# Effect of magnesium sulfate combined with labetalol on serum sFlt-1/PlGF ratio in patients with early-onset severe pre-eclampsia

YING WANG*, JING BAO* and MIN PENG

Department of Obstetrics, Maternity and Child Health Care Hospital of Hubei, Wuhan, Hubei 430000, P.R. China

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**Abstract.** The aim of the present study was to investigate the therapeutic effect of magnesium sulfate combined with labetalol on the early-onset severe pre-eclampsia (ES-PE) and explore the role of soluble fms-like tyrosine kinase-1 (sFlT-1), placental growth factor (PlGF), and sFlt-1/PlGF ratio in the treatment. A total of 164 ES-PE patients admitted to the Maternity and Child Health Care Hospital of Hubei (Wuhan, China) were assigned to this observational study. Among them, 83 patients were enrolled in group A and treated with magnesium sulfate combined with labetalol hydrochloride, and 81 patients were enrolled in group B and treated with magnesium sulfate. The therapeutic effect, adverse reactions and pregnancy outcomes in the two groups were analyzed. Serum sFlt-1 and PlGF concentrations, before and after treatment, were measured by enzyme-linked immunosorbent assay (ELISA). Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive value of pre-treatment serum sFlt-1/PlGF ratio for the clinical outcome. The effective rate was significantly higher in group A than that in group B. Group A presented superior pregnancy outcomes over group B. The serum sFlt-1 concentration and sFlt-1/PlGF ratio after treatment were significantly lower than those before treatment in groups A and B, whereas PlGF concentration was significantly higher after treatment in both groups. After treatment, group A had markedly lower serum sFlt-1 concentration and sFlt-1/PlGF ratio than group B, and markedly higher PlGF concentration than group B. The area under curve (AUC) of serum sFlt-1/PlGF ratio before treatment for the prediction of the clinical efficacy was 0.737. In conclusion, magnesium sulfate combined with labetalol could be effectively used for the treatment of ES-PE. The results of ELISA revealed that the balance of sFlT-1 and PlGF was improved after treatment and the sFlT-1/PlGF ratio was decreased. The assessment of sFlt-1/PlGF ratio before treatment was shown to have a certain predictive value for the efficacy of ES-PE treatment.

*Correspondence to:* Dr Min Peng, Department of Obstetrics, Maternity and Child Health Care Hospital of Hubei, 745 Wuluo Road, Wuchang, Wuhan, Hubei 430000, P.R. China
E-mail: pn99ze@163.com

*Contributed equally

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## Introduction

Pre-eclampsia (PE), a disorder peculiar to pregnancy, is one of the main causes of health problems in pregnant women and fetuses worldwide, featured with hypertension and proteinuria after 20 weeks of pregnancy (1,2). PE is divided into early-onset PE (before 34 weeks) and late-onset PE (after 34 weeks). The two subtypes are caused by different factors and are accompanied by different complications. Early-onset PE accounts for 5-20% of all PE cases (3). Early-onset severe pre-eclampsia (ES-PE), characterized as a serious condition with a sudden onset, is the leading factor responsible for poor prognosis in pregnant women and perinatal children, manifested as convulsion and coma (4).

