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Regulation of magnesium sulfate combined with nifedipine and labetalol on disease-related molecules in serum and placenta in the treatment of preeclampsia

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Abstract. – OBJECTIVE: To explore the regulatory effect of magnesium sulfate combined with nifedipine and labetalol on disease-related molecules in serum and placenta in the treatment of preeclampsia.

PATIENTS AND METHODS: Altogether 100 patients with preeclampsia admitted to the Children & Women's Healthcare of Laiwu City were selected. They were divided into control group and experimental group according to different treatment methods. Among them, 51 patients in the control group were treated with magnesium sulfate combined with nifedipine, and 49 patients in the experimental group were treated with labetalol on the basis of the treatment in the control group. The therapeutic effects of the two methods were compared. The levels of the following factors in the two groups were compared: kallikrein expression, pregnancy-associated plasma protein A (PAPP-A), pregnancy-specific β1 glycoprotein (SPI), placental growth factor (PLGF), human placental prolactin (HPL), transforming growth factor β1(TGF-β1), vascular cell adhesion molecule 1 (VCAM-1) and E-selectin in serum and placenta tissues.

RESULTS: After treatment, the blood pressure in the experimental group was lower than that in the control group ($p<0.05$). The expression of kallikrein in serum and placental tissue of the patients in the experimental group was higher than that of the patients in the control group ($p<0.05$); PAPP-A level was lower than that in the control group ($p<0.05$); TGF-β1 level was higher than that in the control group ($p<0.05$); VCAM-1 and E-selectin were lower than those in the control group ($p<0.05$), and kallikrein and TGF-β1 in serum and placenta in the non-occurrence group were higher than those in the occurrence group ($p<0.05$). The serum and placenta PAPP-A, VCAM-1, and E-selectin in the non-occurrence group were lower than those in the occurrence group ($p<0.05$).

CONCLUSIONS: Magnesium sulfate combined with nifedipine and labetalol has good efficacy in the treatment of preeclampsia. They can promote the expression of endogenous kallikrein, reduce the level of pregnancy-related hypertension predictors, and weaken the infiltration ability of cytotrophoblasts.

Key Words:
Magnesium sulfate, Nifedipine, Labetalol, Preeclampsia.

Introduction

Preeclampsia is a specific disease in pregnancy. Its high morbidity and mortality are closely related to the severity of preeclampsia[1-3]. The incidence rate is estimated to be 3%-10% of all pregnant women; preeclampsia is also the main cause of maternal death, accounting for 15%-20% in developed countries[4]. Some scholars suppose that preeclampsia is related to the childbearing age and placental causes. It is generally suggested that it is caused by placental release of anti-angiogenic factors into circulation after placental ischemia, and it is easy to cause lifelong complications of cardiovascular and renal diseases, increasing women's stroke risk by 6 times[5-7].

At present, the only way is believed to be delivery, but selective delivery is required[8,9]. According to the American College of Obstetricians and

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Gynecologists in 2013, the gold standard for the treatment of preeclampsia is magnesium sulfate injection, since magnesium sulfate has neuroprotective effect by reducing neuro-inflammation and cerebral edema while alleviating blood pressure. However, the short action time cannot ensure stable blood pressure of patients[10-12]. Nifedipine is a calcium channel blocker with strong arterial vasodilation activity and acts directly on vascular smooth muscle cells and peripheral resistance vessels, producing vasodilation effect to reduce systemic blood pressure. However, due to its relaxation effect on uterus, many health care providers do not trust it[13,14]. Magnesium sulfate combined with nifedipine can significantly reduce blood pressure, and further reduce the incidence of pregnancy complications and adverse outcomes of perinatal infants, but it lacks support of research and data[15]. Labetalol, a selective α-1 and non-selective β-receptor antagonist, can induce peripheral vasodilation, prevent reflex tachycardia and maintain cardiac output. However, labetalol must be replaced in the treatment of black women and patients with contraindications such as asthma[16,17]. According to Flint et al[18], magnesium sulfate combined with nifedipine and labetalol can stabilize the blood pressure level of patients with gestational hypertension, improve hemodynamics and coagulation indexes, and has certain curative effect on eclampsia.

