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Efficacy of combined medication of nifedipine and magnesium sulfate on gestational hypertension and the effect on PAPP-A, VEGF, NO, Hcy and vWF

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ABSTRACT

Objective: To investigate the effects of combined medication of nifedipine and magnesium sulfate on the blood pressure, pregnancy-associated plasma protein A (PAPP-A), vascular endothelial growth factor (VEGF), nitric oxide (NO), homocysteine (Hcy) and von Willebrand factor (vWF) in gestational hypertension patients.

Methods: A total of 220 gestational hypertension patients were enrolled as the subjects, and divided into two groups randomly, i.e. the observation group and the control group. In observation group, patients took combined medication of nifedipine and magnesium sulfate, while those in the control group only took magnesium sulfate for treatment. Clinical efficacy, and the changes in blood pressure, PAPP-A, VEGF, NO, Hcy and vWF before and after treatment were compared between two groups.

Results: In the observation group and the control group, total effectiveness rates were 92.7% and 70.9%, respectively ($p < 0.05$). After treatment, we found significant decreases in PAPP-A, VEGF, NO, Hcy and vWF in patients of two groups, with more significant decreases in the observation group ($p < 0.05$). Incidence rates of the adverse reactions in two groups were 5.5% and 6.4%, respectively, without any statistically significant differences ($p > 0.05$). In the observation group, patients had fewer complications ($p < 0.05$).

Conclusion: Combined medication of magnesium sulfate and nifedipine can decrease the levels of PAPP-A, VEGF, NO, Hcy and vWF in serum as well as the blood pressure of patients with gestational hypertension, with a reduction in incidence rate of complications and improvement in efficacy.

1. Introduction

Gestational hypertension refers to dysfunction in blood supply to specific organs caused by systemic spasm in micro-arteries, resulting in organ injuries, or even deficiency in blood supply to fetus, which severely threatens the maternal-baby safety (Barden et al., 2004). Generally, gestational hypertension is diagnosed in the middle or advanced stage of pregnancy. In clinical treatment, in prerequisite of securing the maternal-baby safety, physicians should adopt the suitable measures to sustain the blood pressure at a normal level by effectively mitigate the vascular spasm and regulating the blood circulation, while preventing the potential complications (Muti et al., 2015; Sulaiman et al., 2005). It is reported that the content of pregnancy-associated plasma protein A (PAPP-A) is positively correlated with the blood pressure of pregnant woman (Tsatsaris et al., 2012). Vascular endothelial growth factor (VEGF), a vascular endothelial cell-specific heparin binding growth factor, can induce the angiogenesis to guard the integrity of vessels, showing a key role in sustaining the blood pressure. In-depth studies have revealed the close correlation between PAPP-A, or VEGF and the gestational hypertension (Kaaja et al., 2005); following the spasm in small arteries, gestational hypertension patients may suffer from dysfunction in blood circulation or ischemia of the placenta, and the secondary oxidative stress can trigger the injuries to vascular endothelium, giving rise to an increase in PAPP-A. Thus, measurement of PAPP-A and VEGF can provide evidence for clinical diagnosis and treatment of gestational

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hypertension. Currently, in clinical treatment, combined medication of nifedipine and magnesium sulfate has been regarded as a mainstream strategy. Nifedipine, a calcium antagonist, can block the calcium influx in myocardial and vascular smooth muscle cells. Magnesium sulfate, mainly used for prophylaxis of seizure, can dilate the vessels. Combined medication of these two drugs has been confirmed in decreasing the blood pressure of patients, but their effects on the levels of PAPP-A and VEGF in serum of patients remain elusive. Thus, in this study, using combined medication of nifedipine and magnesium sulfate for treatment of gestational hypertension, we observed the efficacy, and evaluated the effects on the levels of PAPP-A and VEGF, so as to provide theoretical evidence for clinical treatment of the gestational hypertension.

2. Data and methods

2.1. Data resource

A total of 220 gestational hypertension patients who were admitted to the hospital between March 2014 and March 2017 were enrolled as the subjects which were later randomized into the observation group and the control group, with 110 in each. The observation group consisted of 81 primiparas and 29 multipara with an average age of (27.2 ± 2.8) years old; the average of gestational weeks was (34.6 ± 4.2) weeks; the averages of systolic pressure and diastolic pressure were (158.2 ± 7.7) mmHg and (98.2 ± 4.6) mmHg, respectively; patients in the observation group received combined medication of nifedipine and magnesium sulfate. The control group consisted of 83 primiparas and 27 multipara with an average age of (28.0 ± 2.1) years old; the average of gestational weeks was (33.9 ± 5.0) weeks; the averages of systolic pressure and diastolic pressure were (158.1 ± 8.0) mmHg and (98.4 ± 4.8) mmHg, respectively; patients in the gained the approval from the Ethic Committee of the hospital, and comparisons of the baseline data between two groups showed no statistically significant difference ($p > 0.05$), suggestive of the comparability.