At present, the pathogenesis of ES-PE is not clear. The expression of complement system's activator factors in the maternal circulation of ES-PE pregnant women is higher than that of healthy pregnant women (5,6). A previous *in vitro* study has shown that activation of the complement system can mediate the abnormal expression of angiogenic factors, which are related to the pathogenesis of PE (7). Soluble Fms-like tyrosine kinase-1 (sFlT-1) and placental growth factor (PlGF) are major anti-angiogenic factors (8). Previous studies have shown that increase of sFlT-1 levels and decrease of PlGF levels can break the balance of placental angiogenesis, resulting in insufficient invasion of trophoblast cells to the endometrium, ischemia and hypoxia in the placenta, eventually leading to PE (9,10). Thus, sFlT-1 and PlGF may play important roles in the pathogenesis of ES-PE (11). Clinically, ES-PE is mainly treated with decompression, spasmolysis and sedation (12). Magnesium sulfate has a long history of application in obstetrics. Magnesium sulfate is the first-line treatment of PE patients and is the preferred drug treatment for ES-PE (13). However, despite the wide application of magnesium sulfate as a tocolytic, and its ability to improve placental function, magnesium sulfate is not ideal for treatment because of the increase of the blood pressure caused after drug withdrawal (14). Labetalol is a β blocker that slows sinus rhythm, reduces blood pressure and peripheral vascular resistance, and is mainly used in the treatment of hypertension (15). The use

of magnesium sulfate and labetalol in PE has been explored by a number of studies (16-18); however, little is known about the efficacy of their combination in ES-PE treatment and their combined effect on sFlt-1/PlGF ratio.

In the present study, magnesium sulfate was combined with labetalol in the treatment of ES-PE patients to explore the efficacy of this regimen and its effect on sFlt-1/PlGF ratio.

## Patients and methods

*General information*. A total of 164 ES-PE patients admitted to the Maternity and Child Health Care Hospital of Hubei (Wuhan, China) from April 2014 to January 2016 were assigned to this observational study. Among them, 83 patients were enrolled in group A and treated with magnesium sulfate combined with labetalol hydrochloride, and 81 patients were enrolled in group B and treated with magnesium sulfate. Patients in group A were 22-37 years of age, with an average age of 27.6±4.3 years, and the patients' gestational age was 24-34 weeks, with an average of 28.7±2.6 weeks. In group B, patients were 22-35 years of age, with an average age of 27.2±5.5 years, and the patients' gestational age was 23-35 weeks, with an average of 28.3±2.4 weeks. The study was approved by the Ethics Committee of the Maternity and Child Health Care Hospital of Hubei. Patients who participated in this research had complete clinical data. All research subjects had full knowledge of the study and provided signed written informed consents.

*Inclusion and exclusion criteria*. The study followed the 'Strengthening the Reporting of Observational Studies in Epidemiology' (STROBE) guidelines. Inclusion criteria: Patients diagnosed with ES-PE according to the diagnostic criteria issued by the International Society for the Study of Hypertension in Pregnancy (ISSHP) (19); patients with varying degrees of abdominal pain, dyspnea, headache, urinary protein excretion, and edema; patients with a systolic blood pressure (SBP) of ~160 mmHg and a diastolic blood pressure (DBP) of ~110 mmHg; patients with complete clinical data. Exclusion criteria: Patients previously treated with other antihypertensive drugs; patients with contraindications to the drugs of the study; patients with chronic hypertension before pregnancy; patients with liver and kidney dysfunction, autoimmune diseases, connective tissue diseases, diabetes, malignant tumors, cholestasis during pregnancy, hematological diseases, abnormal blood coagulation, cognitive dysfunction, or mental illness.

*Treatment methods*. After admission, the two groups of patients were ordered to rest in bed and received supplementary oxygen, anticonvulsant treatment, diuretic therapy, and fetal lung maturation-promoting therapy. In group B, patients underwent an intravenous infusion of 15 ml of 25% magnesium sulfate (CFDA approval no. H12020994; Tianjin Kingyork Pharmaceuticals Co., Ltd.) mixed with 20 ml of 10% glucose, followed by an intravenous drip of 60 ml of 25% magnesium sulfate and 1,000 ml of 5% glucose at a 1 g/h, once a day. In group A, in addition to the drugs used in group B, an intravenous drip of 1,000 mg of labetalol hydrochloride (CFDA approval no. H20052264; Hainan Lionco Pharmaceutical Co., Ltd.) and 5% glucose was administered at 1-4 mg/min, once a day. Both groups were treated for 7 days.