At present, there are few researches on the treatment of preeclampsia with magnesium sulfate combined with nifedipine and labetalol. Our aim is to provide a better clinical reference for the treatment of preeclampsia.

Patients and Methods

General Information

This is a prospective study. Altogether 100 patients (aged 22-35 years) with preeclampsia admitted to the Children & Women's Healthcare of Laiwu City were selected. They were divided into control group and experimental group according to different treatment methods. Among them, 51 patients in the control group were treated with magnesium sulfate combined with nifedipine, and 49 patients in the experimental group were treated with labetalol on the basis of the treatment in the control group.

Inclusion and Exclusion Criteria

Inclusion criteria: (1) patients diagnosed with preeclampsia, and the diagnostic criteria included the newly onset hypertension and proteinuria after 20 weeks of pregnancy[19]. Systolic pressure was more than 140 mmHg (1 mmHg=0.133 kPa) or diastolic pressure more than 90 mmHg with proteinuria more than 0.3 g/24 h; (2) patients with abnormal liver function (elevated AST or ALT concentration), continuous elevated blood pressure, persistent headache or visual impairment or other cranial nerve symptoms, oligohydramnios or growth restriction in the fetus.

Exclusion criteria: (1) patients with heart failure; (2) patients with elevated blood pressure and proteinuria before pregnancy; (3) patients who have taken aspirin intervention before treatment. This investigation was approved by the Ethics Committee of the Children & Women's Healthcare of Laiwu City. All patients and their families were informed, and the informed consent forms were signed by patients.

Treatment Methods

The control group was treated with magnesium sulfate combined with nifedipine. The load of magnesium sulfate (Harbin Pharmaceutical Group Sanjing Pharmaceutical Co., Ltd., SFDA Approval No. H23021033, Heilongjiang, China) was 5 g dissolved in 100 ml of 5% glucose injection (Beijing Fei Sen Euska Pharmaceutical Co., Ltd., SFDA Approval No. H20033557, Beijing, China), VT, 30 drops/min. The total amount of magnesium sulfate was controlled under 25 g per day. Nifedipine (Nanjing Baijingyu Pharmaceutical Co., Ltd., H32024516, Jiangsu, China) was given orally, 10 mg, twice a day. The experimental group was given labetalol (Jiangsu Tianhe Pharmaceutical Co., Ltd., H32026119, Jiangsu, China), 100 mg, PO, three times a day on the basis of the treatment in the control group.

Observation Indicators

The therapeutic effects, blood pressure changes, pregnancy complications and neonatal outcomes of the two groups were compared. The levels of kallikrein, PAPP-A, SPI, PLGF, HPL, TGF-β1, VCAM-1 and E-selectin in serum and placenta tissues of the two groups were compared.

Detection Methods

Evaluation criteria for curative effect

Effective: After receiving treatment, the patient's blood pressure and proteinuria decreased, and other accompanying symptoms were significantly improved. Ineffective: none of the above

symptoms changed or aggravated. Effective rate = the number of effective cases/total number *100%.

Comparison of blood pressure between the two groups before and after treatment

Mercury sphygmomanometer (diving model: health box type A family pack) was used to detect the blood pressure under quiet breathing 0.5 h before treatment and 2 h after treatment.

Detection of kallikrein expression in serum and placenta

The peripheral blood of patients after treatment and placental tissue after delivery were collected, and the expression of releasing enzyme in serum and placental tissue was detected by enzyme immunoassay. The specific operation was carried out by professional laboratory technicians. The Kallikrein assay kit was purchased from Shanghai Yiji Industrial Co., Ltd. (Art. No.: GD-VM8321, Shanghai, China).

