, 127 developed eclampsia: 37 received $MgSO_4$ (36 from the Magpie Trial with 18 on the intravenous and 18 on the intramuscular maintenance regimen, respectively, and 1 from the Thai study) and 90 who received placebo (all from the Magpie Trial). Additional details regarding the number of women used for the analysis are provided in Supplemental Table S2.

### Pharmacokinetic Exposure

Using the established pharmacokinetic model,[4] individual AUCs were predicted based on actual dose amount,

route of administration (intravenous or intramuscular) and covariates of body weight and serum creatinine. Individual AUC values for the change from baseline serum magnesium concentration were calculated using the clearance (CL) function derived from the population pharmacokinetic model according to the following equations:

$$CL_i = 3.72 \cdot \left(\frac{0.8\ mg/dL}{Cr_i}\right)^{0.731} \cdot \left(\frac{WT_i}{85\ kg}\right)^{0.75}$$

$$AUC_i = \frac{DOSE_{IV,i}}{CL_i}\ and\ AUC_i = \frac{F \cdot DOSE_{IM,i}}{CL_i}$$

where $Cr_i$ is the serum creatinine concentration for patient $i$, $WT_i$ is the body weight for patient $i$, $DOSE_{IV,i}$ is the total intravenous dose for patient $i$ received, $DOSE_{IM,i}$ is the total intramuscular dose for patient $i$ received, and $F$ is the absolute bioavailability for intramuscular dosing, which was estimated as 0.862 based on the published literature.[7]

## Dose Amount

In the Magpie Trial, the start and stop dates of $MgSO_4$ treatment, route of administration, and total dose administered were recorded. Specific loading and maintenance doses and the timing of $MgSO_4$ administration were determined from the study protocol. The date of first eclampsia episode was recorded, but not the time of occurrence for the majority (92.4%) of the women. Therefore, the exact amount of $MgSO_4$ administered at the time of eclampsia occurrence could not be precisely determined. As a result, the total $MgSO_4$ dose administered up to the day of first eclampsia was used in the AUC calculation.

## Estimation of AUC

A summary of the baseline characteristics of women in the analysis population is presented in Supplemental Table S3. In the Magpie Trial, 2 of the pharmacokinetic model-identified covariates (maternal weight and serum creatinine concentration) were not collected but were assigned the median values of the Stanford study data set (85 kg and 0.8 mg/dL, respectively). As a result, the AUC values in the Magpie Trial were informed only by total dose and route of administration, not by individualized CL estimates from the population pharmacokinetic model. For the Thai study, maternal weight and serum creatinine were available for 383 and 168 women, respectively. Missing values were assigned the median values in the Thai study of 73 kg (n = 6) and 0.6 mg/dL (n = 221), respectively.

## E-R Model Development

Logistic regression was applied to quantify the serum magnesium AUC-eclampsia occurrence relationship

according to the following equation:

$$Logit\,(p) = \log\left(\frac{p_i}{1 - p_i}\right) = b_0 + b_1 \cdot AUC_i$$
$$+ b_x \cdot cov_{x,i}$$

where $p_i$ is the probability of eclampsia occurrence and $logit(p)$ is the log odds of the probability of eclampsia occurrence, $cov_{x,i}$ is the value of covariate $x$ for patient $i$, $b_0$ is the intercept, and $b_1$ and $b_x$ are the coefficients of AUC and covariate x, respectively. Age, previous use of anticonvulsants (yes/no), and a combined measure of blood pressure and urinary protein were evaluated as potential covariates. Preeclampsia severity was treated as a dichotomous variable in the analysis of the Magpie Trial (severe vs not severe based on blood pressure, urinary protein, and signs or symptoms of imminent eclampsia). However, for the purposes of this analysis, we categorized women into 3 levels: level 2 was diastolic blood pressure (BP) $\geq$ 110 mm Hg on 2 occasions or systolic BP $\geq$ 170 mm Hg on 2 occasions plus $\geq$ 3+ proteinuria; level 1 was diastolic BP $\geq$ 100 mm Hg on 2 occasions or systolic BP $\geq$ 150 mm Hg on 2 occasions plus $\geq$ 2+ proteinuria; and level 0 was women who were neither level 2 nor level 1. These criteria were similar to the definition of severe preeclampsia in the Magpie Trial, but signs and symptoms of imminent eclampsia data were unavailable to replicate the exact definition used in the Magpie Trial. Antihypertensive use was not evaluated as a covariate in our analysis, but its use after trial entry was generally similar between patients who received $MgSO_4$ and placebo in the Magpie Trial, with methyldopa, nifedipine, and hydralazine as the antihypertensive agents used most frequently. A piece-wise logistic regression model was applied for age to also improve the model fitting according to the following equation:

