Effects of Nifedipine and Labetalol Combined with Magnesium Sulfate on Blood Pressure Control, Blood Coagulation Function, and Maternal and Infant Outcome in Patients with Pregnancy-Induced Hypertension

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Objective. The purpose is to investigate the influence of nifedipine, labetalol, and magnesium sulfate on blood pressure control, blood coagulation, and maternal and infant outcome in those suffering from pregnancy-induced hypertension (PIH). Methods. From January 2019 to April 2021, 100 participants with PIH in our center were randomly assigned to a control group and a research group. As a control, nifedipine combined with magnesium sulfate was administered. Nifedipine, labetalol, and magnesium sulfate were administered to the research group. The curative effect, blood pressure level, blood coagulation function, vascular endothelial function, and pregnancy comparisons were made between the two groups. Results. Based on the results of the study, the effective rate totaled 92.00%, while as for the control group, it was 80.0%, which indicates that there was a statistically significant difference between the effective rates of the research group and that of the control group, and the difference was statistically significant ($P < 0.05$). Blood pressure and blood coagulation function did not differ significantly between the two groups before treatment, and the difference was not statistically significant ($P > 0.05$). After treatment, both groups experienced a significant drop in systolic and diastolic blood pressure. After treatment, a higher PT index was found in the research group than in the control group. Likewise, the Fbg, D-D, and PLT were lower compared to those in the control group, and the difference was statistically significant ($P < 0.05$). Neither group had significantly different vascular endothelial function before treatment, and the difference was not statistically significant ($P > 0.05$). After treatment, the ET-1 of the two groups decreased, and the level of NO increased. There was a lower ET-1 in the research group than in the control group as well as a higher NO level in the research group than in the control group, and the difference was statistically significant ($P < 0.05$). Compared with the pregnancy outcome, in comparison to the controls, the research group had a higher vaginal delivery rate. Significantly, fewer cases of fetal distress, intrauterine asphyxia, and placental abruption were reported in the research group than in the control group, and the difference was statistically significant ($P < 0.05$). Conclusion. Nifedipine, in combination with magnesium sulfate and labetalol, is effective at treating PIH, reducing blood pressure, improving blood coagulation, preventing cardiovascular events and vascular endothelial function, and further improve the pregnancy outcome.

1. Introduction

With the improvement of living standards, the weight of many pregnant women has increased excessively during pregnancy. Annually, the number of hypertensive disorders complicating pregnancy (HDCP) increases due to the lack of regular antenatal examinations and uneven distribution of medical resources [1, 2]. HDCP can be divided into gestational hypertension, preeclampsia-eclampsia, and eclampsia if blood pressure rises after 20 weeks of pregnancy. If hypertension persists until 12 weeks after delivery, it can be divided into some categories: high blood pressure with pre-eclampsia and chronic hypertension during pregnancy. The survey shows that the global incidence of pregnancy induced...
hypertension is as high as 8%; the incidence of preeclampsia is 7% [3, 4]. According to statistics, the incidence of (HDSP) in China is 5% to 12%. The World Health Organization (WHO) has released statistics that about 50,000 women around the world die of epilepsy and its complications every year [5]. The risk is higher in less developed regions such as Asia and Africa, where the case fatality rate of patients with pregnancy-induced hypertension (PIH) is about 10%. In less developed areas, the case fatality rate of PIH in Latin America is about 25% [6]. Therefore, as a global disease, PIH has attracted widespread attention because of its serious threat to maternal and infant safety.

Fetal growth restriction may occur when β-blockers are used during early pregnancy. The side effects of the drug are scalp tingling and vomiting. Nifedipine was often chosen as calcium channel blockers because it can effectively inhibit calcium influx, dilate blood vessels, and relax smooth muscle. Clinical use of nifedipine can prevent threatened preterm labor. Importantly, the side effects on pregnant women are relatively small because of the long antihypertensive stable duration and the small effect on the circulatory system. The main drugs of PIH treatment commonly used in clinic are magnesium sulfate, which has the effects of sedation, spasmylosis, and antihypertensive. But due to the single use of drugs, it is difficult to achieve the ideal therapeutic effect [7]. Labetalol, a commonly used α-receptor and β-receptor blocker, could act directly on the blood vessels of the human body, reducing the patient’s blood pressure by dilating the blood vessels. While the cardiac output and pulse output will not change during the treatment.