Detection of PAPP-A, SPI, PLGF and HPL levels in serum and placenta

The levels of PAPP-A, SPI, PLGF and HPL in serum and placental fluid were measured by enzyme-linked immunosorbent assay (ELISA) using a microplate reader (Thermo Fisher Scientific MK3, Waltham, MA, USA). The specific test operation was operated by professional laboratory technicians. PAPP-A (Art. No.: EHPAPPA), PLGF (Art. No.: EHPGF), and HPL (Art. No.: EHIAPRL) kits were purchased from Thermo Fisher Scientific (Waltham, MA, USA). The SPI test kit was purchased from Shanghai Yiji Industrial Co., Ltd. (Art. No.: BN65497096, Shanghai, China).

Detection of TGF-β1, VCAM-1 and E-selectin in serum and placenta tissue

The levels of TGF-β1, VCAM-1 and E-selectin in serum were detected by enzyme-linked immunosorbent assay kit (ELISA; Beijing Beiruida Pharmaceutical Technology Co., Ltd., model: YS72-YS-E-AMT, Beijing, China). The localization of TGF-β1, VCAM-1, and E-selectin in placental tissue was detected by immunohistochemistry kit (Neo Bioscience Co., Ltd., Beijing, China) using streptavidin-peroxidase (SP) method of immunohistochemistry. The specific test operation was operated by professional laboratory technicians.

Statistical Analysis

SPSS 19.0 (SPSS Inc., Chicago, IL, USA) was used to analyze the collected data. The counting data were expressed by rate, and χ^2 was used for the comparison of rates. The measurement data were expressed by mean±standard deviation (mean±SD). The comparison between the two groups was conducted by *t*-test. ROC curve was used to analyze the predictive value of PAPP-A, TGF-β1, VCAM-1, and E-selectin levels in serum for adverse neonatal outcomes. The *p*-value less than 0.05 was regarded as statistical significance.

Results

Clinical Data

The age of the control group and the experimental group was (24.5±2.7) years and (23.7±2.5) years, respectively. There was no statistical difference in general clinical data between the two groups ($p > 0.05$; Table I).

Clinical Efficacy

Twenty four hours after treatment, there was no significant difference in the effective rate between the two groups ($p < 0.05$), but the effective rate in the experimental group was higher than that in the control group (Table II).

Comparison of Blood Pressure etween the two Groups Before and After Treatment

After treatment, systolic pressure (Figure 1A) and diastolic pressure (Figure 1B) in the experimental group were lower than those in the control group ($p < 0.05$; Figure 1).

Pregnancy Complications

There were no serious complications in the experimental group such as eclampsia, but there were 3 cases of placental abruption, 1 case of premature delivery, and 9 cases of cesarean section. The incidence of complications was 26.53%. In the control group, eclampsia was in 1 case, placental abruption in 6 cases, premature delivery in 3 cases, cesarean section in 14 cases, and the incidence of complications was 47.06%, with statistically significant difference between the two groups ($p < 0.05$; Table III).

Adverse Outcomes of Newborns

The control group had 3 cases of perinatal death, 4 cases of fetal growth restriction, 1 case of neonatal necrotizing enteritis, 5 cases of fetal distress, 5 cases of neonatal asphyxia, and 3 cases of premature infants. In the experimental group, there was 1 case of

Table I. Clinical data.