$$\log\left(\frac{p_i}{1 - p_i}\right) = b_0 + b_1 \cdot AUC_i + b_2 \cdot Age_i$$
$$+ \delta \cdot (Age_i - k) \cdot I\,((Age_i - k\,) > 0)$$

where $\kappa$ represents a knot point in the slope of age, $\delta$ is the difference in slope before and after the knot point, and $I()$ is an indicator function that returns a 1 if the condition is true and returns a 0 otherwise.

## Model Simulations

The probability of eclampsia occurrence was predicted for 27 different types of women with all possible combinations of age (20, 30, and 40 years), maternal body weight (60, 85, and 110 kg), and serum creatinine concentrations (0.5, 0.8, and 1.2 mg/dL). The alternative

regimens were selected (in part) based on the findings of an international survey on clinical practice patterns of MgSO$_4$ or their previous application in research contexts for eclampsia prophylaxis, tocolysis, or fetal neuroprotection and were prespecified by the study authors prior to the simulation analysis.[8,9] Supplemental Table S4 describes the features of each regimen.

### Analysis Software

Analysis data-set creation was done in SAS (version 9.4l SAS Institute Inc., Cary, North Carolina). E-R model development, simulations and plotting were performed in R (version 3.5.1; The R Project for Statistical Computing [www.r-project.org]).

## Results

### Individual Serum Magnesium AUC Estimates

For the Magpie Trial, the median AUC estimates were 769 mg·h/L (geometric mean, 706 mg·h/L) and 906 mg·h/L (geometric mean, 775 L·h) for the intravenous and intramuscular dosing regimens, respectively. Because of the imputation of values for missing body weight and serum creatinine, the AUC values for this study were solely derived from individual dosing information; hence, AUC distribution was relatively narrow. Using lower imputed values for body weight and serum creatinine (80 kg and 0.7 mg/dL, respectively), resulted in an AUC that was approximately 5% lower, which suggested that the AUC values were relatively insensitive to small deviations in body weight and serum creatinine from the median values derived from the Stanford study. For the Thai study, the median AUC was higher (1351 mg·h/L, geometric mean = 1278 mg·h/L) with a wider distribution, which was consistent with infusion durations longer than 24 hours, maintenance doses higher than 1 g/h, and CL values that could be individualized for each woman using body weight and serum creatinine concentrations. The frequency distributions for estimated AUC values for the Magpie Trial and the Thai study are presented in Supplemental Figure S3.

### Eclampsia Occurrence

Most of the eclampsia seizures occurred on the first day of treatment with MgSO$_4$. The distribution of onset day of eclampsia is presented in Supplemental Figure S4.

### Exposure-Response Model Results

An overview of the E-R model development is summarized in Supplemental Table S5. Level of blood pressure/urinary protein and anticonvulsant drug use before MgSO$_4$ treatment did not show a significant relationship with eclampsia, but age and AUC demonstrated a clear relationship. There was no collinearity observed between these 2 covariates, and there was also no statistically significant interaction between AUC and age when tested during model building, confirming that they independently contributed to the E-R model. The final logistic E-R model included a piece-wise linear age effect with a knot point at 22 years. The AIC (Akaike Information Criterion) score of the final model dropped 24 points compared with the E-R model with age included as a linear covariate.