During the treatment, side effects such as palpitation and headache may occur after taking nifedipine. At present, it is considered that nifedipine and labetalol have good therapeutic effect on PIH. Placental blood flow rarely changes, effectively prevent blood pressure from falling too much, having the effect of increasing prostacyclin level, antiplatelet aggregation, and promoting fetal lung maturation. It is often recommended for patients with moderate and severe PIH. Labetalol’s advantage lies in the effective control of blood pressure in pregnant women. While the placenta is not affected by drugs, which can have a satisfactory effect on the perinatal final maternal and infant outcome [8, 9]. Labetalol, as a first-line drug for reducing blood pressure in PIH, is mainly due to its mild effect on lowering blood pressure and does not affect placental blood flow, which will not lead to symptoms such as low blood pressure and rapid heart rate [10, 11]. Therefore, the present study outlines the clinical effectiveness of nifedipine and magnesium sulfate combined with labetalol in PIH, to guide clinical decision making in the selection of a better treatment plan.

2. Materials and Methods

2.1. General Information. Our hospital treated 100 patients with pregnancy-induced hypertension from January 2019 to April 2021, and the study focused on their outcomes. A random sampling of patients was taken into account to divide them into the study and control groups. The control group was treated with Adalat combined with magnesium sulfate, and the research group was treated with the combination of Adalat, labetone, and magnesium sulfate. An average age of (32.56 ± 3.42) years was found in the control group, which ranged from 20 to 44 years old; a 24-year-old was the youngest participant in the study, followed by an average of 34 years old, and a 44-year-old was the oldest. There was no significant difference in the general data between the two groups, and the difference was not statistically significant (P > 0.05). Patients signed informed consent, and the study was approved by the Medical Ethics Association of the hospital where it was conducted.

2.2. Inclusion Criteria. (i) It accords with the diagnostic manifestation of pregnancy-induced hypertension in western medicine, specifically referring to the diagnostic guidelines of HDCP and the 9th edition of Obstetrics and Gynecology [12, 13]; (ii) all patients are singleton pregnancy, and the fetus and various indexes are normal after related imaging examination; (iii) the patients have no hypertension, diabetes, and abnormal blood coagulation in the past years; (iv) the clinical data of the patients in this study are complete.

2.3. Exclusion Criteria. (i) This study involved patients who are allergic to certain drugs; (ii) patients with other major organ diseases and/or neuropsychiatric diseases; (iii) patients having hematological tumors or other blood system diseases; (iv) patients with insufficient clinical data or withdrawal; (v) patients with severe injuries to liver, kidney, and other organs.

2.4. Methods. After admission, all patients were given routine diet education guidance, close monitoring of blood pressure. Medical officers assist patients to complete the relevant examinations. Medical staff should carefully record the blood pressure control of patients, instruct patients to maintain a light diet, emphasize dietary taboos and matters needing attention in life, supervise the use of drugs, and strengthen the observation of adverse drug reactions.

Drug regimen for patients in the control group: magnesium sulfate injection (Anyang Kyushu Pharmaceutical Co., Ltd., national drug standard H41023035, specification: 10 ml:2.5 g), 20 ml was mixed with 100 ml 5% glucose injection (Jiangsu Shenlong Pharmaceutical Co., Ltd., national medicine standard word H32024365, specification: 100 ml/bag), intravenous drip for 0.5 h, and then 60 ml magnesium sulfate injection combined with 1000 ml 5% glucose injection was mixed with intravenous drip for maintenance treatment. At the same time, patients were given oral nifedipine tablets (Guangdong South China Pharmaceutical Group Co., Ltd., Chinese medicine H44023986, specification: 10 mg × 100 s) 3 times a day, 10 mg each time.