	Control group (n=51)	Experimental group (n=49)	χ^2/t	*p*
Age	24.5± 2.7	23.7± 2.5	1.522	0.1313
BMI (kg/cm²)	21.96± 2.63	22.14± 2.05	0.3779	0.7064
Pregnancy (weeks)	25.1±2.1	24.6±2.4	1.098	0.2752
Smoking history			0.013	0.9105
Yes	12 (23.53)	12 (24.49)		
No	39 (76.47)	37 (75.51)		
Education level			0.491	0.483
University and above	32 (62.75)	34 (69.39)		
High school and above	19 (37.25)	15 (30.61)		
Residence			1.080	0.299
Urban	36 (70.59)	39 (79.59)		
Rural	15 (29.41)	10 (20.41)		
Menstrual condition			0.112	0.915
Yes	40 (78.43)	38 (74.51)		
No	11 (21.57)	11 (22.45)		
Uterine fibroids			0.265	0.607
Yes	17 (33.33)	14 (28.57)		
No	34 (66.67)	35 (71.43)		
Other surgical history			0.331	0.565
Yes	20 (39.22)	22 (44.90)		
No	31 (60.78)	27 (55.10)		
Drug allergy history			0.114	0.736
Yes	4 (7.84)	3 (6.12)		
No	47 (92.16)	46 (93.88)		

Table II. Clinical efficacy.

	Control group (n=51)	Experimental group (n=49)	χ^2	*p*
Effective	39 (76.47)	42 (85.71)	1.387	0.239
Ineffective	12 (23.53)	7 (14.29)	1.387	0.239

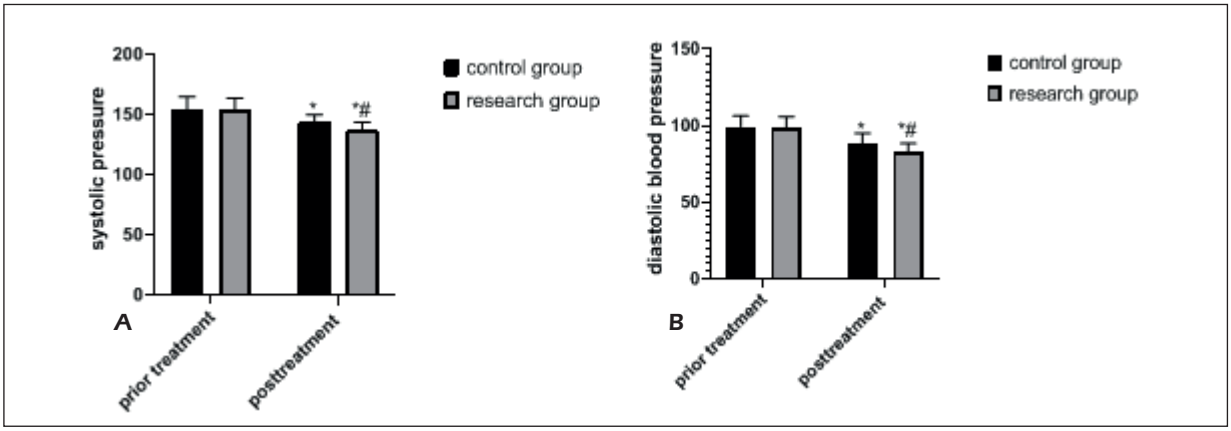

Figure 1. Blood pressure (mmHg) before and after treatment in both groups. **A**, Comparison of systolic blood pressure before and after treatment between control group and experimental group. **B**, Comparison of diastolic blood pressure between control group and experimental group before and after treatment. The results of t-test analysis showed that the systolic blood pressure and diastolic blood pressure of the experimental group were lower than those of the control group after treatment.
*indicates that compared with the same group, $p<0.05$; #indicates that compared with the control group, $p<0.05$.

Table III. Pregnancy complications n (%).

	Control group (n=51)	Experimental group (n=49)	χ^2	*p*
Placental abruption	6 (11.76)	3 (6.12)	0.971	0.324
Premature birth	3 (5.88)	1 (2.04)	0.960	0.327
Cesarean section	14 (27.45)	9 (18.37)	1.164	0.281
Puerperal convulsion	1 (1.96)	0 (0.00)	0.971	0.325
Total	24 (47.06)	13 (26.53)	4.518	0.034

Table IV. Adverse outcomes of newborns n (%).