Enrollment criteria: (1) patients with clinical symptoms conforming to the diagnostic criteria of gestational hypertension in *Gynaecology and Obstetrics* (2nd edition), with a systolic pressure ≥130 mmHg and/or diastolic pressure ≥90 mmHg, and positive responses to detection of urine proteins; (2) patients in gestational weeks not shorter than 20 weeks; (3) patients with singleton pregnancy; (4) patients without history of hypertension, severe heart disease, hepatic or renal diseases, or diabetes mellitus; (5) patients with no allergy to the drugs in this study; (6) patients with clear consciousness and no obstruction in communication; (7) patients who and whose family had signed the written informed consents.

Exclusive criteria: (1) patients >35 years old; (2) patients with gemellary pregnancy or multiple pregnancy; (3) patients who took anti-hypertensive drugs within 1 week prior to the treatment; (4) patients with other pregnancy complications at the time of admission; (5) patients with mental disorders or obstruction in communication.

2.2. Methods

2.2.1. Treatment procedures

Patients in the control group underwent intravenous infusion of magnesium sulfate: 25% magnesium sulfate (Nanchang Baiyun Pharmaceutical Co., Ltd., Lot No.: 20121231) + 100 mL 10% glucose injection (Dali Pharmaceutical Co., Ltd., Lot No.: 20130301). Infusion rate was controlled within 1–2 g/h, and the total intake of magnesium sulfate was 25 –30 g. In addition to the intravenous infusion of magnesium sulfate, patients in the observation group also took nifedipine orally (Shanxi Taiyuan Pharmaceutical Co., Ltd., Lot No.: 20130227), 10 mg/8h (Shi et al., 2015). For patients in gestational weeks shorter than 38 weeks, they received one course of treatment consisting of consecutive 7 days, while those not shorter than 38 weeks, they received one couse of treatment consisting of 3 days.

2.2.2. Observation index

2.2.2.1. Efficacy evaluation (Smith et al., 2005). (1) Excellence: no clinical symptoms (including dizziness or edema), decreases in urinary protein by ++ and decrease in blood pressure to the normal range, or decreases in systolic pressure >30 mmHg, and diastolic pressure >10 mmHg, and gestational weeks not shorter than 37 weeks; (2) Effectiveness: Obvious mitigation in dizziness or edema, decrease in urinary protein by +, decrease in blood pressure but not reaching to the normal range, or decreases in diastolic or systolic pressure <10 mmHg, gestational weeks between 36 weeks and 37 weeks; (3) Ineffective: no evident decreases in urinary protein levels or blood pressure, no recovery, or deterioration in clinical symptoms, gestational weeks <36 weeks. The total effectiveness rate = (Excellence + Effectiveness)/total cases × 100%.

2.2.2.2. Measurement of blood pressure. Systolic and diastolic pressures of patients were measured before treatment and after one course of treatment.

2.2.2.3. Detection of the levels of VEGF, PAPP-A, NO, Hcy and vWF in serum. We collected the fasting venous blood in the morning before treatment and after one course of treatment to determine the content of VEGF, PAPP-A, NO, Hcy and vWF in serum, with VEGF ELISA kit, PAPP-A ELISA Kit (Shanghai Biotechnology Co., Ltd), nitrate reductase method, enzymic method and immunoturbidity method, respectively.

2.2.2.4. Adverse reactions in the treatment were all recorded.

2.2.2.4.1. Pregnancy complications. In this study, pregnancy complications mainly referred to the uterine inertia, postpartum hemorrhage, fetal distress in uterus, placental abruption and neonatal asphyxia.

2.3. Statistical analysis

Data analysis was carried out in SPSS 19.0 software. Enumeration data, in form of %, were compared using chi-square test. Measurement data, in form of $(\bar{x} \pm s)$, were compared using t test. $p < 0.05$ suggested that the difference had statistical significance.

3. Results

3.1. Evaluation of efficacy

In the observation group, the total effectiveness rate was 92.5%, significantly higher than 70.8% in the control group ($p < 0.05$). Evaluation of efficacy in two groups is shown in Table 1.

3.2. Comparison of the blood pressures before and after treatment between two groups

Before treatment, the average of blood pressure in patients of two groups was higher than 150 mmHg ($p > 0.05$); after treatment, significant decrease was identified in the blood pressure of patients in two groups ($p < 0.05$), while the decrease was more evident in the observation group ($p < 0.05$; Table 2).

