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Original Article

Efficacy of nifedipine tablets plus aspirin in patients with gestational hypertension and the effect on coagulation function and hemorheology

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Abstract: Objective: This study aimed to investigate the clinical efficacy of Nifedipine tablets plus Aspirin for hypertensive disorder complicating pregnancy and the effect on coagulation function and hemorheology. Methods: A retrospective analysis of the clinical data from 108 patients with gestational hypertension hospitalized between March 2016 and March 2017 was carried out. These patients were randomly assigned into a research group and a control group, with 54 patients in each group. Patients were treated with Aspirin in the control group, and the combination of Nifedipine tablets and Aspirin in the research group so as to compare the clinical efficacy and the effect on coagulation function and hemorheology after therapy. Albumin, total protein, 24-hour urinary protein and mean arterial pressure (MAP) were observed and compared between the two groups. Results: The overall effective rate of treatment in the research group was significantly higher than that in the control group ($P < 0.05$). The prothrombin time (PT) and fibrinogen (FIB) levels were markedly superior to those before therapy in the research group ($P < 0.001$), and the PT and FIB after treatment were remarkably better in the research group than in the control group ($P < 0.001$). The levels of plasma viscosity (PV), low-shear whole blood viscosity (LBV), and high-shear whole blood viscosity (HBV) after therapy were markedly reduced than before therapy in the two groups ($P < 0.05$), and the levels of PV, LBV, and HBV after therapy were significantly lower in the research group than those in the control group ($P < 0.05$). Adverse reactions after therapy were reported at a significantly lower incidence in the research group than the control group ($P < 0.05$). Adverse pregnancy outcomes were reported at a significantly lower incidence in the research group than in the control group ($P < 0.05$). The research group significantly outperformed the control group on Albumin, total protein, 24-hour urinary protein and mean arterial pressure ($P < 0.05$). Conclusion: Nifedipine tablets plus Aspirin for patients with gestational hypertension can effectively improve coagulation function and hemorheological parameters, with high safety.

Keywords: Nifedipine tablets, Aspirin, hestational hypertension, efficacy, coagulation function

Introduction

Gestational hypertension (GH) is defined as an obstetric disorder in which pregnancy coexists with blood pressure increase. Clinical studies have shown that [1], the incidence of the disease in China is about 7%-12%, and it is directly associated with intrauterine distress and maternal death. Thus the control of hypertensive disorder complicating pregnancy by effective measures is of great significance to reduce maternal and fetal death rate, and improve the outcome of delivery. It has been documented [2] that this disease often occurs in the second and third trimester of pregnancy, presenting as maternal edema, convulsions, hypertension and coma and other symptoms. There is no definitive conclusion yet on the etiology of hypertensive disorder complicating pregnancy in domestic and foreign medical research, but it is inferred that it may be related to many factors such as parturients, placenta and fetus. Advanced age, prior history of pre-eclampsia, family genetic history and multiple gestations are regarded as the risk factors for GH [3-5]. Some scholars believe that GH will lead to abnormal coagulation function of parturients, so that their hormones are out of balance, thereby resulting in elevated thrombin. Thrombin, a hemostatic drug, can directly act on the last step of blood coagulation and promote the conversion of soluble fibrinogen (FIB) in plasma

into insoluble FIB, so as to quickly stop bleeding [6-8]. Abnormalities in coagulation function may cause long-term hypercoagulability for patients, leading to hypertension. Clinical therapy is usually adopted to relieve patients' symptoms like spasmolysis, hypotension and improvement of microcirculation. Nifedipine tablets, the first generation of Ca^{2+} channel blockers, function by decreasing blood pressure, improving hemorheological parameters, and coronary and peripheral artery dilatation. Aspirin, a commonly used anticoagulant drug, acts as an inhibitor of the coagulation of platelets, improves the hypercoagulation, and improves the outcome of delivery [9]. Clinical practice has confirmed that a single drug cannot meet the requirements of clinical therapy. Therefore, to confirm the efficacy of Nifedipine tablets combined with Aspirin for the treatment of hypertensive disorder complicating pregnancy, our results are reported as follows.

Materials and methods

General data

A retrospective analysis of the clinical data from 108 patients with gestational hypertension admitted to our hospital between March 2016 and March 2017 was carried out. The patients were randomly assigned into a research group and a control group, with 54 patients in each group. The mean age of patients in the research group was (27.64 ± 2.08) years. According to disease classification criteria in Guidelines for the Diagnosis and Treatment of Hypertensive Disorder Complicating Pregnancy [10], 14 patients were mild, 25 were moderate and 15 were severe, with an average of (27.31 ± 2.43) gestational weeks. The mean age of patients in the control group was (27.68 ± 2.06) years, 12 patients were mild, 28 were moderate and 14 were severe, with an average of (27.29 ± 2.41) gestational weeks. There was no significant difference in clinical data between the two groups (P>0.05), with comparability.

