

Risk Factors for Sub-therapeutic Serum Concentrations of Magnesium Sulfate in Severe Preeclampsia of Chinese Patients

Jingjing Li

Nanjing Medical University Second Affiliated Hospital <https://orcid.org/0000-0002-4133-0343>

Lian Tang

Suzhou Municipal Hospital

Ruiheng Tang

Suzhou Municipal Hospital

Lan Peng

Suzhou Municipal Hospital

Liqiang Chai

Suzhou Municipal Hospital

Liping Zhu

Suzhou Municipal Hospital

Yanxia Yu (✉ yuyxsz@163.com)

Suzhou Municipal Hospital <https://orcid.org/0000-0001-6105-0114>

Research article

Keywords: Severe preeclampsia, Magnesium sulfate, Risk factors, Receiver operating characteristic curve, Logistic regression

Posted Date: June 3rd, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-21153/v2>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Version of Record: A version of this preprint was published on October 1st, 2020. See the published version at <https://doi.org/10.1186/s12884-020-03277-0>.

Abstract

Background: Magnesium sulfate (MgSO_4) is the standard drug for eclampsia prophylaxis and treatment. In China, the effective therapeutic serum magnesium level is 1.8–3.0 mmol/L. There is little information on how to achieve and maintain effective therapeutic concentrations. This study aimed to investigate risk factors for sub-therapeutic serum concentrations of MgSO_4 in patients with severe preeclampsia.

Methods: Patients with severe preeclampsia who received MgSO_4 intravenous infusion were retrospectively reviewed. The maternal demographic characteristics, regimens for the administration of MgSO_4 , and lab test results of patients were collected. Multivariate logistic regression analysis and receiver operating characteristic (ROC) curve analysis were conducted for the risk factors influencing the serum magnesium concentration.

Results: A total of 93 patients with severe preeclampsia were included in the study. 52 (55.91%) patients did not attain therapeutic serum magnesium levels. A multivariate logistic regression analysis identified creatinine clearance (Ccr), whether the loading dose was given, and measurement time of serum magnesium concentration (referring to the time interval from measurement of blood magnesium concentration to the beginning of maintenance dose administration) as independent risk factors for sub-therapeutic serum magnesium concentration ($P < 0.05$). ROC curve analysis indicated that the continuous variable Ccr had a significant predictive value for the serum magnesium concentration, which resulted in a cutoff point of 132.82 mL/min; while measurement time had limited predictive value, with cutoff point of 2.375 h.

Conclusions: Ccr, whether the loading dose was given, and measurement time were independent risk factors for sub-therapeutic serum magnesium concentration. A loading dose of MgSO_4 everytime before the maintenance dose, as well as an infusion time of more than 2.375 hours for MgSO_4 maintenance dose are recommended for all the patients with severe PE. Routine evaluation of serum magnesium levels is a recommended practice for women with severe PE whose Ccr is ≥ 132.82 mL/min.

Background

Preeclampsia (PE) is a multi-system disorder of widespread vascular endothelial malfunction and vasospasm, characterized by elevation of blood pressure after 20 weeks of gestation in a formerly normotensive woman, with proteinuria, or in the absence of proteinuria, new-onset hypertension with the new onset of end-organ dysfunction, affecting 6–8% of all pregnancies^[1]. Adverse outcomes tend to occur more frequently in severe cases of PE and eclampsia^[2].

Magnesium sulfate (MgSO_4) is the preferred pharmacological intervention to treat severe PE because it can prevent the recurrent seizures of eclampsia^[2, 3]. Total dose of MgSO_4 reported worldwide for the treatment of PE and eclampsia was ranged from 2 g/24 hours to 54 g/24 hours^[4–8]. Serum magnesium

level of 2.0–3.5 mmol/L is considered therapeutic by several authors^[9]. While in China, optimal control of convulsions is thought to be most effective with therapeutic serum magnesium level at 1.8–3.0 mmol/L^[4]. Sub-therapeutic serum magnesium level may increase risk for eclamptic seizures^[9]. On the other hand, MgSO₄ overdose may result in serious toxicities, including maternal loss of the patellar reflex, respiratory paralysis, cardiac conduction and cardiac arrest^[10, 11]. To date, there is little information on whether serum magnesium level can reach the effective therapeutic concentration and the influencing factors in patients with severe PE in China. In the present study, the clinical data of 93 patients with severe PE treated with MgSO₄ were analyzed retrospectively to explore the risk factors for serum magnesium not reaching the therapeutic concentration.