Age $\leq$ 22 years: Logit(P) $= -6.29 - 0.00164 \cdot$ AUC $+$ $0.154 \cdot$ age

Age $>$ 22 years: Logit(P) $= -4.72 - 0.00164 \cdot$ AUC $+$ $0.010 \cdot$ age

Figure 1 illustrates an overlay of the observed and model-predicted eclampsia rates as a function of magnesium AUC and age. Predicted eclampsia rates reasonably matched the observed rates for each of the age and AUC groups (segmented into quantiles), except for the AUC group of women with the lowest magnesium exposure (0-371 mg·h/L), where the model underpredicted the observed eclampsia rate. All women in this lowest quantile had treatment duration that was less than 12 hours, and 8 of 13 (61.5%) had their first seizure within the first 20 minutes. Removal of these women from the analysis resulted in an observed eclampsia rate of 1.6% in this AUC quantile, which was more consistent with the observed rate. In total, 37 women treated with MgSO$_4$ had eclampsia, 21 of whom (56.8%) were $\leq$22 years old. In the placebo arm, 90 women had eclampsia, of whom 53 (58.9%) were $\leq$22 years old.

Using the final E-R model, overall mean eclampsia rates were predicted for each regimen for 27 different types of women, as previously defined. Table 1 presents the estimated magnesium C$_{max}$ and predicted mean overall eclampsia rates, for both all women and women older than age 22 years. Supplemental Figure S5 and Figure S6 graphically depict the simulated eclampsia rates for each of these types of women for all the intravenous- and intramuscular-based regimens, respectively.

Criteria for evaluating the safety and efficacy of these regimens included a predicted range of magnesium C$_{max}$ values that did not exceed the reported safety margin of 3.5 mmol/L[10,11] and an overall mean predicted eclampsia rate $\leq$ 0.7% (the overall observed eclampsia rate in all MgSO$_4$-treated women in the Magpie and Thai studies [37 of 5290]).

As shown in Table 1, all alternative regimens had predicted eclampsia rates that were lower compared with placebo for all women and for women older than 22 years. The intravenous regimens with higher maintenance doses of 2 g/h for 24 hours (either with
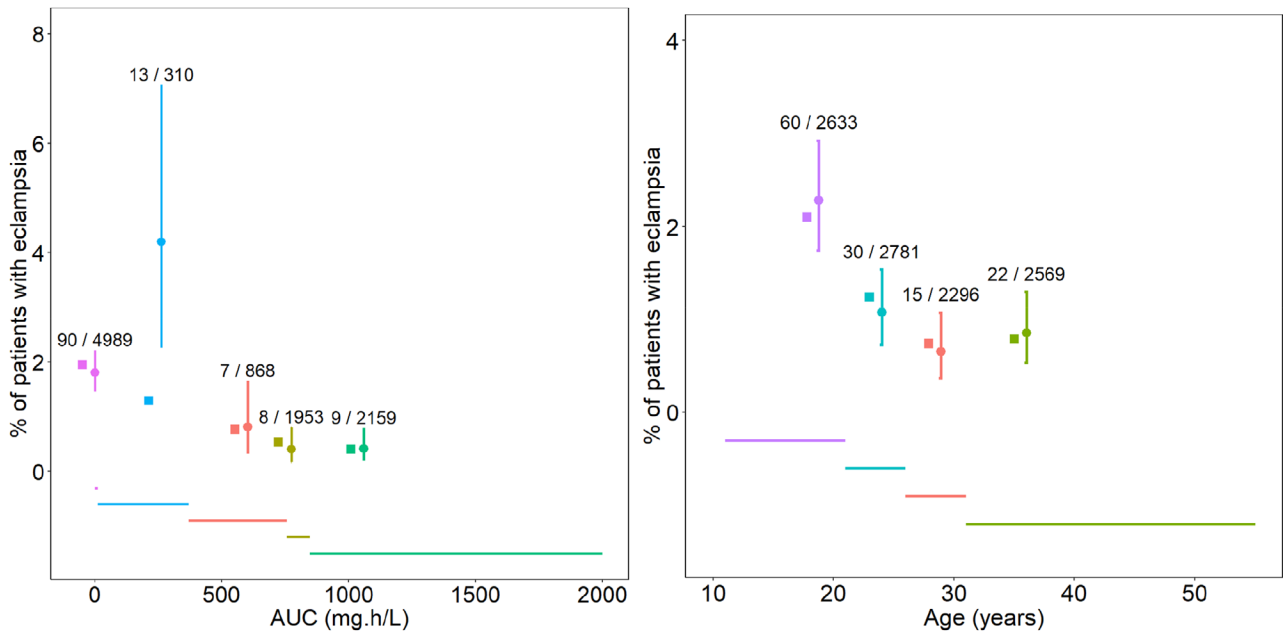
**Figure 1.** Observed and E-R model-predicted eclampsia rate versus estimated AUC (left) and age (right). AUC, area under the curve; E-R, exposure-response. Horizontal lines: parameter ranges in each quantile; AUC quantiles: 0 (placebo), 0-371 mg·h/L (less than half of a standard dose), 371-757 mg·h/L (less than a standard dose), 757-848 mg·h/L (equivalent to a standard intravenoous dose, 28 g), and >848 mg·h/L (equivalent to a standard intramuscular dose, 39 g and higher dose). Age quantiles: < 22, 22-26, 27-31, >31 years. Solid dot and vertical line: mean and 95%CI of observed eclampsia rate for each quantile. Solid squares: model-predicted eclampsia rate for each quantile.

