Efficacy and safety of combination of magnesium sulfate, phentolamine and nifedipine in treatment of patients with hypertensive disorder complicating pregnancy

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Abstract. Efficacy and safety of the combination of magnesium sulfate, phentolamine and nifedipine in the treatment of patients with hypertensive disorder complicating pregnancy (HDCP) and its effect on hemodynamics and urinary protein level were investigated. One hundred and six patients with HDCP diagnosed at the Affiliated Hospital of Beihua University from February 5, 2016 to May 9, 2017 were retrospectively analyzed. Patients were divided into the magnesium sulfate group and the combination group, according to the therapeutic schemes. The efficacy 1 week later was observed. The general clinical data of the patients were recorded, and data were acquired with respect to hemodynamic indexes before and after treatment [changes of S/D ratio of umbilical artery flow, and cardiac index and total peripheral resistance (TPR)], the 24-h urinary protein level, clinical efficacy and safety [adverse drug reactions (ADR) and maternal and neonatal outcomes]. Before treatment, there was no statistically significant difference between the two groups in terms of S/D ratio of umbilical artery flow ($P>0.05$), while after treatment the S/D ratio was significantly lower than that before treatment in both groups ($P<0.05$). Before treatment, there was no statistically significant difference between the two groups in terms of cardiac index ($P>0.05$). TPR after treatment was significantly lower than that before treatment in both groups ($P<0.001$). Compared with the magnesium sulfate group, patients in the combination group had significantly lower 24-h urinary protein level after treatment ($P<0.001$), significantly higher total effective rate ($P<0.05$), significantly lower incidence rate of ADR ($P<0.001$), and significantly lower incidence rate of adverse maternal and neonatal outcomes ($P<0.001$). In conclusion, the combination of magnesium sulfate, phentolamine and nifedipine can significantly improve the hemodynamic indexes, the 24-h urinary protein level, the clinical efficacy, ADR and maternal and neonatal outcomes of patients with HDCP, therefore it is worthy of use in the clinic.

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Introduction

Hypertensive disorder complicating pregnancy (HDCP), a common condition with a high incidence rate in the Obstetrics and Gynecology Department, usually occurs after 20 weeks of gestation (1,2). With the changes of the social environment in recent years, the incidence rate of the disease has been increasing year by year due to unhealthy living habits and dietary structure (3,4). Severe HDCP poses a threat to maternal and child health which can lead to massive intra-abdominal hemorrhage and patient death (4).

As an anticonvulsant, magnesium sulfate is currently the first choice for the prevention and treatment of HDCP (5). It inhibits the dilatation of peripheral vessels through central inhibition, and indirectly reduces blood pressure by relieving vasospasm (6,7). However, although magnesium sulfate is clinically effective in the treatment of HDCP, it has a slow effect and its therapeutic dose greatly influences the patients' blood concentration (8,9). According to recent studies, nifedipine, a long-acting calcium antagonist, inhibits angiotensin converting enzymes and significantly lowers blood pressure, and its safety is better than that of antihypertensive drugs of the same type (10,11). Phentolamine, a blocker that is mainly used for treating peripheral vascular diseases (12), blocks norepinephrine, increases myocardial contractility and reduces the related resistance of peripheral vessels, effectively dilating blood vessels (13). Antihypertensive drugs are effective on HDCP patients, but there is no conclusion as to which therapeutic regimen is the most effective. Therefore, the efficacy and safety of the combination of magnesium sulfate, phentolamine and nifedipine in the treatment of HDCP patients and its effect on hemodynamics and urinary protein level were investigated in this study.

Patients and methods

General information. One hundred and six patients with HDCP diagnosed at the Affiliated Hospital of Beihua

Table I. General clinical data [n (%)].