Inclusion criteria

① The respondents had no history of hypertensive disorder before pregnancy; ② They were all single pregnancies; ③ They did not receive antihypertensive treatment within the past 14 days; ④ This study was approved by the ethics committee of our hospital, and patients and their families had knowledge of the purpose and process of this experimental study, and signed the informed consent form.

Exclusion criteria

① Patients who were allergic to drugs; ② Those who had abnormal kidney, liver and other tissue function; ③ Those who had malignant tumors; ④ Those who were suffering mental and other cognitive impairment or communication disorders; ⑤ Those with gestational diabetes mellitus.

Methods

Patients in both groups underwent routine physical examination at admission, including liver function, hematology, blood pressure, electrocardiogram, proteinuria, etc. Meanwhile, they were informed of maintaining adequate rest and a low-sodium diet, and were administered regular clinical therapies such as antihypertensive, sedative, and diuretic therapy. Patients in the control group were treated with Aspirin (manufacturer: Guangdong Jiuming Pharmaceutical Co., Ltd., SFDA Approval No.: H44021139, Specification: 50 mg), administered orally with warm water as a dose of 50 mg bid for 14 days; Patients in the research group was treated with the addition of Nifedipine tablets (manufacturer: Shanghai Shikangte Pharmaceutical Co., Ltd., SFDA Approval No.: H20068147, Specification: 20 mg) to Aspirin, taken orally with warm water at a dose of 15 mg bid for 14 days.

Observation indicators

Efficacy determination: After therapy, if the adverse symptoms of the patients completely disappeared, the blood pressure dropped to the normal range, and the protein urine test result was negative, it was regarded as a cure. If notable improvement in the adverse clinical symptoms was observed for these patients, the blood pressure value was ≤ 150/100 mmHg but ≥ 140/90 mmHg, and the protein urine value was under 0.5 g, it was considered as effective. If the clinical symptoms and blood pressure level of the patients were not improved and the protein urine value was 0.5 g or above, it was deemed as ineffective, and the

Table 1. Comparison of the clinical efficacy [n (%)]

Group	n	Cured	Effective	Ineffective	Overall effective rate
Research group	54	25 (46.30%)	26 (48.15%)	3 (5.56%)	94.44% (51/54)
Control group	54	16 (29.63%)	23 (42.59%)	15 (27.78%)	72.22% (39/54)
X^2					9.600
P					0.002

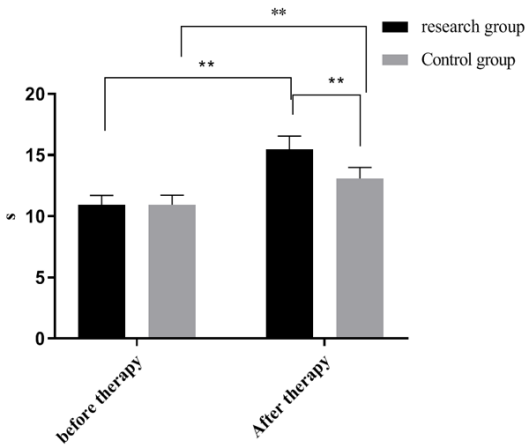

Figure 1. Comparison of PT values before and after therapy in two groups ($\bar{x}$ ± s). Note: Abscissa represents the timing of before and after therapy, whole ordinate represents PT value, s; The PT values before and after therapy were (10.41 ± 1.07) s and (14.68 ± 1.55) s in the research group, respectively; the PT values before and after therapy were (10.39 ± 1.11) s and (12.46 ± 1.27) s in the control group respectively; There was a significant difference in PT values before and after therapy in the research group (t = 16.660, **P < 0.01); There was a significant difference in PT values before and after therapy in the control group (t = 9.018, **P < 0.01); There was a significant difference in PT values before and after therapy in the two groups (t = 8.141, **P < 0.01).

overall response rate = cure rate + effective rate.

Coagulation function indicators: Five ml of fasting venous blood was collected from patients in both groups before and after therapy, and serum was collected after centrifugation. The plasma prothrombin time (PT) and FIB in the samples were measured by the Rayto RAC-050 automatic coagulation analyzer (manufacturer: Shandong Biobase Regenerative Medicine Co., Ltd.) in strict accordance with the instructions.

Hemorheological parameters: Five ml of fasting venous blood was collected from patients in both groups before and after therapy, and the plasma viscosity (PV), low-shear whole blood viscosity (LBV), and high-shear whole blood viscosity (HBV) levels were measured by hemorheology analyzer (manufacturer: Zibo Hengtuo Analytical Instrument Co., Ltd.).