Table 1
Evaluation of efficacy [n (%)].

Group	Case (n)	Excellence	Effectiveness	Ineffective	Total effectiveness rate
Observation group	120	58(48.33)	53(44.17)	9(7.50)	92.5
Control group	120	35(29.17)	50(41.67)	35(29.17)	70.8
U/χ^2 value		3.960			17.190
p value		0.000			0.000

Table 2
Comparison of the blood pressures before and after treatment between two groups ($\bar{x} \pm s$, mmHg).

Group	Case (n)	Systolic pressure				Diastolic pressure			
		Before treatment	After treatment	*t*	*p*	Before treatment	After treatment	*t*	*p*
Observation group	120	158.2 ± 7.7	130.4 ± 6.9	28.592	0.000	98.2 ± 4.6	82.2 ± 4.1	27.873	0.000
Control group	120	158.1 ± 8.0	144.3 ± 6.5	14.237	0.000	98.4 ± 4.8	89.2 ± 4.3	15.309	0.000
t		0.095	14.672			0.321	12.657		
p		0.923	0.000			0.746	0.000		

3.3. Comparisons of the levels of PAPP-A, VEGF, NO, Hcy and vWF in serum of patients in two groups

Before treatment, no statistically significant difference was identified in comparisons of the levels of PAPP-A, VEGF, NO, Hcy and vWF in serum between two groups ($p > 0.05$); after treatment, we found significant decreases in the levels of PAPP-A, VEGF, NO, Hcy and vWF in patients of two groups ($p < 0.05$), while patients in the observation group experienced more acute decreases ($p < 0.05$; Table 3).

3.4. Adverse reactions

In the control group, there were 8 patients (6.7%) with adverse reactions, including nausea and vomiting; in the observation group, there were 7 patients (5.8%) showing adverse reactions, including nausea, vomiting and dizziness. No statistically significant difference was identified in comparison between two groups ($\chi^2 = 0.08$, $p = 0.775$).

3.5. Comparison of the incidence rates of pregnancy complications between two groups

In the observation group, the incidence rates of the postpartum hemorrhage, uterine inertia, placental abruption, fetal distress in uterus and neonatal asphyxia were 10.00%, 8.33%, 4.17%, 15.00% and 12.50%, significantly lower than 23.33%, 20.83%, 11.67%, 30.00% and 27.50% in the control group ($p < 0.05$; Table 4).

4. Discussion

Gestational hypertension, with an incidence rate of 10%, is a kind of stenosis in lumen caused by the spasm in small arteries, manifesting obstruction in blood circulation and injuries to the endothelial cells, thereby evolving into the multi-organ lesions. The clinical characteristics of gestational hypertension include hypertension, urinary proteins, coma and edema or even failure of multiple organs, and due to the high incidence, gestational hypertension, in some severe cases, can cause death of puerpera or perinatal infant (Goeschen et al., 2003; Zou et al., 2013). However, symptoms usually emerge after 20 weeks of gestation, and, at that time, puerpera and fetus have been injured somehow. Thus, enhancing the monitoring of puerpera can ensure the early diagnosis and treatment of gestational hypertension, showing a magnificent significance for securing the maternal-infant safety.

At present, magnesium sulfate in combination with nifedipine has been regarded as the major method in treatment of gestational hypertension patients (Zhao et al., 2013). Mg^{2+}, from magnesium sulfate, can inhibit the release of acetyl choline (ACh) to interfere with the transportation of neurotransmitter, and the chemical signal transduction between nerve and muscle, thereby suppressing the uterus contraction; in addition, magnesium sulfate can dilate the vessels, with alleviation in spasm and reduction in blockage of vessels, showing significant efficacy on a variety of hypertension (Daniel et al., 2004). Sibai et al. (2007) compared the efficacy between the single and combined use of these two drugs, and found that the effectiveness rate of the combined medication is as high as 94.44%, significantly higher than 75.0% of single applica-

Table 3
Comparisons of the levels of PAPP-A, VEGF, NO, Hcy and vWF in serum of patients in two groups ($\bar{x} \pm s$).

Group	Case (n)	PAPP-A (ng/L)		VEGF (ng/L)		NO (mmol/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	120	24.62 ± 2.58	20.44 ± 1.86[a]	45.02 ± 14.16	22.17 ± 13.71[a]	762.49 ± 115.33	931.48 ± 120.59[a]
Control group	120	24.84 ± 2.50	23.53 ± 2.04[a]	44.29 ± 14.68	29.52 ± 15.33[a]	759.28 ± 115.35	865.33 ± 120.42[a]
t		0.646	11.801	0.377	3.752	0.136	2.662
p		0.521	0.000	0.709	0.000	0.894	0.009

Group	Case (n)	Hcy (μmol/L)		vWF (%)	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	120	16.44±4.26	11.59±3.18[a]	159.48±15.37	132.66±10.30[a]
Control group	120	15.87±4.31	13.68±3.29[a]	158.40±15.25	143.53±10.14[a]
t		0.647	3.142	0.343	5.162
p		0.521	0.002	0.734	0

Note:
[a] $p < 0.05$ *vs.* levels before treatment.