Methods

Study population

The ethics committee of Suzhou Municipal Hospital approved our study protocol (K2017037). This was a retrospective analysis of electronic medical records of all women with severe PE admitted to our institution for delivery who received IV MgSO₄ for seizure prophylaxis from January 2016 to December 2018. Inclusion criteria were: (1) singleton pregnancy, (2) aged 18–45 years, (3) the baseline serum magnesium concentrations were measured before IV infusion of MgSO₄, and (4) serum magnesium levels were measured during IV infusion of a maintenance dose. We excluded patients with multifetal pregnancies or other pregnancy complications, such as hepatic diseases, kidney diseases, etc. Diagnostic criteria of PE include the development of hypertension after 20 weeks of gestation in women with previously normal blood pressure, and proteinuria or in the absence of proteinuria, new-onset hypertension with new onset of thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, cerebral or visual symptoms. The diagnostic standards of hypertension shall be in accordance with a systolic blood pressure of 140 mmHg or higher, or a diastolic blood pressure of 90 mmHg or higher on two occasions at least 4 hours apart. Proteinuria is defined as the excretion of 0.3 g or more of protein in a 24-hour urine collection. Alternatively, a protein/creatinine ratio of at least 0.3 (each measured as mg/dL) is used. On the condition of other approaches are not readily available, a determination of dipstick test reading of 1+ is considered as the cutoff for the diagnosis of proteinuria. PE is diagnosed as severe based on classic criteria of blood pressures greater than or equal to 160/110 mmHg and proteinuria greater than or equal to dipstick reading of 2+. Other notable parameters symptoms are: persistent headache, visual disturbances, epigastric pain, intrauterine growth retardation and impaired hepatic and renal function tests^[3, 4].

The patients with serum magnesium level 1.8 to 3.0 mmol/L after IV infusion of MgSO₄ were assigned to Group A, and those with serum magnesium level < 1.8 mmol/L were assigned to Group B. We collected data on maternal age, gestational age, height and weight, creatinine clearance (Ccr), alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, baseline serum magnesium concentrations, whether the loading dose was given, and measurement time (referring to the time interval

from measurement of blood magnesium concentration to the beginning of maintenance dose administration). The Cr was calculated from the serum creatinine by the Cockcroft-Gault equation: , where Cr was the serum creatinine. For women, the formula requires multiplication by 0.85.

IV administration of MgSO₄

A 5 g IV loading dose was or was not administered over 30 minutes, followed by a maintenance dose of 1.5 g/h for 10 hours using an infusion pump (Terufusion infusion pump TE-135, Terumo Corporation, Tokyo, Japan).

Measurement of magnesium level in the serum

Serum magnesium level was measured by 2 mL of venous blood sampling, which were collected into serum separator tubes (Becton Dickinson Franklin Lakes, NJ, USA). The blood samples were centrifuged at 3000 rpm for 5 minutes within 30 minutes of collection. We used automatic biochemical analyzer (HITACHI 7600, Tokyo, Japan) to measure total magnesium, and serum magnesium concentrations of 1.8–3.0 mmol/L were considered therapeutic window for severe PE.

Statistical analysis

On-admission factors were expressed as number (%), mean \pm standard deviation (SD) or median (quartile). For categorized parameters chi-square test was used, while for quantitative variables Student's t-test or Mann-Whitney U test were used to compare two groups. A univariate logistic regression analysis was used to test the association between each risk factor and the sub-therapeutic blood magnesium concentration. Variables with a P-value < 0.1 on the univariate analysis were included in a multivariate logistic regression analysis. Multivariable analysis was determined by logistic regression for independent risk factors associated with sub-therapeutic blood magnesium concentration. The area under ROC curve and the cut-off values were evaluated. We also calculated the odds ratio (OR) and 95% confidence intervals (CI). Statistical analysis was proceed using SPSS version 22.0 (RRID: SCR_002865). Differences with a P-value < 0.05 were considered statistically significant.