the same loading dose as the standard regimen or with a higher loading dose of 6 g), and the intravenous regimen with both a higher loading dose (12 g) and a higher maintenance dose of 3 g/h for 12 hours met the efficacy criterion, but the estimated $C_{max}$ for these regimens exceeded the safety criteria. Of the alternative intravenous regimens, only the 8-g intravenous loading dose over 60 minutes followed by 2 g/h for a 10-hour regimen nearly met the selection criteria, with the same mean eclampsia rate as the standard Zuspan regimen, but the upper range of predicted $C_{max}$ for this regimen was 3.55 mmol/L, just above the safety criteria. Of the alternative intramuscular maintenance regimens evaluated, all met the safety criteria. Two regimens using the same loading dose as the Pritchard regimen (but with fewer maintenance intramuscular injections) met the efficacy criterion: 4 g intravenous/ 10 g intramuscular loading dose followed by 8 g every 6 hours × 3 doses or 10 g every 8 hours × 2 doses. In addition, 1 regimen without an intravenous loading dose (10 g intramuscularly every 8 hours × 3 doses) also met the efficacy criterion, with a mean eclampsia rate of 0.70%. Although the other intramuscular regimen without intravenous loading (10 g intramuscularly every 12 hours × 2 doses) did not meet the efficacy criterion, it had a predicted eclampsia rate that was lower compared with placebo (1.0% vs 2.1% for all women).

## Discussion

### Principal Findings
Our E-R model generally performed well, enabling simulations of eclampsia rates that we used to systematically assess various dosing regimens and identify promising alternative regimens prior to conducting large comparative clinical trials.[12]

### Results
We identified several promising alternative regimens that were predicted to perform as well as the standard Zuspan or Pritchard regimens. Currently, there are limited published data for these alternatives. To our best knowledge, this was the first to apply PKPD modeling to estimate the relationship between magnesium sulfate exposure and eclampsia prevention.

### Clinical Implications
Some of the alternative regimens require careful consideration of differences in the context in which women with preeclampsia are treated globally. For instance, the regimen of 8 g intravenously over 60 minutes followed by a continuous infusion of 2 g/h for 10 hours would remain challenging in low-resource settings, in which safe intravenous administration (eg, with a controlled infusion pump) is still limited to high-level facilities. Administration of the same total dose (28 g) for shorter treatment duration when compared with the standard

**Table 1.** Summary of Predicted Magnesium Peak Plasma Concentration ($C_{max}$) and Eclampsia Rates for Standard and Alternative Dosing Regimens of Magnesium Sulfate