Comparison of adverse reactions and adverse pregnancy outcomes: The occurrence of adverse reactions and adverse pregnancy outcomes after therapy were statistically compared between the two groups.

Comparison of changes in various indicators: Albumin, total protein, 24-hour urinary protein and mean arterial pressure were observed and compared between the two groups.

Statistical methods

The experimental data were statistically analyzed and processed by SPSS 20.0 software. Chi-squared test was adopted with the enumeration data which were expressed with [n (%)], while t-test was used in measurement data expressed with ($\bar{x}$ ± sd). P < 0.05 meant that there was astatistically significant difference. GraphPad prism 8 software was used to illustrate the figures.

Results

Comparison of the clinical efficacy in the two groups

After therapy, the total effective rate was significantly higher in the research group than that in the control group, and a significant difference was detected (P < 0.05), as shown in **Table 1**.

Comparison of coagulation function indicators before and after therapy

After therapy, the PT and FIB in the two groups were significantly better compared with those before therapy, with a significant difference (P < 0.05), and significantly higher PT and FIB lev-

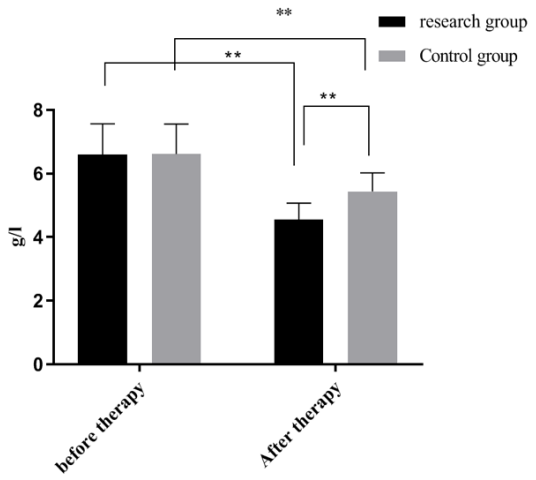

Figure 2. Comparison of FIB values before and after therapy ($\bar{x} \pm s$). Note: Abscissa represents the timing of before and after therapy, while ordinate represents FIB value, g/l; The FIB values before and after therapy were (5.92 ± 1.36) g/l and (4.19 ± 0.73) g/l in the research group, respectively; the FIB values before and after therapy were (5.95 ± 1.33) g/l and (5.02 ± 0.83) g/l in the control group, respectively; *indicates that there was a significant difference in FIB values before and after therapy in the research group (t = 8.236, **P < 0.01); **indicates that there was a significant difference in FIB values before and after therapy in the control group (t = 4.359, **P < 0.01); ***indicates that there was a significant difference in FIB values before and after therapy in the two groups (t = 5.518, **P < 0.01).

els in the research group were detected with a significant difference (P < 0.05), as shown in **Figures 1** and **2**.

Comparison of hemorheological parameters before and after therapy

After therapy, the PV, LBV and HBV values in two groups were markedly reduced than before therapy and a significant difference was observed (P < 0.05), and the PV, LBV and HBV values in the research group were remarkably lower than those in the control group with a significant difference (P < 0.05), as shown in **Table 2**.

Comparison of the occurrence of adverse reactions after therapy in the two groups

After therapy, the total incidence of adverse reactions was considerably reduced in the research group as opposed to the control group with a significant difference (P < 0.05), as shown in **Table 3**.

Comparison of adverse pregnancy outcomes

It was found after treatment that the research group had remarkably lower incidence of adverse pregnancy outcomes compared with the control group with a significant difference (P < 0.05), as shown in **Table 4**.

Comparison of all indicators

The research group exceeded the control group on all indicators of albumin, total protein, 24-hour urinary protein and mean arterial pressure, with a significantly statistical difference (P < 0.05), as shown in **Table 5**.

Discussion

The remarkable rise in estrogen and progesterone levels in women of childbearing potential during pregnancy is found to be associated with increased blood viscosity, and placental prolactin secretion, leading to increasing insulin sensitivity [11-13]. GH gives rise to the decrease in blood perfusion of the whole body and various tissues and organs of parturients, which poses a serious threat to the life and health of mothers and infants. After the onset of the disease, parturients will have more risk of abortion and macrosomia in the case that the blood pressure value and plasma viscosity are not controlled in a timely manner [14]. Nifedipine is an α and β receptor blocker, and its mechanism of action is to block the influx and release of calcium ions, inhibit their channels, slow down the contraction of smooth muscle, dilate the coronary artery and peripheral vessels, protect myocardial cells, stabilize blood pressure without affecting intraplacental blood flow and renal function, and play a role in inhibiting platelet aggregation and protecting neonatal development [15, 16]. Nifedipine has a rapid and prolonged hypotensive effect, which brings about a significant improvement in blood perfusion in the organs and tissues. The pharmacological action of Aspirin is believed to be anti-inflammatory and analgesic, anticoagulant, and it acts as an inhibitor of platelet aggregation. Meanwhile, it functions in reducing vascular sensitivity, effectively preventing the formation of thrombosis, and increasing blood flow. Oral administration is more conducive to the absorption of the body, with an exact effect and long-term antihypertensive maintenance. Moreover, it helps to control blood pressure