Results

The study included ninety-three women with severe PE who received IV infusion of MgSO₄ for seizure prophylaxis. Among these patients, there were 41 (44.09%) and 52 (55.91%) patients who did (Group A) and did not (Group B) attain therapeutic serum magnesium levels. Table 1 shows the maternal demographic characteristics, lab test results, the regimens for the administration of MgSO₄, and serum magnesium levels of the patients in the two groups. The two groups showed no significant difference in age, height, body mass index (BMI), gestational age, ALT, albumin, and whether the loading dose was given. The baseline serum magnesium concentrations were similar in both groups (0.76 vs. 0.73, P > 0.05). The median (quartile) serum magnesium concentration of women in Group A was 2.08 (1.89, 2.25),

while it was 1.39 (1.21, 1.61) for Group B. Women in Group A had significantly lower weight, lower Ccr, higher AST, and higher measurement time than women in Group B ($P < 0.05$).

Through univariate analysis, we found that weight, BMI, Ccr, albumin, measurement time, and whether the loading dose was given were statistically significant risk factors for sub-therapeutic blood magnesium concentration ($P < 0.1$, Table 2). Multivariate regression analysis showed that Ccr ($P = 0.000$; 95% CI:1.008–1.030), whether the loading dose was given ($P = 0.038$; 95% CI:0.117–0.941) and measurement time ($P = 0.008$; 95% CI:0.688–0.947) were independent risk factors for sub-therapeutic blood magnesium concentration (Table 3).

Independent risk factors of continuous variables were analyzed by ROC curve (Table 4). The area under ROC curve of Ccr was 0.715 with the cut-off value of 132.82 mL/min. The area under the ROC curve of measurement time was 0.650 with the cut-off value of 2.375 h (Figure 1). The results showed that when $Ccr \geq 132.82$ mL/min or the duration of $MgSO_4$ maintenance dose was less than 2.375 h, the blood magnesium concentration was less likely to reach the target range.

Discussion

The results of this study indicated 52 (55.91%) patients did not attain therapeutic serum magnesium levels and maternal Ccr, whether the loading dose was given and measurement time were major determinants of attainment of therapeutic serum magnesium concentration.

The elimination of $MgSO_4$ occurs primarily in the kidney, and PE associated renal damage can result in increased serum magnesium levels^[12]. A previous publication showed that the glomerular filtration rate of normal pregnant women was 149 mL/min/1.73 m² body surface area^[13]. We used Ccr to estimate the glomerular filtration rate, which was calculated by the Cockcroft-Gault equation. From our study, the median (quartile) Ccr of Group A was 127.03 (97.49, 154.91), lower than normal pregnant women, while Group B was 161.55 (131.56, 189.19) ($P < 0.05$). This suggests the reverse association between Ccr and sub-therapeutic levels. Our study further found that when maternal $Ccr \geq 132.82$ mL/min, the blood magnesium concentration of severe preeclampsia patients was less likely to reach the target range. We prefer to recommend routine evaluation of serum magnesium levels in augmented renal clearance women because they are at significant risk for being sub-therapeutic. It is also necessary to observe closely for signs of toxicity in severe PE cases with delayed renal clearance of $MgSO_4$.

The pharmacokinetic basis of $MgSO_4$ dosing regimens for eclampsia prophylaxis and treatment is not clearly established^[14], and there is no report of the time required to reach therapeutic range of serum magnesium concentration after the beginning of administration of maintenance dose. However, a pharmacodynamics study showed that with IV 4 g loading and 2 g/h maintenance dose, blood magnesium concentration was twice the baseline value within 30 minutes, and plateaued at 2–4 hours with minimum fluctuation^[5, 14, 15]. At 2 hours after administration, serum magnesium ranged broadly from 1.0–3.5 mmol/L^[12]. With our $MgSO_4$ IV infusion regimen (5 g loading dose and 1.5 g/h maintained

for 10 hours, or no loading dose and 1.5 g/h maintained for 10 hours), our data suggested that for the duration of MgSO₄ maintenance dose of more than 2.375 hours, the blood magnesium concentration was more likely to reach the target range of 1.8–3.0 mmol/L.