The patients in the research group were given oral labetalol hydrochloride tablets (Zhengzhou Kaili Pharmaceutical Co., Ltd., Chinese medicine H41024906, specification: 50 mg × 20 tablets × 2 plates) 3 times a day, 100 mg each time. For the following two weeks of treatment, both groups were evaluated for clinical efficacy.
2.5. Observation Index

2.5.1. Evaluation of Curative Effect [13]. Effective: (i) as a result of the treatment, the systolic blood pressure was below 140 mmHg; the diastolic blood pressure was below 90 mmHg, and the urine protein <0.3 g/24 h, 90% > N ≥ 66.67%. (ii) systolic blood pressure 140–150 mmHg, diastolic blood pressure 90–100 mmHg, and urinary protein <1.0 g/24 h, 66.7% > N ≥ 33.3% after 7 days of treatment. Ineffective: (iii) after 7 days of treatment, the systolic blood pressure fluctuated in 150–160 mmHg, and diastolic blood pressure 100–110 mmHg, albuminuria ≥ 1 g, 24 h, N < 33.3%. Total effective rate = (number of effective cases + effective cases)/total number of cases × 100%.

2.5.2. Blood Coagulation Index and Vascular Endothelial Function. Prothrombin time (PT) and fibrinogen (Fbg) were detected before treatment and 2 weeks after treatment (CA-7000 automatic blood coagulation analyzer). The D-dimer (D-dimer) (enzyme-linked immunosorbent assay), platelet count (PLT), endothelin-1 (ET-1), and nitric oxide (NO) were detected.

2.5.3. Blood Pressure Level and Pregnancy Outcome. Researchers recorded both groups’ blood pressure levels before and after treatments. At the same time, the pregnancy outcomes of the two groups were recorded (vaginal delivery, fetal distress, intrauterine asphyxia, placental abruption).

2.6. Statistical Analysis. SPSS23.0 statistical software was adopted to process the data. The measurement data were presented as (x ± s). The group design t-test was adopted for the comparison, and the analysis of variance was adopted for the comparison between multiple groups. Dunnett’s test was adopted for comparison with the control group. The counting data were presented in the number of cases and the percentage, χ² test was adopted for comparison between groups, and bilateral test was employed for all statistical tests.

3. Results

3.1. Comparative Study of Curative Effects. There were no patients who quit the study. In the research group, a 92.00% success rate was achieved in 31 cases whose effectiveness was marked; 15 cases whose effectiveness was marked, and four cases whose effectiveness was ineffective. The comparison group had 28 cases that were significantly effective, 12 cases that were effective, and 10 cases that were ineffective, with an efficacy rate of 80%. Studies conducted in the research group had a higher efficacy rate than in the control group, and the difference was statistically significant (P < 0.05). Figure 1 shows all the results of the data analysis.

3.2. Blood Pressure Level Comparison. A comparison of blood pressure levels between the two groups before and 2 weeks after treatment did not reveal any significant differences, and the difference was not statistically significant (P > 0.05). Systolic and diastolic blood pressure decreased significantly after treatment in both groups. Significantly, in the research group, both systolic and diastolic blood pressures were higher than those in the control group, with the difference being statistically significant, and the difference was statistically significant (P < 0.05). The data results are summarized in Table 1.

3.3. Comparison of Blood Coagulation Function Indexes. Neither group had significantly different indexes of blood coagulation before treatment, and the difference was not statistically significant (P > 0.05). A significant increase in PT indexes was observed in the research group after treatment, and the Fbg, D-D, and PLT were significantly lower than those in the control group. Differences between them were statistically significant, and the difference was statistically significant (P < 0.05). All the data results are shown in Table 2.

3.4. Comparison of Vascular Endothelial Function. Prior to treatment, there were no significant differences in vascular endothelial function between the two groups, and the difference was not statistically significant (P > 0.05). After treatment, the level of ET-1 of the two groups decreased, and the level of NO increased. Compared to the control group, the research group’s ET-1 was lower, and its level of NO was higher than the control group’s; the difference was statistically significant (P < 0.05). The results of the data analysis are presented in Table 3.

3.5. Comparison of Pregnancy Outcome. Compared with the pregnancy outcome, it was more common for women in the research group to give birth via vaginal delivery than in the control group, and the incidences of fetal distress, intrauterine asphyxia, and placental abruption in the research group were lower than those in the control group, and the difference was statistically significant (P < 0.05). All the data results are shown in Figure 2.