Table 4
Comparison of the incidence rates of pregnancy complications between two groups [n (%)].

Group	Case (n)	Postpartum hemorrhage	Uterine inertia	Placental abruption	Fetal distress in uterus	Neonatal asphyxia
Observation group	120	12(10.00)	10(8.33)	5(4.17)	18(15.00)	15(12.50)
Control group	120	28(23.33)	25(20.83)	13(11.67)	36(30.00)	33(27.50)
χ^2		7.31	7.17	3.87	6.63	7.27
p		0.007	0.007	0.046	0.01	0.007

tion. In this study, we also found that the effectiveness rate and anti-hypertensive efficiency in the observation group were all superior to those in the control group ($p < 0.05$), suggesting that magnesium sulfate in combination with nifedipine exerts a synergistic effect, with a significant decrease in blood pressure of patients. As for the comparison of incidence rate of adverse reaction, no statistical significance was identified in the difference ($p > 0.05$). Patients in the observation group had fewer complications than the control group ($p < 0.05$), suggestive of a better safety in combined medication, without any new adverse reactions.

VEGF can permeabilize the vessels while promote the angiogenesis, so as to secure the normal development of vessels and reduce the endothelial damage. In a variety of studies on gestational hypertension, scholar has found that impeded growth of vascular endothelium and poor development of placenta-related vessels are associated closely with the gestational hypertension, and the fluctuation in VEGF level can reflect the severity of disease (Santamaria et al., 2016). Rotchell et al. (2008) noted that VEGF in serum is involved in the vascular endothelial cell growth and nourishing the injured cell functions, playing a crucial role in the development of gestational hypertension. Increased VEGF indicates vessel injury, and, thus, VEGF serves as an auxiliary indicator in diagnosis of gestational hypertension and evaluation of the severity of disease. In this study, after treatment, patients in the observation group had a lowered VEGF ($p < 0.05$) in comparison with the control group, implicating that magnesium sulfate in combination with nifedipine can significantly decrease the VEGF to ameliorate the endothelial injury and improve the efficacy. PAPP-A, a protein secreted by X cells in placenta, plays a critical role in maternal-infant metabolism. Spasm in small arteries triggers oxidative stress, giving rise to the release of superoxide radical and inflammatory cytokines, which gains the possibility to aggravate the vascular endothelial injuries (Golding, 2008; McLaughlin et al., 2008). Humbert et al. (2008) reported increased PAPP-A level in gestational hypertension patients, and that PAPP-A is positively correlated with the severity, with a potential of indicator in monitoring the gestational hypertension. In this study, patients in the observation group, after treatment, had a significant reduction in PAPP-A level ($p < 0.05$), which shows that magnesium sulfate in combination with nifedipine can decrease the PAPP-A level, thereby alleviating the endothelial injury and improving the pregnancy outcome. NO, generated from the vascular endothelial cells, is a kind of vascular dilator with potent effect on dilation of vessels. It has been reported that in healthy pregnant woman, a large amount of NO generated in plasma can modulate the cardiovascular system, while in gestational hypertension patients, NO secretion is decreased (Veerbeek et al., 2015). Endothelin (ET), as the most potent vasoconstrictor substance, is closely related with the hemodynamics, and a significant elevation in the advanced stage of pregnancy can slow down the blood flow. Besides, it has been proved that physiological changes in the gestational hypertension are caused by the deficiency in NO release and massive secretion of ET, and their interplay contributes to the increased blood pressure (SAS Institute Inc 2007). Hcy, a kind of metabolite synthesized by the interplay between cysteine and methionine, is correlated with the disease condition. High Hcy hyperlipidemia can induce the gestational hypertension through injuring the vascular endothelial cells, showing a critical role in the development. vWF is a marker indicating the vascular endothelial cell injuries. Thus, restoration and maintenance of the dynamic balance among these factors are quite significant for gestational hypertension patients.

5. Conclusion

Combined medication of magnesium sulfate and nifedipine can decrease the levels of PAPP-A, VEGF, NO, Hcy and vWF in serum as well as the blood pressure of patients with gestational hypertension, with a reduction in incidence rate of complications and improvement in efficacy. However, further studies are anticipated to elucidate the mechanism involving the decreases of PAPP-A and VEGF.

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