Groups	Combination group (n=53)	Magnesium sulfate group (n=53)	t/χ^2 value	P-value
Age (years)	26.48±6.93	26.53±7.03	0.037	0.971
Body mass index (kg/m^2)	18.47±3.14	18.68±2.41	0.386	0.700
Gestational age (weeks)	34.56±4.68	34.32±4.59	0.267	0.790
Pregnancy history			0.050	0.824
Primipara	40 (75.47)	39 (73.58)		
Multipara	13 (24.53)	14 (26.42)		
Excessive nutritional supplement			0.632	0.230
Yes	41 (77.36)	43 (81.13)		
No	12 (22.64)	10 (18.86)		
History of preeclampsia			0.376	0.540
Yes	5 (9.43)	7 (13.21)		
No	48 (90.57)	46 (86.79)		
History of chronic nephritis			0.050	0.824
Yes	13 (24.53)	14 (26.42)		
No	40 (75.47)	39 (73.58)		
Hypertension			0.099	0.952
Mild	23 (43.40)	23 (43.40)		
Moderate	15 (28.30)	16 (30.19)		
Severe	15 (28.30)	14 (26.42)		

University (Jilin, China) from February 5, 2016 to May 9, 2017 were retrospectively analyzed, and divided into the magnesium sulfate group (n=53) and the combination group (n=53) according to the therapeutic schemes. Patients in the combination group, were treated with magnesium sulfate, phentolamine and nifedipine, and were 22-40 years of age with an average age of 26.48±6.93 years. Patients in the magnesium sulfate group were treated with magnesium sulfate alone, and were 22-38 years of age with an average age of 26.53±7.03 years. Inclusion criteria: patients with HDCP only treated in the Affiliated Hospital of Beihua University; those who had no abortion caused by abnormal chromosome; with no endocrine abnormality, any reproductive system infection or autoimmune disease (14). Exclusion criteria: patients with hypertension, hepatitis B virus, gallstones, AIDS and blood diseases were excluded, as well as pregnant women with abnormal pregnancy history. Patients included had complete clinical data. The study was approved by the Ethics Committee of the Affiliated Hospital of Beihua University. Patients and their families signed an informed consent form in advance.

Therapeutic regimens. Patients in the magnesium sulfate group were treated with magnesium sulfate alone (Hebei Tiancheng Pharmaceutical Co., Ltd.; SFDA approval no. H20033861). The patients received an intravenous drip with 100 ml of 5% glucose solution (Newland Pharmaceutical Co., Ltd.; SFDA approval no. H20065564) rapidly for 30 min, and then 40 ml of 25% magnesium sulfate for 6-8 h, that was dissolved in 500 ml of 5% glucose. Patients in the combination group were treated with phentolamine (Shanghai Xudong Haipu Pharmaceutical Co., Ltd.; SFDA approval no. H31020589) on the basis of the magnesium sulfate group. The patients received an intravenous drip with 20 mg of phentolamine, that was dissolved in 200 ml of 5% glucose, and then 20 mg of nifedipine (Guangdong Xinfeng Pharmaceutical Co., Ltd.; SFDA approval no. H44021999) were orally administered once daily. Both groups of patients were treated for 1 week.

Observational indexes. The general clinical data of patients in the two groups were recorded, and data were acquired with respect to hemodynamic indexes before and after treatment [changes of S/D ratio of umbilical artery flow, cardiac index and total peripheral resistance (TPR)], the 24-h urinary protein level, clinical efficacy and safety [adverse drug reactions (ADR) and maternal and neonatal outcomes]. Markedly effective: patients with HDCP that had normal clinical symptoms and signs, and significantly reduced blood pressure, without HDCP-related complications; systolic blood pressure was reduced by ≥30 mmHg, diastolic blood pressure by ≥20 mmHg, urinary protein by ≥20 mg. Effective: the clinical symptoms and signs were significantly improved with less complications; blood pressure was reduced by ≤10 mmHg, urine protein by ≤20 mg. Invalid: the clinical symptoms and signs were unchanged and blood pressure was not reduced, with more complications (4). Total effective rate = (markedly effective + effective)/total cases x100%.