*Outcome measures and efficacy evaluation*. Meditech ABPM-05 dynamic blood pressure measuring device (Shanghai Chuangxin Medical Instruments Co., Ltd.) was used to measure the SBP and DBP in the two groups of patients, before and after treatment. Mindray BS-820 automatic biochemical analyzer (Shenzhen Mindray Bio-Medical Electronics Co., Ltd.) was used to quantify the 24 h urine protein (24hUP) and 24 h urine volume (24hUV). The detection process was carried out in strict accordance with the manufacturer's instructions.

The clinical efficacy in the two groups was evaluated according to the clinical symptoms, SBP and DBP. Marked response: Clinical symptoms, such as headache, edema and proteinuria, had almost disappeared, DBP was <90 mmHg and SBP was <140 mmHg. Moderate response: Clinical symptoms, such as headache, edema, and proteinuria, were alleviated, DBP was 90-110 mmHg and SBP was 140-160 mmHg. No response: Clinical symptoms and blood pressure were not notably improved or even aggravated. Treatment efficacy rate=(marked response + moderate response)/(total no. of cases) x100%.

*Detection method*. Blood samples of 3 ml of elbow venous blood were collected from all patients, before and after treatment, and were placed in a coagulation tube. The samples were centrifugalized at 1,500 x g at 4°C for 10 min by a DT5-3 low-speed tabletop centrifuge (Beijing Era Beili Centrifuge Co., Ltd.). The upper supernatant was collected for further experimentation. Serum sFlt-1 and PlGF concentrations were measured, before and after treatment, by enzyme-linked immunosorbent assay (ELISA) (20), in strict accordance with the manufacturer's instructions of human sFlt-1 and PlGF ELISA kits (ml038106, ml024102; Shanghai Enzyme-linked Biotechnology Co., Ltd.). The blank wells (without enzyme reagents and samples) and the sample wells were set up. A total of 40 $\mu$l of sample dilution and 10 $\mu$l of the sample (dilution ratio was 5 times) were added into the sample well and sealed for incubation at 37˚C for 30 min. The liquid in each well was then discarded and the well was dried and washed 5 times. Enzyme-labeling reagent (50 $\mu$l) was added into the sample well and incubated at 37˚C for 30 min. The liquid in each well was discarded and the well was dried and washed 5 times. Next, 50 $\mu$l of developer A and developer B were added into the well and incubated at 37˚C for 15 min in the dark for color development. Finally, 50 $\mu$l of stop solution were added into each well, and the blue liquid turned yellow. The blank wells were adjusted to zero value. The optical density of each well was detected at a wavelength of 450 nm using a Model 680 automatic microplate reader (Bio-Rad Laboratories, Inc.), and the concentrations of sFlt-1 and PlGF were calculated. sFlt-1 sensitivity ranges from 12.5 to 400 pg/ml and PlGF sensitivity ranges from 2.5 to 80 pg/ml.

*Statistical analysis*. SPSS 22.0 software (IBM Corp.) was used for statistical analysis and the data were visualized using GraphPad Prism 6 software (GraphPad Software, Inc.).

Table I. General information of patients in groups A and B [n (%), mean ± SD].