4. Discussion

HDCP is a kind of disease which coexists with hypertension and pregnancy, in addition to preeclampsia and gestational hypertension, chronic hypertension related to preeclampsia, eclampsia, and chronic hypertension complicating pregnancy are also among its complications. The main clinical manifestations are urinary protein, elevated blood pressure, and limb edema, which could lead to a series of consequences, such as fetal growth retardation, placental abruption, preterm delivery, fetal death, and postpartum hemorrhage. In severe cases, serious complications including heart failure, convulsion, liver failure, coma, and renal failure may occur [14]. Among the causes of maternal death, HDCP ranked second [15]. Preeclampsia is defined as follows: after 20 weeks of pregnancy, expecting mothers without history of hypertension find that their blood pressure has increased (~ systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg), accompanied by changes in urinary protein or pathological changes in the vital organ system, or placental-fetal lesions, accounting for about 3.9% of all
Table 1: Comparison of blood pressure between the two groups.

|                | Systolic blood pressure | Diastolic pressure |
|----------------|-------------------------|--------------------|
|                | Before treatment | After treatment | Before treatment | After treatment |
| Control group  | 164.83 ± 14.95 | 134.39 ± 12.44 | 99.94 ± 7.53 | 83.19 ± 5.86 |
| Research group | 165.39 ± 15.44 | 120.39 ± 9.83 | 99.91 ± 7.55 | 78.39 ± 5.64 |

|        | t value | P value |
|--------|---------|---------|
| Control group | 0.184 | >0.05 |
| Research group | 6.243 | <0.05 |

Table 2: Comparison of coagulation function indexes between the two groups.

|                | PT (s) | Fbg (g/L) | D-D (mg/L) | PLT (×10^9/L) |
|----------------|--------|-----------|------------|---------------|
|                | Before treatment | After treatment | Before treatment | After treatment | Before treatment | After treatment | Before treatment | After treatment |
| Control group  | 8.01 ± 1.05 | 10.93 ± 1.22 | 7.68 ± 1.34 | 5.49 ± 1.21 | 1.52 ± 0.36 | 1.29 ± 0.31 | 52.23 ± 24.05 | 39.94 ± 23.11 |
| Research group | 7.99 ± 1.04 | 12.48 ± 1.21 | 7.71 ± 1.36 | 4.12 ± 0.66 | 1.55 ± 0.40 | 0.73 ± 0.36 | 52.97 ± 24.11 | 18.49 ± 9.31 |

|        | t value | P value |
|--------|---------|---------|
| Control group | 0.096 | <0.05 |
| Research group | 6.378 | <0.05 |

Table 3: Comparison of vascular endothelial function between the two groups.

|                | ET-1 (ng/L) | NO (mol/L) |
|----------------|-------------|------------|
|                | Before treatment | After treatment | Before treatment | After treatment |
| Control group  | 69.96 ± 3.45 | 57.76 ± 3.64 | 40.64 ± 3.23 | 70.56 ± 4.64 |
| Research group | 69.42 ± 2.64 | 39.91 ± 2.95 | 40.65 ± 3.18 | 50.85 ± 3.44 |

|        | t value | P value |
|--------|---------|---------|
| Control group | 0.878 | >0.05 |
| Research group | 26.939 | <0.05 |

Figure 1: Comparison of curative effect between the two groups.

Figure 2: Comparison of pregnancy outcomes between the two groups.
pregnancies [16]. The present study outlines the clinical effectiveness of nifedipine and magnesium sulfate combined with labetalol in PIH, to guide clinical decision making in the selection of a better treatment plan.