Our study is the first report on whether the serum magnesium during the maintenance administration of MgSO₄ can reach the therapeutic range in patients with severe PE in China. Phuapradit and colleagues^[16] reported that when the regimen of their patients with diagnosis of severe PE were given a 5 g MgSO₄ intravenous bolus infusion and 1 g/h continuous infusion and continued 24 hours postpartum, only 56.2% patients had the serum magnesium concentration above the therapeutic level of 2.0–3.5 mmol/L need to prevent seizures as suggested by Pritchard^[17]. With our MgSO₄ IV infusion regimen (5 g loading dose and 1.5 g/h maintained for 10 hours, or no loading dose and 1.5 g/h maintained for 10 hours), only 44.09% of patients attained therapeutic serum magnesium levels during IV infusion of a maintenance dose, which was in agreement with previous reports^[16]. It is generally believed that the baseline magnesium serum concentrations complicate the metabolism of MgSO₄^[18]. The baseline serum concentrations may have influence on the serum magnesium concentration measured during IV infusion of a maintenance dose. The reported baseline serum magnesium concentrations were consistently < 1 mmol/L for women with PE and eclampsia^[14]. Also, our study confirmed that the baseline serum magnesium concentrations were 0.7 mmol/L or thereabouts in patients with severe PE, and the baseline serum magnesium concentration had no effect on the therapeutic serum magnesium concentration after administration of MgSO₄.

Previous studies reported disagreement as to the recommended IV administration dosage and therapeutic levels of MgSO₄. Published dose regimens for MgSO₄ vary widely, with loading doses of 4–6 g intravenously over 20–30 minutes and maintenance doses of 1–2 g/h (and up to 3 g/h)^[8,17]. The most common MgSO₄ regimen is a loading dose of 6 g intravenously over 15 to 20 minutes followed by 2 g/h as a continuous infusion^[2,19–21]. A therapeutic range of 2.0–3.5 mmol/L has been recommended based on retrospective data^[9]. However, Chinese guidelines for the diagnosis and treatment of hypertension and preeclampsia in pregnancy recommend the therapeutic serum magnesium level of 1.8–3.0 mmol/L, with a loading dose 2.5–5 g and a maintenance dose of 1–2 g/h for 6–12 hours^[4]. But the guideline does not clearly state that the loading dose needs to be given every day before the maintenance dose of MgSO₄ is administered. Therefore, a loading dose of MgSO₄ is usually only administered to the patients who begin to receive treatment of MgSO₄ for eclampsia prophylaxis on the first day in Chinese clinical practice. Our study found that patients with severe PE who were not given a loading dose were less likely to reach the target serum magnesium range. It has been repeatedly shown that the protocol of 4 g loading and 2 g/h maintenance infusion in preeclampsia-eclampsia patients can attain better therapeutic levels of serum magnesium compared to other protocols with no detectable difference in maternal and neonatal outcomes^[9,22]. Hence, we may consider recommending that a loading dose be used before the maintenance dose of MgSO₄ is administered every time in China.

We elevated maternal BMI was associated with sub-therapeutic MgSO_4 serum concentrations, which was in agreement with previous reports^[12, 23, 24]. But the association between elevated BMI and sub-therapeutic MgSO_4 levels was not confirmed in our research, because : (1) the finding was based on a small sample of cases, which may lead to weakening of statistical significance, and (2) maternal BMI is correlated with gestational age, so the effects of these two parameters on serum magnesium levels cannot be clearly differentiated. Our study found there was no significant difference between Group A and Group B regarding gestational age, which may result in no significant impact of BMI on serum magnesium levels.

There are limitations to this retrospective study due to limited clinical data. (1) Its retrospective nature precluded the best assessment methodology. (2) The influence of serum magnesium levels on efficacy of seizure prevention was not evaluated in our study. (3) We excluded the severe PE patients with serious co-morbidities such as hepatic diseases, kidney diseases, etc. The exclusion of these patients may limit our data collection. (4) Including subjects who did not receive a loading dose may dilute findings from those who received a standard approach. Because of the small sample size, the ROC curves generated were not particularly strong for a predictive test. Further prospective cohort studies with a larger sample size are necessary to draw any definitive conclusions on these issues. (5) The minimum effective treatment concentration of MgSO_4 for prophylaxis and treatment of severe PE has largely been based on clinical and laboratory observations in earlier studies rather than standard exposure-response studies^[6,17] Although some pharmacokinetic studies of MgSO_4 administration in preeclamptic women are reported^[25-29], there has been no rigorous evaluation of therapeutic serum magnesium concentration^[14]. In the future studies, it is necessary to do the standard pharmacokinetic-pharmacodynamic (PK/PD) modeling and simulation studies to determine the minimum effective treatment concentration and dosage of MgSO_4 for prophylaxis and treatment of severe PE.