| Factors | Group A (n=83) | Group B (n=81) | $t/\chi^2$ | P-value |
|---|---|---|---|---|
| Age (years) | 27.6±4.3 | 27.2±5.5 | 0.520 | 0.604 |
| Gestational age (weeks) | 28.7±2.6 | 28.3±2.4 | 1.023 | 0.308 |
| Maternal type | | | 0.236 | 0.627 |
| Primipara | 44 (53.01) | 46 (56.79) | | |
| Multipara | 39 (46.99) | 35 (43.21) | | |
| BMI ($kg/m^2$) | 22.86±2.26 | 22.35±2.43 | 1.392 | 0.166 |
| Mode of delivery | | | 0.195 | 0.658 |
| Cesarean section | 25 (30.12) | 27 (33.33) | | |
| Natural labor | 58 (69.88) | 54 (66.67) | | |
| Smoking | | | 0.316 | 0.574 |
| Yes | 15 (18.07) | 12 (14.81) | | |
| No | 68 (81.93) | 69 (85.19) | | |
| Drinking | | | 0.075 | 0.785 |
| Yes | 16 (19.28) | 17 (20.99) | | |
| No | 67 (80.72) | 64 (79.01) | | |
| Place of residence | | | 1.005 | 0.316 |
| Urban area | 60 (72.29) | 64 (79.01) | | |
| Rural area | 23 (27.71) | 17 (20.99) | | |
| Hemoglobin | 126.15±24.43 | 119.58±22.07 | 1.806 | 0.073 |
| Platelet count ($x10^9/l$) | 166.13±77.06 | 168.26±67.76 | 0.188 | 0.851 |
| White blood cell count ($x10^9/l$) | 16.02±2.21 | 15.68±2.29 | 0.968 | 0.335 |
| Serum total protein (g/l) | 54.31±7.02 | 54.73±6.95 | 0.385 | 0.701 |
| Serum albumin (g/l) | 27.49±4.36 | 28.15±4.01 | 1.008 | 0.315 |
| Alanine aminotransferase (U/l) | 36.43±22.19 | 33.84±20.57 | 0.775 | 0.440 |
| Serum creatinine ($\mu$mol/l) | 77.82±7.56 | 76.25±7.32 | 1.351 | 0.179 |
| Cholesterol ($\mu$mol/l) | 6.81±0.95 | 6.73±1.02 | 0.520 | 0.604 |
| Triglyceride (mmol/l) | 4.08±0.92 | 3.97±0.89 | 0.778 | 0.438 |

BMI, body mass index.

Measurement data were expressed as the mean ± standard deviation (SD) and were compared between the two groups by independent samples t-test. Count data were expressed as the case number and percentage [n (%)], and were compared between the two groups by Chi-square test (Fisher's exact test was used when the minimum theoretical frequency in the Chi-square test was <5). Intergroup comparisons between the pre-treatment and the post-treatment data were analyzed by one-way ANOVA, whereas the pairwise comparisons were analyzed by the Bonferroni post hoc test. ROC curve analysis was carried out to evaluate the predictive value of sFlt-1/PlGF ratio for clinical efficacy. P<0.05 was considered to indicate a statistically significant difference.

## Results

*General information of the two groups*. Groups A and B were not significantly different in age, gestational age, maternal type, body mass index (BMI), mode of delivery, smoking, drinking, place of residence, hemoglobin, platelet count, white blood cell count, serum total protein, serum albumin, alanine aminotransferase, serum creatinine, cholesterol and triglycerides (P>0.05) (Table I).

*Treatment efficacy, adverse reactions and pregnancy outcomes in the two groups*. The effective rate was 91.57% in group A, significantly higher than that in group B (80.25%) (P<0.05). Groups A and group B were not markedly different in the incidence rate of adverse reactions (P>0.05). Group A had superior pregnancy outcomes over group B. Details are shown in Tables II-IV.

*SBP, DBP, 24hUP and 24hUV before and after treatment in the two groups*. No significant difference in SBP, DBP, 24hUP and 24hUV was detected between groups A and B before treatment (P>0.05). After treatment, SBP, DBP and 24hUP were markedly decreased in both groups (P<0.001), whereas 24hUV was markedly increased (P<0.001). After treatment, SBP, DBP and 24hUP in group A were significantly lower than those in group B (P<0.001), whereas 24hUV was significantly higher in group A than in group B (P<0.001). The data are presented in Table V.