Statistical analysis. SPSS 19.0 software [Bizinsight (Beijing) Information Technology Co., Ltd.] was used for statistical analysis. Count data were expressed as the number

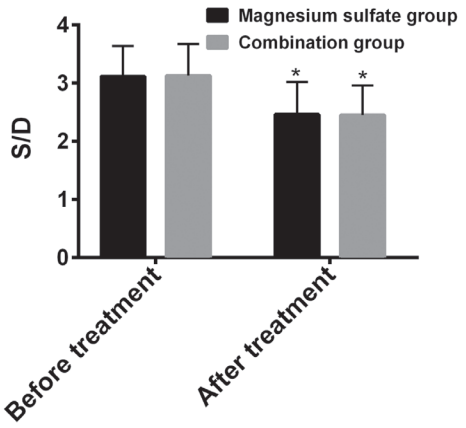

Figure 1. Changes of S/D ratio of umbilical artery flow. The S/D ratio of umbilical artery flow after treatment was significantly lower than that before treatment in both groups (*P<0.05).

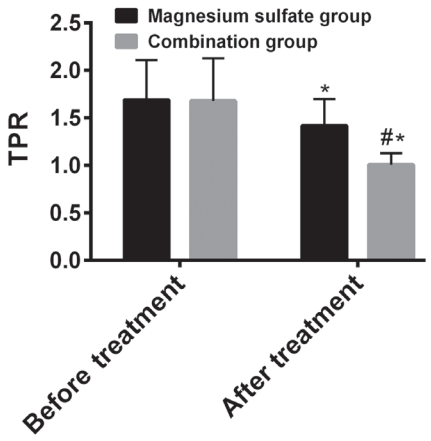

Figure 3. Changes of TPR. TPR after treatment was significantly lower than that before treatment in both groups (*P<0.001) and TPR after treatment was significantly lower in the combination group than that in the magnesium sulfate group (#P<0.001). TPR, total peripheral resistance.

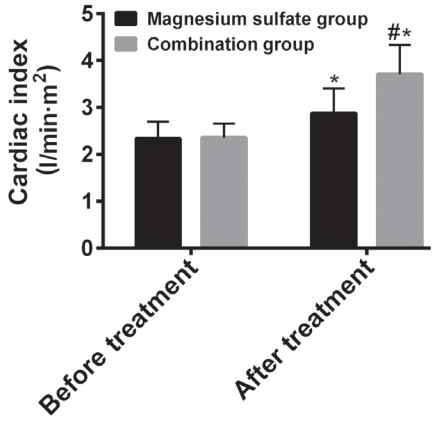

Figure 2. Changes of cardiac index. The cardiac index after treatment was significantly higher than that before treatment in both groups (*P<0.05) and cardiac index after treatment was significantly higher in the combination group than that in the magnesium sulfate group (#P<0.05).

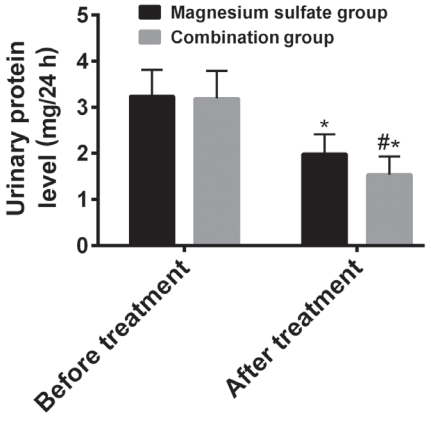

Figure 4. Changes of urinary protein level. The 24-h urinary protein level after treatment was significantly lower than that before treatment in both groups (*P<0.001) and the 24-h urinary protein level after treatment was significantly lower in the combination group than that in the magnesium sulfate group (#P<0.001).

of cases and percentage [n (%)], and were tested by χ^2 test. Measurement data were expressed as the mean ± standard deviation (mean ± SD), and t-test was used for comparisons between two groups, while one-way ANOVA, with Least Significant Difference post hoc test, for comparisons of multiple groups. P<0.05 was considered to indicate a statistically significant difference.

Results

General clinical data. There was no statistically significant difference between the two groups in general data (P>0.05). The two groups of patients were comparable. Details are shown in Table I.