	Control group (n=51)	Experimental group (n=49)	χ^2	*p*
Perinatal death	3 (5.88)	1 (2.04)	0.960	0.327
Fetal growth restriction	4 (7.84)	2 (4.08)	0.627	0.429
Fetal distress in uterus	5 (9.80)	2 (4.08)	1.257	0.262
Neonatal asphyxia	5 (9.80)	1 (2.04)	2.670	0.102
Premature	3 (5.88)	1 (2.04)	1.001	0.317
Neonatal necrotizing enteritis	1 (1.96)	0 (0.00)	0.971	0.325
Total	21 (41.18)	7 (14.29)	8.964	0.003

perinatal death, 2 cases of fetal growth restriction, 0 cases of neonatal necrotizing enteritis, 2 cases of fetal distress, 1 case of neonatal asphyxia, and 1 case of premature infant. The difference was statistically significant ($p < 0.05$; Table IV).

Expression Level of Serum and Placenta Tissue Related Factors

After treatment, kallikrein and TGF-β1 in serum and placental tissue of the patients in the experimental group were higher than those in the control group ($p < 0.05$). PAPP-A, VCAM-1, and E-selectin levels in serum and placental tissue of the experimental group were lower than those in the control group ($p < 0.05$). SPI, PLGF, and HPL in the experimental group were not significantly different from those in the control group ($p < 0.05$; Table V).

Relationship Between Disease Related Molecules and Adverse Outcomes of Newborns

The levels of kallikrein and TGF-β1 in serum and placenta of the non-occurrence group were higher than those of the occurrence group ($p <$

Table V. Expression levels of serum and placenta related factors.

Test item	Detection site	Control group	Experimental group	*t*	*p*
Kallikrein	Serum	1.35±0.04	1.59±0.04	29.99	<0.001
	Placenta	1.34±0.11	1.58±0.07	12.96	<0.001
PAPP-A (mIU/ml)	Serum	1.85±0.46	1.06±0.35	9.636	<0.001
	Placenta	1.87±0.33	1.22±0.37	9.280	<0.001
SPI (μg/ml)	Serum	0.91±0.09	0.92±0.07	0.619	0.538
	Placenta	0.89±0.07	0.91±0.06	1.531	0.129
PLGF (pg/ml)	Serum	334.12±45.45	328.23±41.45	0.676	0.500
	Placenta	365.46±44.35	356.18±45.34	1.035	0.303
HPL (μg/ml)	Serum	15.66±1.23	15.23±1.34	1.673	0.098
	Placenta	16.94±1.43	16.54±1.56	1.337	0.184
TGF-β1 (pg/ml)	Serum	223.07±21.08	262.08±37.53	6.441	<0.001
	Placenta	67.32±2.41	72.83±3.46	9.271	<0.001
VCAM-1 (%)	Serum	78.30±10.67	45.14±3.82	20.520	<0.001
	Placenta	98.04±2.05	86.59±4.02	18.050	<0.001
E-selectin (%)	Serum	58.43±3.29	45.57±2.61	21.600	<0.001
	Placenta	67.26±2.43	54.51±0.81	34.91	<0.001

Table VI. Relationship between disease related molecules and adverse outcomes of newborns.

Test item	Detection site	Occurrence group (n=28)	Non-occurrence group (n=72)	*t*	*p*
Kallikrein	Serum	1.35±0.03	1.52±0.12	7.386	<0.001
	Placenta	1.33±0.11	1.52±0.14	6.443	<0.001
PAPP-A (mIU/ml)	Serum	1.81±0.46	1.32±0.56	4.118	<0.001
	Placenta	1.87±0.32	1.44±0.48	4.371	<0.001
TGF-β1 (pg/ml)	Serum	218.81±21.62	251.28±36.38	4.421	<0.001
	Placenta	66.79±2.34	71.27±3.88	5.709	<0.001
VCAM-1 (%)	Serum	80.48±10.28	54.89±15.84	7.912	<0.001
	Placenta	98.08±1.84	90.24±6.43	6.334	<0.001
E-selectin (%)	Serum	58.96±3.09	49.86±6.95	6.661	<0.001
	Placenta	66.69±2.45	58.81±6.47	6.256	<0.001

0.05). The serum and placenta PAPP-A, VCAM-1 and E-selectin of the non-occurrence group were lower than those of the occurrence group ($p < 0.05$), as shown in Table VI.