Conclusions

In conclusion, the incidence of sub-therapeutic serum magnesium concentration during the maintenance administration in Chinese severe PE patients is high and associated with Ccr, whether the loading dose was given, and measurement time. Thus, to achieve targeted therapeutic serum magnesium concentrations, we recommend a loading dose of MgSO_4 everytime before, as well as an infusion time of more than 2.375 hours for MgSO_4 maintenance dose for all the patients with severe PE. Women with severe PE and whose Ccr is ≥ 132.82 mL/min are recommended to do routine evaluation of serum magnesium levels.

Abbreviations

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; Ccr: creatinine clearance; CI: confidence intervals; IV: intravenous; MgSO_4 : magnesium sulfate; OR: odds ratio; PE:

preeclampsia; PK/PD: pharmacokinetic-pharmacodynamic; ROC: receiver operating characteristic; SD: standard deviation.

Declarations

Acknowledgements

Not applicable.

Author`s contributions

Design of the study: JJL, LT, YXY; Data acquisition: RHT, LP, LQC, LPZ; Data analysis: JJL, LT, RHT, YXY; Draft the manuscript: JJL, LT, RHT, YXY; Manuscript revise and final version approval: YXY. JJL and LT contributed equally to this work. All authors have read and approved the final manuscript.

Funding

This work was supported by two grants, A201726 and Q2018163, from the Foundation of Jiangsu Pharmaceutical Association of China. Funders had no influence on the design of the study, the data collection and analysis, and the manuscript writing.

Availability of data and materials

The data of this study is available from the corresponding authors on reasonable request.

Ethic approval and consent to participate

The present study was approved to collect the clinical data with informed consent by the ethics committee of Suzhou Municipal Hospital (K2017037).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹Department of Pharmacy, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Jiangsu Suzhou, China. ²School of Medicine, Xuzhou Medical University, Jiangsu Xuzhou, China. ³Department of Obstetrics, The Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou Municipal Hospital, Jiangsu Suzhou, China.

References

- [1] Norwitz ER, Repke JT. Preeclampsia Prevention and Management. *J Soc Gynecol Investig*, 2000,7(1):21-36.
- [2] Sibai BM. Magnesium Sulfate Prophylaxis in Preeclampsia: Lessons Learned from Recent Trials. *Am J Obstet Gynecol*, 2004,190(6):1520-1526.
- [3] American College of Obstetricians and Gynecologists, Task Force on Hypertension. Hypertension in Pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. *Obstet Gynecol*, 2013,122(5):1122-1131.
- [4] Hypertensive Disorders in Pregnancy Subgroup, Chinese Society of Obstetrics and Gynecology, Chinese Medical Association. Diagnosis and treatment of hypertension and pre-eclampsia in pregnancy: a clinical practice guideline in China 2015. *Chin J Obstet Gynecol*, 2015,50(10):721-728. DOI: 10.3760/cma.j.issn.0529-567X.2015.10.001
- [5] Sibai BM, Graham JM, McCubbin JH. A Comparison of Intravenous and Intramuscular Magnesium Sulfate Regimens in Preeclampsia. *Am J Obstet Gynecol*, 1984,150(6):728-733.
- [6] Chesley LC, Tepper I. Levels of Magnesium Attained in Magnesium Sulfate Therapy for Preeclampsia and Eclampsia. *Surg Clin North Am*, 1957,37(2):353-367.
- [7] Eastman NJ, Steptoe PP. The Management of Pre-eclampsia. *Can Med Assoc J*, 1945,52(6):562-568.
- [8] American College of Obstetricians and Gynecologists (ACOG). ACOG Practice Bulletin No. 202 Summary: Gestational Hypertension and Preeclampsia. *Obstet Gynecol*, 2019,133(1):211-214.
- [9] Sibai BM, Lipshitz J, Anderson GD, Dilts Jr PV. Reassessment of Intravenous MgSO₄ Therapy in Preeclampsia-Eclampsia. *Obstet Gynecol*, 1981,57(2):199-202.