The present study outlines the clinical effectiveness of nifedipine and magnesium sulfate combined with labetalol in PIH, to guide clinical decision making in the selection of a better treatment plan. With the development of modern medical technology and the deepening of clinical research on preeclampsia, the methods to control the development of preeclampsia have also made considerable progress, effectively reducing neonatal mortality and maternal prenatal complications [17, 18]. There is no complete understanding of the etiology and pathogenesis of pregnancy-induced hypertension. In the past ten years, the theory of “placental superficial implantation”, as a theory to explain HDCP, has been gradually accepted by most scholars [19]. Current studies have confirmed that the erosion function of trophoblasts in early pregnancy decreases, which leads to the shallow implantation of placenta into the endometrium and triggers the occurrence of PIH. Similar to allogeneic transplantation during pregnancy, embryonic trophoblast cells need to erode into the decidua of the mother’s uterus, invade the spiral artery, and then replace the arterial endothelial cells to establish an interactive circulation between the fetus and the mother, which can provide necessary nutritional support for the development of the embryo. In normal pregnancy, the diameter of placental villi decreased significantly with the increase of the diameter of spiral arterioles between decidua and uterus. This physiological change increases the total area of gas exchange between mother and fetus, which is beneficial to the normal growth and development of fetus. If there are abnormalities in this process, the erosion ability of extravillous trophoblasts is impaired; the uterine spiral artery is not eroded enough by trophoblasts, and the erosion range is reduced [20].

Clinical studies have found that PIH has many effects on pregnant women, fetuses, and newborns. Some scholars have suggested that it may be related to the occurrence of some neonatal diseases, such as septicemia, infection, retinopathy, intracranial hemorrhage, and so on. It will also be affected in the aspects of hormone system, blood cytology, blood glucose and blood lipid metabolism, nervous system development as well as long-term intelligence, physical strength, psychology, and quality of life. The uterine spiral artery has not experienced the changes of normal pregnancy, but still maintains the sensitivity to vasoconstrictive substances and relatively narrow diameter. This will lead to shallow placenta implantation than normal pregnancy, decreased blood perfusion, and a series of clinical symptoms of HDCP [21]. The increase of blood pressure after pregnancy will lead to the damage of vascular endothelium and the release of endogenous vasodilator factor, vasodilator factor, and NO. Under the influence of prostacyclin (PGIa), it increases the synthesis of thromboxane A (TXA), which induces the imbalance of the ratio of vasoconstrictor factor to vasodilator factor, leading to a further increase in blood pressure. There are corresponding pathological changes in each target organ, which affect the quality of life of pregnant women and the life safety of mothers and infants [22–24]. An important pathological feature of hypertension during pregnancy is systemic arterial spasm; the result of which is an increase in peripheral resistance and blood pressure, the decrease of blood flow through placenta and placental function compared with normal pregnancy, and the enhancement of vascular permeability. Blood viscosity increased in a state of hypercoagulability, followed by intravascular coagulation and microvascular thrombosis.

When using drugs to control blood pressure in HDCP, methyldopa, and labetalol combined with nifedipine should be considered firstly [25]. Due to the different physical types, receptors, and pharmacological mechanisms of medicine in pregnant women, it is not possible to determine that labetalol hydrochloride can play a better effect on each body in the group. Limited by the scope of the trial, we rule out not only the existence of other kinds of augmentation drugs but also the good history of the treatment of PIH. The preferred drug for controlling blood pressure in HDCP is α-adrenergic agonist methyldopa. Its pharmacological effect is to stimulate the α-receptor and inhibit the peripheral sympathetic nerve. Its curative effect has been confirmed, and its side effects are drowsiness, constipation, dry mouth, and bradycardia. Unfortunately, this drug is not used in our market [26]. Labetalol hydrochloride tablets have the advantages of long-term tolerance and safety to both mother and fetus. As a salicylamide derivative, its chemical structure can effectively select α and β-adrenergic receptors [27]. There are mainly α receptors in peripheral resistance vessels and volume vessels, which can dilate the above vessels after blocking α receptors. The coronary blood flow increased significantly; the myocardial oxygen consumption was reduced, and the cardiac load was reduced. The clinical effect is quick, and it does not reduce blood pressure to too low and does not affect the blood perfusion of placenta, brain, uterus, kidney, and fetus. β-adrenoceptor mainly acts on the atrioventricular junction. Blocking β-receptor can prolong the conduction time of myocardial bioelectric signals in this area, thus reduce the heart rate and myocardial oxygen consumption. It slows down the heart rate and lowers blood pressure at the same time [28]. The heart rate of patients will not decrease indefinitely after slowing down to a certain extent, and then tend to stabilize by themselves. According to the clinical pharmacological study [29], labetalol hydrochloride tablets also have the functions of reducing platelet consumption, inhibiting platelet aggregation, and promoting fetal lung maturation. But there are inevitable limitations.