Table II. Comparison of treatment efficacy rate between groups A and B [n (%)].

| Group | n | Marked response | Moderate response | No response | Effective rate (%) |
|---|---|---|---|---|---|
| Group A | 83 | 39 (46.99) | 37 (44.58) | 7 (8.43) | 91.57 |
| Group B | 81 | 32 (39.51) | 33 (40.74) | 16 (19.75) | 80.25 |
| $\chi^2$ | - | - | - | - | 4.356 |
| P-value | - | - | - | - | 0.037 |

Table III. Comparison of adverse reactions between groups A and B [n (%)].

| Group | n | Nausea and vomiting | Headache | Bad appetite | Facial flushing | Total incidence (%) |
|---|---|---|---|---|---|---|
| Group A | 83 | 3 (3.61) | 2 (2.41) | 4 (4.82) | 1 (1.20) | 12.05 |
| Group B | 81 | 1 (1.23) | 1 (1.23) | 2 (2.47) | 3 (3.70) | 8.64 |
| $\chi^2$ | - | 0.232 | 0.000 | 0.149 | 0.282 | 0.512 |
| P-value | - | 0.630 | 0.983 | 0.700 | 0.596 | 0.474 |

Table IV. Comparison of pregnancy outcome between groups A and B [n (%)].

| Group | n | Fetal distress | Placental abruption | Post-partum hemorrhage | Neonatal asphyxia | Preterm birth | Total incidence (%) |
|---|---|---|---|---|---|---|---|
| Group A | 83 | 2 (2.41) | 1 (1.20) | 4 (4.82) | 4 (4.82) | 3 (3.61) | 16.87 |
| Group B | 81 | 7 (8.64) | 5 (6.17) | 9 (11.11) | 10 (12.35) | 9 (11.11) | 49.38 |
| $\chi^2$ | - | 3.070 | 1.634 | 2.224 | 2.974 | 3.397 | 19.620 |
| P-value | - | 0.080 | 0.201 | 0.136 | 0.085 | 0.065 | <0.001 |

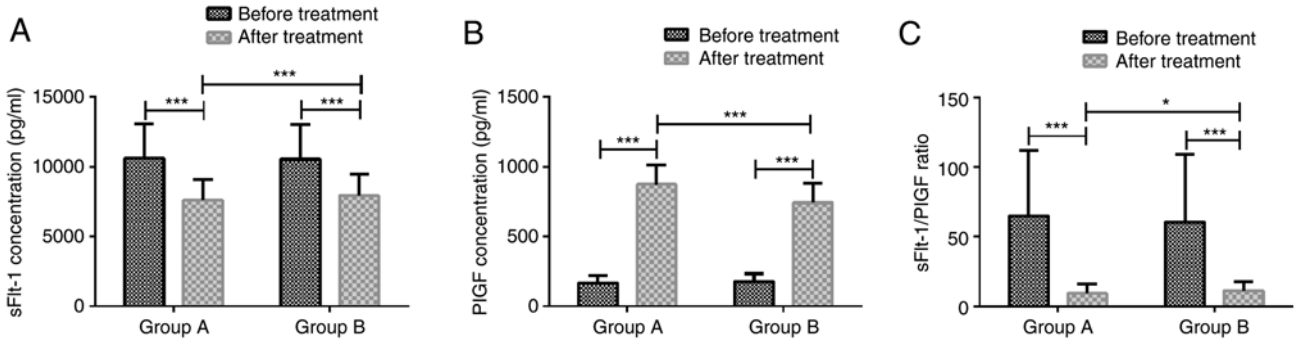


Figure 1. Serum sFlt-1 and PlGF concentrations, and their ratio before and after treatment in groups A and B. (A) Serum sFlt-1 concentration, (B) serum PlGF concentration and (C) sFlt-1/PlGF ratio before and after treatment in groups A and B. *P<0.05; ***P<0.001. sFlT-1, soluble fms-like tyrosine kinase-1; PlGF, placental growth factor.