- [10] Magpie Trial Follow-Up Study Collaborative Group. The Magpie Trial: A Randomised Trial Comparing Magnesium Sulphate with Placebo for Pre-Eclampsia. Outcome for Women at 2 Years. *BJOG*, 2007,114(3):300-309.
- [11] Lu JF, Nightingale CH. Magnesium Sulfate in Eclampsia and Pre-eclampsia: Pharmacokinetic Principles. *Clin Pharmacokinet*, 2000,38(4):305-314.
- [12] Leetheeragul J, Boriboonhirunsarn D, Reesukumal K, Srisaimanee N, Horrasith S, Wataganara T. A Retrospective Review of On-Admission Factors on Attainment of Therapeutic Serum Concentrations of Magnesium Sulfate in Women Treated for a Diagnosis of Preeclampsia. *J Matern Fetal Neonatal Med*, 2020,33(2):258-266.
- [13] Hladunewich MA, Myers BD, Derby GC, Blouch KL, Druzin ML, Deen WM, Naimark DM, Lafayette RA. Course of Preeclamptic Glomerular Injury After Delivery. *Am J Physiol Renal Physiol*, 2008,294(3):F614-620.
- [14] Okusanya BO, Oladapo OT, Long Q, Lumbiganon P, Carroli G, Qureshi Z, Duley L, Souza JP, Gülmezoglu AM. Clinical Pharmacokinetic Properties of Magnesium Sulphate in Women with Pre-eclampsia and Eclampsia. *BJOG*, 2016,123(3):356-366.
- [15] Taber EB, Tan L, Chao CR, Beall MH, Ross MG. Pharmacokinetics of Ionized Versus Total Magnesium in Subjects with Preterm Labor and Preeclampsia. *Am J Obstet Gynecol*, 2002,186(5):1017-1021.
- [16] Phuapradit W, Saropala N, Haruvasin S, Thuvasethakul P. Serum level of magnesium attained in magnesium sulfate therapy for severe preeclampsia. *Asia Oceania J Obstet Gynaecol*, 1993,19(4):387-390.
- [17] Pritchard JA. The Use of the Magnesium Ion in the Management of Eclamptogenic Toxemias. *Surg Gynecol Obstet*, 1955,100(2):131-140.
- [18] Chuan FS, Charles BG, Boyle RK, Rasiah RL. Population Pharmacokinetics of Magnesium in Preeclampsia[J]. *Am J Obstet Gynecol*, 2001,185(3):593-599.
- [19] Witlin AG, Sibai BM. Magnesium sulfate therapy in preeclampsia and eclampsia. *Obstet Gynecol*, 1998, 92(5):883-889.
- [20] Alexander JM, McIntire DD, Leveno KJ, Cunningham FG. Selective magnesium sulfate prophylaxis for the prevention of eclampsia in women with gestational hypertension. *Obstet Gynecol*, 2006, 108(4): 826-832.
- [21] Cunningham FG, Leveno KJ, Bloom SL, Hauth JC, Rouse DJ, Spong CY. Williams Obstetrics. 23rd ed. *New York: McGraw Hill*, 2010:706-756.