| Intravenous Regimens | Total Dose (g/24 h) | Total Duration (h) | Predicted Mg $C_{max}$ (mmol/L) Min-Max[a] | Predicted Eclampsia Rate (%)[b] | |
|---|---|---|---|---|---|
| | | | | All Ages | Age > 22 Years |
| Placebo (IV/IM combined) | 0 | — | 0 | 2.1 | 1.2 |
| 4 g in 20 min, 1 g/h × 24 h Standard regimen (Zuspan) | 28 | 24.3 | 1.47–2.47 | 0.64 | 0.37 |
| 4 g in 20 min, 2 g/h × 24 h | 52 | 24.3 | 1.96–4.12 | 0.25 | 0.15 |
| 6 g in 20 min, 2 g/h × 24 h | 54 | 24.3 | 1.97–4.16 | 0.24 | 0.14 |
| 12 g in 120 min 3 g/h × 12 h | 48 | 14.0 | 2.43–5.15 | 0.29 | 0.17 |
| 12 g in 120 min 2 g/h × 8 h | 28 | 10.0 | 2.27–3.79 | 0.64 | 0.37 |
| 8 g in 60 min, 2 g/h × 10 h | 28 | 11.0 | 2.01–3.55 | 0.64 | 0.37 |
| 4 g in 20 min, 1 g/h × 12 h | 16 | 12.3 | 1.47–2.22 | 1.0 | 0.61 |
| 4 g in 20 min, 1 g/h × 8 h | 12 | 8.3 | 1.47–2.11 | 1.2 | 0.73 |
| 6 g in 20 min | 6 | 0.3 | 1.82–2.76 | 1.6 | 0.94 |

| Regimens That Include Intramuscular Dosing | Total Dose (g/24 h) | Total Duration (h)/(# IM Injections) | Predicted Mg $C_{max}$ (mmol/L) Min-Max[a] | Predicted Eclampsia Rate (%)[b] | |
|---|---|---|---|---|---|
| | | | | All Ages | Age > 22 Years |
| Placebo (IV/IM combined) | 0 | – | 0 | 2.1 | 1.2 |
| 4 g IV/10 g IM, 5 g Q 4 h × 5 Standard regimen (Pritchard) | 39 | 20.3 (6) | 1.65–2.73 | 0.50 | 0.29 |
| 4 g IV/10 g IM, 8 g Q 6 h × 3 | 38 | 18.3 (4) | 1.65–2.88 | 0.52 | 0.30 |
| 4 g IV/10 g IM, 10 g Q 8 h × 2 | 34 | 16.3 (3) | 1.65–2.82 | 0.59 | 0.35 |
| 4 g IV/10 g IM, 5 g Q 4 h × 2 | 24 | 20.3 (3) | 1.65–2.54 | 0.84 | 0.49 |
| 4 g IV/10 g IM | 14 | 0.3 (1) | 1.65–2.49 | 1.2 | 0.71 |
| 10 g IM | 10 | – (1) | 1.25–1.81 | 1.4 | 0.84 |
| 10 g IM Q 12 h × 2 | 20 | 12.0 (2) | 1.37–2.22 | 1.0 | 0.58 |
| 10 g IM Q 8 h × 3 | 30 | 24.0 (3) | 1.53–2.71 | 0.70 | 0.41 |
| 4 g IV/6 g IM | 10 | 0.3 (1) | 1.48–2.12 | 1.4 | 0.82 |

g, Gram; h, hour; IM, intramuscular; IV, intravenous; Mg, serum magnesium; Q, every.
Dosage form in simulated dosing regimen was $MgSO_4 \cdot 7H2O$, which contains ~10% of magnesium.
[a]Minimum and maximum predicted $C_{max}$ across typical values of body weight (60, 85, 110 kg) and creatinine concentration (0.5, 0.8, 1.2 mg/dL).
[b]All ages is mean of 27 types of women with all possible combinations of age (20, 30, and 40 years), maternal body weight (60, 85, and 110 kg), and serum creatinine concentrations (0.5, 0.8, and 1.2 mg/dL). Age > 22 years is mean of 18 types of women aged 30 and 40 years old with each possible combination of the same maternal body weights and serum creatinine concentrations.

Zuspan regimen would not reduce drug costs, but the shorter treatment duration may reduce other healthcare costs associated with administration of intravenous $MgSO_4$.[13]

Promising intramuscular regimens, especially those without an intravenous loading dose (10 g intramuscularly every 8 hours × 3 doses), had greater magnesium concentration fluctuations within the dosing interval, the clinical consequences of which are unknown because of lack of consensus for maintaining a trough concentration above a certain threshold for eclampsia prophylaxis. Although these alternative intramuscular-only regimens may overcome some of the current challenges with standard regimens in low-resource countries,[14] possibly reducing the associated morbidity and mortality from treatment delays in these settings, they should be tested in rigorous research to generate evidence on their clinical comparative efficacy and safety with the standard regimens. The knot point of 22 years of age used in our model was based on the observed data and the model fitting, such that lower age was associated with a higher risk of eclampsia. We are not aware of any clinical significance to the knot point of 22 years in relation to the risk of eclampsia.