*Serum sFlt-1 and PlGF concentrations, and their ratio before and after treatment in the two groups*. sFlt-1/PlGF ratio was 68.86±47.26 in group A and 64.56±48.35 in group B before treatment, and 9.32±6.69 in group A and 11.37±6.56 in group B after treatment. Groups A and B were not markedly different in serum sFlt-1 level, PlGF level, and sFlt-1/PlGF ratio before treatment (P>0.05). After treatment, serum sFlt-1 concentration and sFlt-1/PlGF ratio were significantly lower than those before treatment in groups A and B (P<0.001), whereas PlGF concentration was significantly higher than that before treatment in both groups (P<0.001). After treatment, group A had markedly lower serum sFlt-1 concentration (P<0.001), lower sFlt-1/PlGF ratio (P<0.05), and markedly higher PlGF concentration (P<0.001) than group B (Fig. 1).

*Predictive value of pre-treatment serum sFlt-1/PlGF ratio for the treatment effect*. In both groups A and B, the sFlt-1/PlGF ratio was notably lower in patients with a marked or moderate

Table V. Comparison of SBP, DBP, 24hUP and 24hUV (mean ± SD).

| Factors | Group A (n=83) | Group B (n=81) | t | P-value |
|---|---|---|---|---|
| SBP (mmHg) | | | | |
| Before treatment | 176.35±15.28 | 174.69±15.63 | 0.688 | 0.493 |
| After treatment | 138.43±14.52 | 156.25±13.48 | 7.734 | <0.001 |
| t | 16.560 | 7.955 | - | - |
| P-value | <0.001 | <0.001 | - | - |
| DBP (mmHg) | | | | |
| Before treatment | 117.28±16.24 | 116.52±15.75 | 0.304 | 0.761 |
| After treatment | 95.13±11.68 | 108.52±12.36 | 6.058 | <0.001 |
| t | 10.080 | 3.598 | - | - |
| P-value | <0.001 | 0.002 | - | - |
| 24hUP (g/l) | | | | |
| Before treatment | 3.41±1.28 | 3.38±1.15 | 0.158 | 0.875 |
| After treatment | 1.25±0.67 | 1.89±1.02 | 3.886 | <0.001 |
| t | 13.200 | 8.993 | - | - |
| P-value | <0.001 | <0.001 | - | - |
| 24hUV (ml) | | | | |
| Before treatment | 946.28±46.42 | 951.53±43.61 | 0.746 | 0.457 |
| After treatment | 2,423.41±196.15 | 1,821.41±185.36 | 20.19 | <0.001 |
| t | 66.760 | 41.110 | - | - |
| P-value | <0.001 | <0.001 | - | - |

SBP, systolic blood pressure; DBP, diastolic blood pressure; 24hUP, 24 h urine protein; 24hUV, 24 h urine volume.