- [22] Charoenvithya D, Manotaya S. Magnesium Sulfate Maintenance Infusion in Women With Preeclampsia: A Randomized Comparison Between 2 Gram Per Hour and 1 Gram Per Hour. *J Med Assoc Thai*, 2013,96 (4):395-398.
- [23] Dayicioglu V, Sahinoglu Z, Kol E, Kucukbas M. The Use of Standard Dose of Magnesium Sulphate in Prophylaxis of Eclamptic Seizures: Do Body Mass Index Alterations Have Any Effect on Success? *Hypertens Pregnancy*, 2003,22(3):257-265.
- [24] Brookfield KF, Su F, Elkomy MH, Drover DR, Lyell DJ, Carvalho B. Pharmacokinetics and Placental Transfer of Magnesium Sulfate in Pregnant Women[J]. *Am J Obstet Gynecol*, 2016,214(6):731.e1-9.
- [25] Salinger DH, Mundle S, Regi A, Bracken H, Winikoff B, Vicini P, Easterling T. Magnesium Sulphate for Prevention of Eclampsia: Are Intramuscular and Intravenous Regimens Equivalent? A Population Pharmacokinetic Study[J]. *BJOG*,2013,120(7):894-900.
- [26] Easterling T, Hebert M, Bracken H, Darwish E, Ramadan MC, Shaarawy S, Charles D, Abdel-Aziz T, Nasr AS, Safwal SM, Winikoff B. A Randomized Trial Comparing the Pharmacology of Magnesium Sulfate When Used to Treat Severe Preeclampsia With Serial Intravenous Boluses Versus a Continuous Intravenous Infusion[J]. *BMC Pregnancy Childbirth*, 2018,18(1):290.
- [27] Pascoal Ana CF, Katz L, Pinto MH, Santos CA, Braga Luana CO, Maia SB, Amorim Melania MR. Serum Magnesium Levels During Magnesium Sulfate Infusion at 1 Gram/Hour Versus 2 Grams/Hour as a Maintenance Dose to Prevent Eclampsia in Women With Severe Preeclampsia: A Randomized Clinical Trial[J]. *Medicine (Baltimore)*, 2019,98(32):e16779.
- [28] Du L, Wenning LA, Carvalho B, Duley L, Brookfield KF, Witjes H Greef RD, Lumbiganon P, Titapant V, Kongwattanakul K, Long Q, Sangkomkarnhang US, Gülmezoglu AM, Oladapo OT. Alternative Magnesium Sulfate Dosing Regimens for Women With Preeclampsia: A Population Pharmacokinetic Exposure-Response Modeling and Simulation Study[J]. *J Clin Pharmacol*, 2019,59(11):1519-1526.
- [29] Du L, Wenning L, Migoya E, Xu Y, Carvalho B, Brookfield K, Witjes H Greef RD, Lumbiganon P, Sangkomkarnhang U, Titapant V, Duley L, Long Q, Oladapo OT. Population Pharmacokinetic Modeling to Evaluate Standard Magnesium Sulfate Treatments and Alternative Dosing Regimens for Women With Preeclampsia[J]. *J Clin Pharmacol*, 2019,59(3):374-385.

Tables

Table 1 Maternal demographic characteristics and serum magnesium levels of the patients in two groups

Variables	Group A	Group B	P-value
	(N = 41)	(N = 52)	
Age (years)	28.00 (26.00, 33.50)	31.00 (28.25, 35.00)	0.078
Height (cm)	159.44 ± 4.42	160.84 ± 5.41	0.109
Weight (kg)	70.00 (65.00, 74.65)	71.80 (67.08, 84.50)	0.048
BMI (kg/m ²)	27.79 (25.64, 29.43)	29.40 (25.67, 31.63)	0.090
Gestational age (weeks)	31.96 ± 3.65	32.48 ± 4.13	0.285
Ccr (mL/min)	127.03 (97.49, 154.91)	161.55 (131.56, 189.19)	0.000
ALT (U/L)	28.00 (21.50, 43.00)	24.50 (20.00, 37.50)	0.200
AST (U/L)	30.00 (22.00, 35.50)	26.50 (23.00, 36.50)	0.007
Albumin (g/L)	27.20 (24.60, 30.15)	28.10 (26.50, 31.78)	0.084
Baseline serum magnesium concentrations (mmol/L)	0.76 (0.71, 0.84)	0.73 (0.68, 0.81)	0.094
Measurement time (h)	5.00 (1.00, 7.00)	1.00 (0.50, 6.00)	0.013
Loading dose 5 g			0.087
Given (n)	18 (43.90%)	14 (26.92%)	
Not given (n)	23 (56.10%)	38 (73.08%)	
Serum magnesium concentration (mmol/L)	2.08 (1.89, 2.25)	1.39 (1.21, 1.61)	0.000

BMI body mass index, Ccr creatinine clearance, ALT alanine aminotransferase, AST aspartate aminotransferase