Magnesium sulfate can also dilate vascular smooth muscle and dilate spastic peripheral blood vessels as a preventative measure and treatment for eclampsia. It can play a role immediately after intravenous injection lasting for 30 min and renal excretion. However, during the treatment of magnesium sulfate, the knee reflex and respiration of the patients should be observed, and the urine volume should be ≥25 mL/h. In addition, the dose and flow velocity should be controlled according to the patient’s signs. Nifedipine can inhibit Ca²⁺ inflow, relax vascular smooth muscle, dilate coronary artery, and increase coronary blood flow, thus lowering blood pressure. Low-dose coronary artery dilatation
does not affect blood pressure, so it is a better antianginal drug [30]. In the treatment of PIH, magnesium sulfate is first of all recommended, which can inhibit the activity of central nervous system and conduct a reduction in the release of acetylcholine from motor nerve-muscle junctions and a relaxation of muscle contractions. As an antihypertensive drug, there are no adverse reactions such as water and sodium retention and edema that are common in general vasodilators. The effect of sublingual administration is faster than that of oral administration. The antihypertensive effect appeared after 10 minutes of spray administration; the effect was the most significant after 1 hour, and the blood pressure increased after about 3 hours (some can last for 11 hours). Intravenous injection within 10 minutes can reduce blood pressure by 21%-26% [31]. Nifedipine is a dihydropyridine calcium channel blocker, which can dilate vascular smooth muscle and improve peripheral vasospasm. Magnesium sulfate combined with nifedipine can better relax peripheral vascular smooth muscle, reduce vascular resistance, and improve uterine artery blood flow. Vascular endothelium injury can release a large number of vasoactive substances, which participate in the regulation of vascular tension, smooth muscle cell proliferation, vascular wall inflammation, and so on [32].

The combined application of labetalol, nifedipine, and magnesium sulfate can effectively improve blood circulation and reduce the damage of hypertension to heart, kidney, and other target organs, thus improving the internal environment [33, 34]. It is consistent with the results of Uwizeyimana et al. [35] and Houehanou et al. [36]. Most of the patients with PIH are in hypercoagulable state. Nifedipine combined with magnesium sulfate and labetalol can dilate blood vessels and reduce blood pressure [37]. Compared with the control group, the research group's total efficacy rate was significantly higher, as were the levels of systolic blood pressure and diastolic blood pressure. It is suggested that labetalol can block both α-receptor and β-receptor, effectively expand blood volume and reduce cardiac preload by blocking α-receptor, and can reduce myocardial oxygen consumption and increase cardiac output by blocking β-adrenoceptor. Results revealed that PT levels in the research group rose, whereas FBG levels and Dmurd levels declined. There was a higher degree of improvement in the PIH group than in the control group, indicating that nifedipine alone or in combination with magnesium sulfate and labetalol could reduce hypercoagulability. ET-1, an endogenous injury factor produced in pathological state can produce the metabolism A2, promote the release of calcium ions from the calcium library, and increase the production of free radicals. NO is a vasodilating factor, which can maintain vascular endothelial function and regulate blood pressure [38, 39]. Both groups experienced a decrease in ET-1 levels as well as an increase in NO levels after treatment, indicating that nifedipine with magnesium sulfate and labetalol can relieve these side effects. The reason may be that nifedipine combined with magnesium sulfate and labetalol can downregulate the expression of endothelin and improve endothelial dysfunction. Nifedipine combined with magnesium sulfate and labetalol can regulate peroxide injury and reduce the release of free radicals to prevent vascular endothelial damage [40, 41]. There are some limitations in this study. First, the sample size of this study is not large, and it is a single-center study, so bias is inevitable. In future research, we will carry out multicenter and large-sample prospective studies, or more valuable conclusions can be drawn.

In conclusion, PIH can be effectively treated with nifedipine, magnesium sulfate, and labetalol, which can effectively reduce blood pressure, improve blood coagulation and vascular endothelial function, and further improve the pregnancy outcome.

Data Availability

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

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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