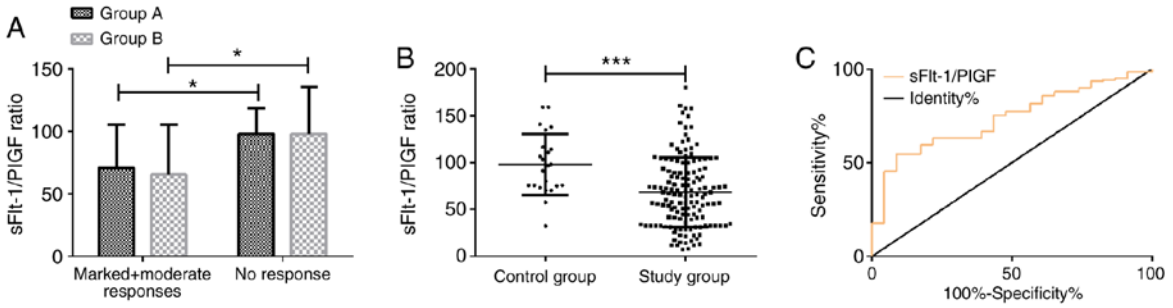


Figure 2. Predictive value of serum sFlt-1/PlGF ratio before treatment for the treatment outcome. (A) Comparison of sFlt-1/PlGF ratio between patients with marked or moderate response to treatment and patients with no response to treatment. (B) Comparison of serum sFlt-1/PlGF ratio between the study and the control group. (C) ROC curve of serum sFlt-1/PlGF ratio before treatment for the prediction of the therapeutic effect. *P<0.05; ***P<0.001. sFlT-1, soluble fms-like tyrosine kinase-1; PlGF, placental growth factor; ROC, receiver operating characteristic.

response than in patients with no response (P<0.05). Group A was not significantly different from group B in reference to the patients with a marked or moderate response to the treatment or the patients with no response at all (P>0.05). Patients with marked or moderate response (141 cases) were considered as the study group, whereas patients with no response (23 cases) were considered as the control group. The serum sFlt-1/PlGF ratio was 68.28±37.28 in the study group and 98.03±32.80 in the control group. The serum sFlt-1/PlGF ratio in the study group before treatment was significantly lower than that in the control group (P<0.001). ROC curve analysis of the serum sFlt-1/PlGF ratio before treatment for predicting the treatment effect demonstrated that the area under curve (AUC) was 0.737 (95% CI, 0.643-0.831), the sensitivity was 54.61%, the specificity was 91.30%, and the best cut-off value was 70.41 (Fig. 2).

## Discussion

ES-PE is very dangerous for pregnant women with hypertension. Characterized by quick onset and rapid progression, ES-PE can cause organ failure, fetal distress and asphyxia (4). ES-PE poses a big threat to the safety of both the mother and the baby (21) and therefore, its treatment is a hot topic in clinical research.

Magnesium sulfate is the preferred drug for ES-PE treatment. Magnesium sulfate can promote peripheral blood vessel relaxation, lower blood pressure, relieve skeletal muscle

spasm, increase uterine artery blood flow, and boost diuretic action (22). Labetalol is a kind of salicylamide derivative, which can block α and β receptors, effectively dilate blood vessels, reduce peripheral blood vessel resistance, decrease myocardial oxygen consumption and cardiac preload, and exert antihypertensive effects (23). Numerous studies have been reported on magnesium sulfate and labetalol in PE patients. In the study by Das *et al* (24), a low dosage of magnesium sulfate was proven to be safe and not toxic for PE pregnant women and neonates. In the study by Sun *et al* (25), CYP2D6 and CYP2C9 gene polymorphisms were associated with the pathogenesis of ES-PE patients, and the allele of G in CYP2D6 gene rs1065852 was considered possibly related to the efficacy of labetalol treatment. In the present study, the effective rate in group A was significantly higher than that in group B. Blood pressure was remarkably decreased to near the normal range in ES-PE patients treated with magnesium sulfate combined with labetalol. Patients in group A had markedly lower 24hUP and markedly higher 24hUV than patients in group B, indicating that the combination of magnesium sulfate and labetalol can promote urination, enhance the permeability of the glomerulus and reduce the production of proteinuria. These results suggest that magnesium sulfate combined with labetalol is effective in treating ES-PE and can relieve the clinical symptoms of patients. In the study by Abdelrahman *et al* (26), 25 ES-PE patients treated with magnesium sulfate combined with labetalol or hydralazine presented good tolerance to the drug treatment, and their blood pressure was effectively and safely controlled. In addition, the fetal heart rate was not significantly changed after treatment, which is similar to the results of the present study. Magnesium sulfate can rarely threaten maternal life; however, magnesium can promote peripheral vasodilation, leading to adverse reactions, such as blushing, nausea, vomiting, and headache (27). In the present study, group A was not markedly different from group B in the incidence of adverse reactions, and group A had notably superior pregnancy outcomes over group B, indicating that magnesium sulfate combined with labetalol is fairly safe and results in better pregnancy outcomes. Xie *et al* (28) reported that labetalol could inhibit the agglutination of platelets and promote fetal lung maturation, without causing a rapid decrease of blood pressure and palpitations. Thus, it can be inferred that, although patients from groups A and B suffered from certain adverse reactions, labetalol did not aggravate the adverse reactions of patients and improved the perinatal outcomes.