Predictive Value of Disease Related Molecules on Adverse Outcomes of Newborns

The AUC, critical level, sensitivity and specificity of kallikrein for predicting adverse neonatal outcomes were 0.870, 1.415, 69.44% and 100.00%, respectively, while the AUC, critical level, sensitivity and specificity of PAPP-A for predicting adverse neonatal outcomes were 0.754, 45.040, 50.00% and 92.86%, respectively. The AUC, critical level, sensitivity and specificity of TGF-β1 for predicting adverse neonatal outcomes were 0.778, 52.381, 65.28% and 85.71%, respectively. The AUC, critical level, sensitivity and specificity of VCAM-1 for predicting adverse neonatal outcomes were 0.882, 69.44, 69.44%, and 96.43%, respectively. The AUC, critical level, sensitivity and specificity of E-selectin for predicting adverse neonatal outcomes were 0.815, 65.87, 69.44%, and 89.29% respectively, as shown in Table VII and Figure 2.

Discussion

There are many risk factors for preeclampsia, including diabetes, obesity, family history, pregnancy and childbirth, multiple pregnancy, and thrombotic vascular diseases. In serious cases, the disease leads to liver and nerve dysfunction. Typical complications include acute kidney injury, refractory hypertension and acute pulmonary edema, which are the main causes of maternal death and morbidity worldwide and have a serious impact on newborns[20-22]. The current mechanism is not clear, so the clinical symptomatic treatment is particularly important. Since severe hypertension and preeclampsia complications are important causes of death, blood pressure control has become the main treatment method at present.

In this study, there was no evident difference between the two groups in the effective rate of treatment; the experimental group was generally more effective, and the blood pressure of the experimental group was lower than that of the control group after treatment ($p < 0.05$), indicating that magnesium sulfate combined with nifedipine and labetalol can improve the effective rate and further control the reduced blood pressure. The incidence of pregnancy complications and

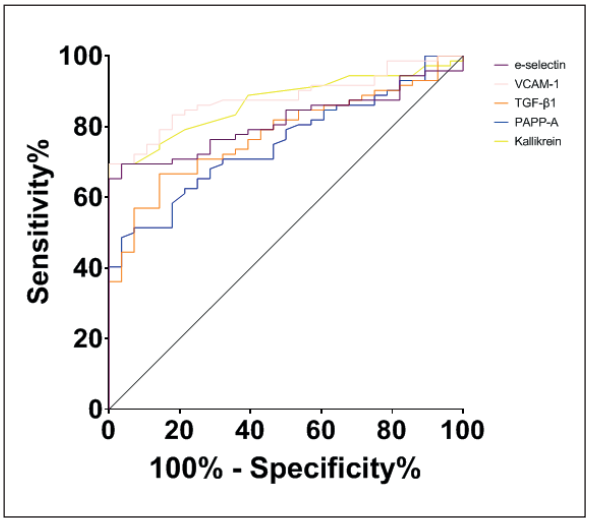

Figure 2. The predictive value of disease-related molecules for adverse neonatal outcomes. According to ROC analysis results, the AUC of kallikrein, PAPP-A, TGF-β1, VCAM-1, and E-selectin for predicting adverse neonatal outcomes were 0.870, 0.754, 0.778, 0.882, and 0.815, respectively.

adverse neonatal outcomes in the experimental group was better than those in the control group ($p < 0.05$), which indicated that magnesium sulfate combined with nifedipine and labetalol had higher safety in treatment. There are few reports on the combination of labetalol, especially with nifedipine. However, the effect of labetalol in the treatment of preeclampsia is better than that of nifedipine, mainly in reducing blood pressure[23,24]. Abdelrahman et al[25] reported that magnesium sulfate combined with labetalol is effective in the treatment of severe pre-eclampsia, with high tolerance and low effect on fetal hemodynamics. Therefore, supplemental use of labetalol may be a better treatment for preeclampsia.