Changes of hemodynamic indexes

i) Changes of S/D ratio of umbilical artery flow. The S/D ratios of umbilical artery flow before and after treatment were respectively 3.12±0.52 and 2.46±0.56 in the magnesium sulfate group, 3.13±0.54 and 2.45±0.51 in the combination group (Fig. 1). Before treatment, there was no statistically significant difference between the two groups in terms of S/D ratio of umbilical artery flow (P>0.05). After treatment the S/D ratio was significantly lower than that before treatment in both groups (P<0.05), and there was no statistically significant difference between the two groups (P>0.05) (Fig. 1).

ii) Changes of cardiac index. The cardiac indexes before and after treatment were respectively 2.34±0.36 and 2.88±0.53 l/min·m^2 in the magnesium sulfate group, 2.36±0.30 and 3.71±0.62 l/min·m^2 in the combination group (Fig. 2). Before treatment, there was no statistically significant difference between the two groups in terms of cardiac index (P>0.05). After treatment the cardiac index was significantly higher than that before treatment in both groups (P<0.05), and it was significantly higher in the combination group than that in the magnesium sulfate group (P<0.05) (Fig. 2).

iii) Changes of TPR. TPR before and after treatment was respectively 1.69±0.42 and 1.42±0.28 in the magnesium sulfate group, 1.68±0.45 and 1.01±0.12 in the combination group (Fig. 3). Before treatment, there was no statistically significant difference between the two groups in terms of TPR (P>0.05). After treatment TPR was significantly lower than

Table II. Efficacy observation [n (%)].

Groups	n	Markedly effective	Effective	Invalid	Total effective rate
Magnesium sulfate group	53	24 (45.28)	20 (37.74)	9 (16.98)	44 (83.02)
Combination group	53	31 (58.49)	20 (37.74)	2 (3.77)	51 (96.23)
χ^2 value	-	-	-	-	4.970
P-value	-	-	-	-	0.026

Table III. Comparison of ADR [n (%)].

Groups	Vomiting	Diarrhea	Fever	Weakness	Headache	Rash	Total
Magnesium sulfate group	9 (16.98)	3 (5.66)	6 (11.32)	10 (18.87)	7 (13.21)	2 (3.77)	37 (69.81)
Combination group	1 (1.89)	1 (1.89)	3 (5.66)	9 (16.98)	5 (9.43)	0 (0.00)	19 (35.85)
χ^2 value	-	-	-	-	-	-	12.270
P-value	-	-	-	-	-	-	<0.001

ADR, adverse drug reactions.

Table IV. Comparison of maternal and neonatal outcomes [n (%)].

Groups	Premature delivery	Caesarean delivery	Postpartum hemorrhage	Neonatal asphyxia	Perinatal death	Total
Magnesium sulfate group	8 (15.09)	12 (22.64)	7 (13.21)	7 (13.21)	1 (1.89)	35 (66.04)
Combination group	1 (1.89)	10 (18.87)	2 (3.77)	2 (3.77)	0 (0.00)	15 (28.30)
χ^2 value	-	-	-	-	-	15.140
P-value	-	-	-	-	-	<0.001

that before treatment in both groups (P<0.001), and it was significantly lower in the combination group than that in the magnesium sulfate group (P<0.001) (Fig. 3).

Changes of urinary protein level. The 24-h urinary protein levels before and after treatment were respectively 3.24±0.58 and 1.99±0.43 mg/24 h in the magnesium sulfate group, 3.19±0.60 and 1.54±0.39 mg/24 h in the combination group (Fig. 4). Before treatment, there was no statistically significant difference between the two groups in terms of 24-h urinary protein level (P>0.05). After treatment the urinary protein level was significantly lower than that before treatment in both groups (P<0.001), and it was significantly lower in the combination group than that in the magnesium sulfate group (P<0.001) (Fig. 4).

Efficacy observation. In the magnesium sulfate group, the treatment was markedly effective in 24 patients, effective in 20 patients, and invalid in 9 patients, with a total effective rate of 83.02%. In the combination group, the treatment was markedly effective in 31 patients, effective in 20 patients, and invalid in 2 patients, with a total effective rate of 96.23%. The total effective rate in the combination group was significantly higher than that in the magnesium sulfate group (P<0.05) (Table II).