Table 2 The results of univariate analysis for risk factors associated with sub-therapeutic blood magnesium concentration

Variables	OR	95%CI	P-value
Age	1.066	0.983-1.156	0.121
Height	1.059	0.973-1.152	0.184
Weight	1.047	1.006-1.090	0.024 [□]
BMI	1.117	0.998-1.249	0.054 [□]
Gestational age	1.035	0.931-1.150	0.524
Ccr	1.017	1.007-1.028	0.001 [□]
ALT	0.989	0.973-1.005	0.176
AST	0.994	0.977-1.010	0.449
Albumin	1.099	0.995-1.214	0.062 [□]
Maintenance dose	1.237	0.452-3.385	0.678
Measurement time	0.850	0.742-0.975	0.020 [□]
Whether the loading dose was given	0.471	0.197-1.123	0.089 [□]
Baseline serum magnesium concentrations	0.025	0.000-3.388	0.141

OR the odds ratio, CI confidence intervals, BMI body mass index, Ccr creatinine clearance, ALT alanine aminotransferase, AST aspartate aminotransferase

*Variables with P value < 0.1

Table 3 Independent risk factors associated with sub-therapeutic blood magnesium concentration.

Variables	OR	95% CI	P-value
Weight	/	/	0.467
BMI	/	/	0.774
Ccr	1.019	1.008~1.030	0.000 [△]
Albumin	/	/	0.516
Measurement time	0.807	0.688~0.947	0.008 [△]
Whether the loading dose was given	0.332	0.117~0.941	0.038 [△]

OR the odds ratio, CI confidence intervals, BMI body mass index, Ccr creatinine clearance

^Δ Statistically significant at P < 0.05

Table 4 Results of ROC curve analysis

Variables	Area under ROC curve	Youden index	Cut-off	Sensitivity/%	Specificity/%
Ccr	0.715	0.409	≥ 132.82 mL/min	75.0	65.9
Measurement time	0.650	0.323	≤ 2.375 h	70.7	61.5

Ccr creatinine clearance, ROC receiver operating characteristic

Figures

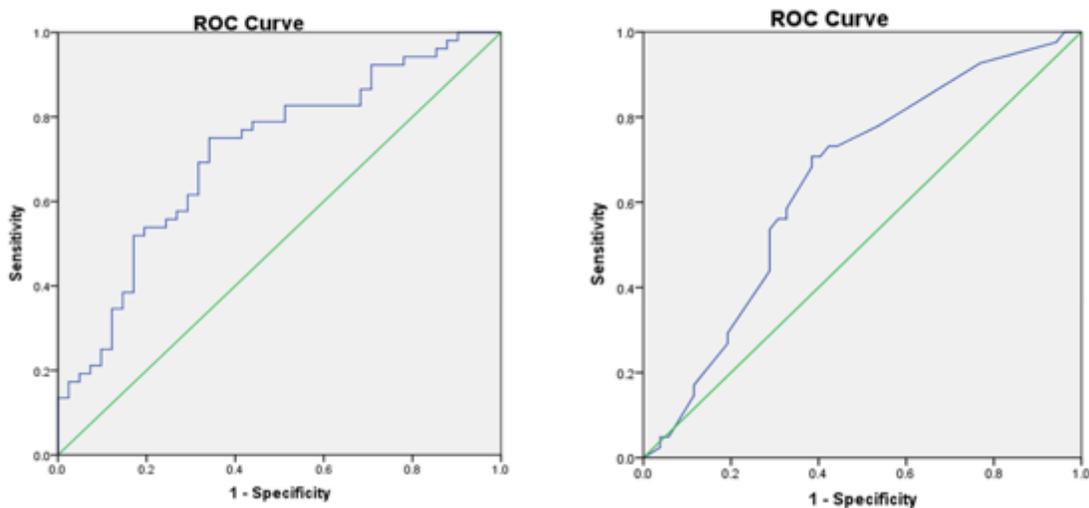


Figure 1

(a) The area under the ROC curve of Ccr was 0.715 with the cut-off value of 132.82 mL/min. (b) The area under the ROC curve of Measurement time was 0.650 with the cut-off value of 2.375 h.