Kallikrein-kinin system promotes angiogenesis and neurogenesis by inhibiting oxidative stress, apoptosis, inflammation, hypertrophy and fibrosis, alleviating cardiovascular, kidney and brain damage. With a wide range of biological activities, it could reduce hypertension, heart and kidney damage and ischemic stroke[26]. The expression of kallikrein in this study is higher than that in the control group, indicating that magnesium sulfate combined with nifedipine and labetalol can stimulate kallikrein-kallikrein system to increase the total expression of kallikrein, and achieve better antihypertensive effect to prevent preeclampsia.

According to Jameson et al[27], PAPP-A detection is a very valuable method to predict adverse pregnancy. In this research, the factor in the serum and placenta tissue of the experimental group is lower than that of the control group ($p < 0.05$), suggesting that magnesium sulfate combined with nifedipine and labetalol can reduce the risk of adverse pregnancy. The results of this study also show that the occurrence of adverse neonatal outcomes in the research group is lower than that in the control group. However, there were no significant changes in SPI, PLGF and HPL in this study. According to the results, we speculate that SPI, PLGF and HPL have no significant effect on adverse pregnancy compared with PAPP-A, or the regulatory targets of the treatment methods in this study are not on these molecules.

Endorphin (Eng) is a cell surface auxiliary receptor of transforming growth factor-β family members. The increase of serum soluble endorphin (sEng) level in preeclampsia women leads to abnormal expression of TGF-β 1 in blood vessels, the combination of TGF-β 1 and sEng, and the reduction of endothelial vasodilation activated by nitric oxide synthase[28]. VCAM-1 is an immunoglobulin superfamily distributed on the surface of endothelial cells, which could mediate adhesion between leukocytes and activated endothelial cells[29]. E-selectin is a glycoprotein composed of a group of endothelial cell adhesion molecules, which mediates the aggregation and adhesion of circulating white blood cells to inflammatory tissues[30]. TGF-β1, VCAM-1 and E-selectin can be used to predict and evaluate hypertensive pregnancy diseases, especially preeclampsia. In this research, the expression levels of TGF-β1, VCAM-1 and E-selectin in serum and placental tissues are better than those in the control group ($p < 0.05$), suggesting that the treatment method in the experimental group can reduce the accumulation of inflammatory factors, local immune response, the expansion of vascular endothelium, and the factors that cause elevated blood pressure.

In this study, we also explored the predictive value of disease-related molecules in adverse neonatal outcomes in preeclampsia. In patients without adverse neonatal outcomes, the levels of kallikrein, TGF-β1, PAPP-A, VCAM-1 and E-selectin are better than those in patients with adverse outcomes. According to the results, we speculate that these disease-related molecules have certain value in predicting preeclampsia. Furthermore, according to ROC analysis, kallikrein has a specificity of up to 100% compared with other disease-related molecules, which indicates that kallikrein has the best predictive value among many molecules.

There are some pregnant and lying-in women who refused to cooperate in the sample collection of this study due to the safety problems, because this research needs to collect placental tissue. So, the sample size is relatively small. In the future investigations, the safety of the study protocol should be taken into account, so that patients would be willing to cooperate with our scheme.

Conclusions

To sum up, magnesium sulfate combined with nifedipine and labetalol is effective in the treatment of preeclampsia. It can reduce blood pressure, improve the outcome of newborns, and reduce the expression levels of related disease molecules, which is worthy of promotion.

Conflict of Interests

The authors declare that they have no conflict of interests.

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