Safety observation

i) Comparison of ADR. The total number of patients with vomiting, diarrhea, fever, weakness, headache and rash was 37 in the magnesium sulfate group and 19 in the combination group. The incidence rate of ADR in the combination group was significantly lower than that in the magnesium sulfate group (P<0.001) (Table III).

ii) Comparison of maternal and neonatal outcomes. The total number of patients with premature delivery, caesarean delivery, postpartum hemorrhage, neonatal asphyxia and perinatal death was 35 in the magnesium sulfate group and 15 in the combination group. The incidence rate of adverse maternal and neonatal outcomes in the combination group was significantly lower than that in the magnesium sulfate group (P<0.001) (Table IV).

Discussion

The general clinical data of patients in this study revealed that the two groups of patients were comparable. Hemodynamic indexes before and after treatment, the 24-h urinary protein level, clinical efficacy and safety of therapeutic regimens were observed. The S/D ratio of umbilical artery flow after treatment was significantly lower than that before treatment

in the both groups, whereas there was no statistically significant difference between the two groups after treatment. According to relevant studies, the S/D ratio of umbilical artery flow is helpful to determine the intrauterine growth of fetus, and reflects whether a pregnant woman has HDCP or whether the fetus has the tendency of intrauterine hypoxia and developmental retardation (15,16). It gradually stabilizes with the increase of gestational age, and its increase caused by HDCP leads to fetal anoxia and even brain tissue injury (17). Therefore, it is believed that the two therapeutic schemes in this study reduce the S/D ratio of umbilical artery flow, with similar effects on the ratio. In this study, TPR after treatment was significantly lower than that before treatment in the two groups, which after treatment was significantly lower in the combination group than that in the magnesium sulfate group. Cardiac index after treatment was significantly higher than that before treatment in both groups, and after treatment it was significantly higher in the combination group than that in the magnesium sulfate group. Changes of TPR and cardiac index are common hemodynamic indexes for observing patients with HDCP (18). The pathological changes of blood vessels caused by HDCP result in small blood vessel spasm, vascular stenosis and increased peripheral resistance, as well as decreased cardiac index in pregnant women (19). Therefore, it is believed that the combination of magnesium sulfate, phentolamine and nifedipine is better than magnesium sulfate alone in improving the hemodynamic indexes of patients with HDCP. In a study by Adamo *et al*, magnesium sulfate combined with other antihypertensive drugs was shown to be better than magnesium sulfate alone in this improvement (20). In this study, the 24-h urinary protein level after treatment was significantly lower than that before treatment in the two groups, and after treatment was significantly lower in the combination group than that in the magnesium sulfate group. Also, the total effective rate in the combination group was significantly higher than that in the magnesium sulfate group. High blood pressure and increased urine protein are the most direct clinical features of HDCP in pregnant women, which are caused by kidney damage as a result of hypertension. According to a relevant study, the 24-h urine protein level is a monitoring index for patients with HDCP (21), the effective downregulation of which indicates improvement of the condition (22). In this study, the incidence rate of adverse maternal and neonatal outcomes (premature delivery, caesarean delivery, postpartum hemorrhage, neonatal asphyxia and perinatal death) in the combination group were significantly lower than that in the magnesium sulfate group. A large number of studies on the treatment of HDCP have confirmed that magnesium sulfate combined with other antihypertensive drugs is more effective in preventing ADR of patients with HDCP and improving maternal and neonatal outcomes (23-25).

The regional limitations of the patients included and the lack of rich monitoring indexes may have affected the statistical results. Therefore, further research on the patients included and valuable monitoring indexes for HDCP will be appropriately added in our future studies.

In summary, the combination of magnesium sulfate, phentolamine and nifedipine can significantly improve the hemodynamic indexes, the 24-h urinary protein level, clinical efficacy, ADR and maternal and neonatal outcomes of patients with HDCP.

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Availability of data and materials

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

Authors' contributions

JZ interpreted the data, drafted the manuscript, conceived and designed the study. JL collected and analyzed the data, and finally revised the manuscript. Both authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Affiliated Hospital of Beihua University (Jilin, China). Patients who participated in this research had complete clinical data. The patients and their families signed an informed consent form in advance.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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