Angiogenic markers are critical in the diagnosis and subsequent prediction and treatment of PE and placental-related diseases (29). The increase of serum sFlt-1 levels and the decrease of PlGF levels result in an increased sFlt-1/PlGF ratio. In women diagnosed with PE combined with intrauterine fetal growth restriction or stillbirth (placenta-related disease), an increase in sFlt-1/PlGF ratio can be detected in the late pregnancy (30). In the study by Ohkuchi *et al* (31), a cut-off value of 45 for the sFlt-1/PlGF ratio resulted in the best sensitivity and specificity for the diagnosis of pre-eclampsia (97 and 95%, respectively), and for the diagnosis of early-onset pre-eclampsia (100 and 95%, respectively). In the study by Schoofs *et al* (32), repeated measurements of the sFlt-1/PlGF ratio identified pathological pregnancy outcomes in patients with intrauterine fetal growth restriction before diagnosis. Thus, the importance of sFlt-1/PlGF ratio in ES-PE diagnosis and prognosis is promising. However, little is known about the changes of sFlt-1/PlGF ratio and its effects during treatment. In the present study, the serum sFlt-1 concentration and sFlt-1/PlGF ratio after treatment were significantly lower than those before treatment in both groups A and B, whereas PlGF concentration was significantly higher than that before treatment. After treatment, group A had markedly lower serum sFlt-1 concentration and sFlt-1/PlGF ratio, and markedly higher PlGF concentration, than group B. These results suggest that the effects of magnesium sulfate combined with labetalol to improve the balance of sFlt-1/PlGF may be one of the mechanisms of ES-PE treatment. Xu *et al* (33) reported that some antihypertensive drugs used during pregnancy could improve the cellular interaction between trophoblasts and endothelial cells exposed to TNF-α. For example, labetalol could act on sFlt-1 to promote the integration of trophoblast cells. The possible reason for this function may be the fact that labetalol can directly act on vascular smooth muscle cells and improve the function of vascular endothelium by regulating the secretion of inflammatory factors in the blood vessels (34). The present study further investigated the role of sFlt-1, PlGF, and their ratio in the treatment of ES-PE patients. The sFlt-1/PlGF ratio before treatment was markedly lower in patients with a marked or moderate response to treatment than in patients with no response in both groups A and B, and the AUC of sFlt-1/PlGF ratio for predicting the treatment effect was 0.737, suggesting that pre-treatment sFlt-1/PlGF ratio has a certain predictive value for the treatment effect. Therefore, sFlt-1/PlGF ratio is a potential predictor of the treatment effect of ES-PE patients. However, this study failed to identify the contributing factors affecting the treatment effect of ES-PE patients or to reveal the underlying mechanism of magnesium sulfate and labetalol for treating ES-PE. These issues will be the aim of our future research.

In conclusion, magnesium sulfate combined with labetalol can be effectively used for the treatment of ES-PE and can reduce the serum sFlt-1/PlGF ratio. The assessment of sFlt-1/PlGF ratio before treatment has a certain predictive value for the efficacy of ES-PE treatment.

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**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Authors' contributions**

YW wrote the manuscript, interpreted and analyzed the patient data. JB designed the study and was responsible for the patient

treatment and the detection methods. MP was responsible for the analysis and discussion of the data. All authors read and approved the final manuscript.

### Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Maternity and Child Health Care Hospital of Hubei (Wuhan, China). Patients who participated in this research, had complete clinical data. Signed written informed consents were obtained from the patients and/or guardians.

### Patient consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests.

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