### Research Implications
Apart from supporting selection of promising regimens for use in future randomized trials, the results of our modeling and simulation study provide an indication of which $MgSO_4$ regimens may have a higher safety risk or potential for reduced efficacy, such that their use in randomized trials would not be recommended. For instance, the alternative regimens using the same loading dose as the Pritchard regimen with higher maintenance infusion rates of 2 and 3 g/h were associated with $C_{max}$ values that exceeded the 3.5 mmol/L safety threshold. Whereas a common regimen, such as 4 g intravenously followed by 1 g/h for 12 hours may be insufficient to protect young women with preeclampsia.

## Strengths and Limitations

Our E-R model provided a robust estimation of the magnesium E-R relationship for eclampsia and provided a mechanism to systematically assess various dosing regimens to help identify promising alternatives prior to conducting large comparative clinical trials.

As the precise relationship between magnesium exposure and efficacy is not well defined, the minimum effective serum magnesium concentration and the PK driver for eclampsia prophylaxis are unknown, likely because of insufficient data for women with preeclampsia progressing to eclampsia to draw reliable conclusions. In the absence of knowledge of the relationship between PK and efficacy, it was assumed that AUC for changing from baseline magnesium was the best PK parameter to correlate with prevention of eclampsia (as opposed to $C_{max}$ or trough concentration, for example) because a specific PK parameter driver for magnesium efficacy is unknown. Our model underestimated the eclampsia rate for women with the lowest serum magnesium exposure (AUC 0-371 mg h/L), which may have been because of the inclusion of women who experienced eclampsia shortly after starting treatment (8 of 13 women had eclampsia within 20 minutes of treatment). There may have been insufficient time for $MgSO_4$ to penetrate the effect site to have activity.

We were unable to individualize the serum magnesium exposure for the majority of women because of missing body weight and creatinine concentration. In addition, the lack of renal function values in the Magpie Trial and use of the median creatinine concentrations from the Stanford Trial could potentially confound and/or bias the estimated MgSO4 exposure levels because magnesium is excreted by the kidneys at a rate proportional to the plasma concentration and glomerular filtration. However, the magnesium AUC was relatively insensitive to small deviations in body weight and serum creatinine. Hence, confidence intervals of MgSO4 exposure and prediction intervals of eclampsia rate were not provided because of the lack of individual exposures, use of median exposure levels from the Stanford study, and use of absorption rate constant and absolute bioavailability values from the literature.[7]

## Conclusions

We developed a robust E-R model to estimate eclampsia outcome following treatment of women with preeclampsia with $MgSO_4$. Of the intravenous regimens evaluated, an 8-g intravenous loading dose over 60 minutes followed by a continuous infusion of 2 g/h for 10 hours had the same mean eclampsia rate as the standard Zuspan regimen, but the upper range of predicted $C_{max}$ included 3.55 mmol/L, just above the safety criterion used for our analysis. The intramuscular regimens with the same loading dose as the Pritchard regimen but fewer maintenance doses (8 g intramuscularly every 6 hours × 3 doses; and 10 g intramuscularly every 8 hours × 2 doses) appeared to perform as well as the Pritchard regimen. In addition, 1 regimen without intravenous loading dose (10 g intramuscularly every 8 hours x 3 doses) also met the efficacy criterion, with a mean eclampsia rate of 0.70%. Future trials to investigate the noninferiority of alternative $MgSO_4$ regimens should consider using the most promising regimens identified in this modeling and simulation study with due consideration of the clinical context of $MgSO_4$ use.

## Declaration of Conflict of Interest

The authors declare that there are no conflicts of interest.

## Data-Sharing Statement

The authors are unable to share the data supporting the results of this study.

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## Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.