Table 2. Comparison of hemorheological parameters before and after therapy ($\bar{x}$ ± sd, mPa·s)

Group	n	PV		LBV		HBV	
		Before therapy	After therapy	Before therapy	After therapy	Before therapy	After therapy
Research group	54	1.73 ± 0.34	1.29 ± 0.08	9.42 ± 1.19	7.49 ± 0.98	4.42 ± 0.68	3.74 ± 0.46
Control group	54	1.75 ± 0.32	1.46 ± 0.13*	9.39 ± 1.22	8.54 ± 1.15*	4.40 ± 0.71	4.01 ± 0.55*
t		1.697	2.536	1.247	3.365	2.361	1.547
P		0.965	0.004	0.978	0.002	0.996	0.001

Note: The PV, LBV and HBV values after therapy in the two groups were significantly lower than those before therapy; *indicates the comparison between the research group and the control group after therapy, P < 0.05.

Table 3. Comparison of the occurrence of adverse reactions after therapy [n (%)]

Group	n	Dizziness	Diarrhea	Palpitation	Urinary tract infection	Overall incidence
Research group	54	1 (1.85%)	0 (0.00%)	2 (3.70%)	0 (0.00%)	5.56% (3/54)
Control group	54	3 (5.56%)	2 (3.70%)	3 (5.56%)	2 (3.70%)	18.52% (10/54)
X^2						4.285
P						0.038

Table 4. Comparison of adverse pregnancy outcomes [n (%)]

Group	n	Fetal distress	Postpartum hemorrhage	Premature labour	Fetal asphyxia	Overall incidence
Research group	54	1 (1.85%)	1 (1.85%)	0 (0.00%)	0 (0.00%)	3.70% (2/54)
Control group	54	3 (5.56%)	2 (3.70%)	3 (5.56%)	3 (5.56%)	20.37% (11/54)
X^2						7.083
P						0.008

Table 5. Comparison of all indicators (x(l)

Group	Albumin (g/L)	total protein (g/L)	24-hour urinary protein (g)	mean arterial pressure (mmHg)
Research group	37.54rch g	65.54rch g	1.324rch	101.32ch gro
Control group	30.54 ± 3.13	56.24ol gr	2.75 ± 0.42	130.65l gro
t	2.634	4.691	2.542	1.256
P	< 0.01	< 0.01	0.001	0.024

within the normal range [17, 18]. Both Nifedipine and Aspirin are common clinical medications for the treatment of GH. The former has an antihypertensive effect, and the latter is thought to be an anticoagulant. Co-medication can definitely enhance the drug efficacy.

This study showed that the clinical therapeutic effect was more significant in the research group. The FIB value after therapy [(4.19 ± 0.73) g/l] was observed at a significantly lower incidence in the research group compared with the control group [(5.02 ± 0.83) g/l]. FIB is a protein with coagulation function synthesized in the liver, with its raised level suggesting the aggregated platelets and the hypercoagulability of blood [19]. Elkon et al. [20] found in the study that in the treatment of moderate hypertensive disorder complicating pregnancy with Nifedipine and low-dose Aspirin, the FIB value after therapy was (4.22 ± 0.81) g/l, which was significantly lower than that in the Aspirin group [(5.06 ± 0.78) g/l], suggesting that concomitant medications could improve the coagulation function of patients with hypertensive disorder complicating pregnancy and relieve clinical symptoms. The research group had considerably better indicators of albumin, total protein, 24-hour urinary protein and mean arterial pressure that the control group. Additionally, the safety of drugs also serves as an essential indicator to evaluate its clinical application

value. This study revealed that the incidence of adverse reactions after therapy was markedly reduced in the research group (5.56%) compared with the control group (18.52%), suggesting that the safety of co-administration remained high. Furthermore, the adverse reactions such as dizziness and diarrhea occurred in patients during medication were mild and controllable, and they recovered spontaneously after drug withdrawal. This study has certain deficiencies as follows: The limited number of samples is considered (from our hospital only), and the study conclusion requires further demonstration.

In conclusion, the combined treatment is worthy of promotion because it is more effective to improve the coagulation function and various hemorheological parameters of patients, and relieve clinical symptoms, with a high safety and exact effects.

Disclosure of conflict of interest

None.

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