Research Paper

Clinical Efficacy Analysis of Nifedipine Combined with Low Molecular Weight Heparin in the Treatment of Pregnancy Hypertension

HUANG LIJUAN*

Department of Clinical Obstetrics, General Hospital of Ningxia Medical University, Yinchuan, Ningxia 750004, P. R. China

This research aims to investigate nifedipine and low molecular weight heparin clinical efficacy in cure patients with hypertension during pregnancy. A retrospective analysis of 180 patients with hypertension during pregnancy admitted to the obstetric ward of our hospital from December 2017 to December 2020 was selected. Among them, 90 patients with hypertension during pregnancy were treated with nifedipine combined with low molecular weight heparin (observation group). Nifedipine was used to treat 90 patients with pregnancy-induced hypertension (control group). Contrast the blood pressure, D-dimer, pregnancy-related complications and adverse events incidence in both groups before and after treatment were compared. The observation group clinical effective rate was 90 % while the control group was 70 % ($p<0.05$). The blood pressure and D-dimer of both groups decreased obviously after treatment, but the observation group decreased more significantly than it ($p<0.01$). The observation group incidence of pregnancy-related complications (uterine weakness, postpartum hemorrhage) was significantly lower than the other ($p<0.05$). There was no diversity in these two groups in incidence of fetal distress, placental abruption and neonatal asphyxia ($p<0.05$), both groups incidence of adverse reactions were almost the same and there was no statistical difference ($p>0.05$). Nifedipine and low molecular weight heparin in patients cure with hypertension during pregnancy can lower blood pressure and reduce the incidence of uterine asthenia, postpartum hemorrhage and other related complications without increasing patient's incidence of adverse reactions. The medication is meaningful for clinical promotion.

Key words: Hypertension during pregnancy, low molecular weight heparin, nifedipine

Hypertension During Pregnancy (HDP) is one of the common complications of pregnancy. Preeclampsia (PE) is an avoidable adverse maternal and infant outcome. The world records about 50 000-100 000 deaths due to serious complications of PE during pregnancy each year.

It refers to the whole body arteriole spasm, which can cause damage to multiple organs. In severe cases, it can cause insufficient blood supply to the fetus and hypoxia in the fetus, which seriously threatens the safety of mothers and infants. HDP is the main death purpose of perinatal of pregnant or lying in women[1].

The clinical symptoms of hypertension in pregnancy mostly occur in the middle and late stages of pregnancy. The traditional definition of chronic hypertension and hypertension in pregnancy is related to pregnancy at the time of diagnosis. Chronic hypertension is often defined as a blood pressure which surpass 140/90 mmHg that occurs before pregnancy or 20 w of pregnancy and HDP means a blood pressure surpass 140/90 mmHg that occurs after 20 w of pregnancy[2,3].

Hypertension in pregnancy can significantly increase the risk of fetal growth restriction, placental abruption, diffuse intravascular coagulation, cerebral edema, acute heart failure and acute renal failure, and is an important cause of maternal and fetal death[4].

Patients with hypertension in pregnancy need to actively control their blood pressure and reduce the occurrence of corresponding complications. At present, patients with hypertension in pregnancy are well tolerated by antihypertensive drugs, few patients with hypertension in pregnancy need to change drugs midway, the treatment of mild chronic hypertension with low side effects of antihypertensive drugs is beneficial to

***Address for correspondence**
E-mail: huanglijuanxi@163.com

pregnant women, but the effect on the perinatal infant is not clear and there is no clear data to prove the benefits and risks of antihypertensive strategies that restrict the activities of pregnant women[5].

At present, the clinically commonly used nifedipine monotherapy is not effective. It needs to further explore the combination of drugs in terms of improving the therapeutic effect and reducing the occurrence of complications.

At this stage, preventive use of Low Molecular Weight Heparin (LMWH) to prevent thrombosis in patients with hypertension in pregnancy has always been the focus of research. Its anticoagulant effect is stable and its application is safe[6,7].

Therefore, in this study, a combination of nifedipine and LMWH was used to treat HDP and its efficacy was observed. It provides a theoretical basis for clinical treatment of HDP.

MATERIALS AND METHODS

General materials:

From December 2017 to December 2020, 180 patients with HDP were included as the research subjects and then divide them into observation group (90 cases) and control group (90 cases) randomly. The exclusion criteria were: The eligible patients took antihypertensive drugs within 1 w before cure; the eligible patients who had other pregnancy complications during admission; the eligible patients with mental disturbances or communication disorders.

Treatment methods:

Guide, control group patients to take nifedipine controlled-release tablets orally, 5 mg/d. Patients with gestation ≤38 w received 1 course of treatment for 7 consecutive days and patients with gestation >38 w conducted a 3 d treatment. The observation group was injected with LMWH sodium (5000 International Unit (IU)) and QD (daily) subcutaneously, contrasts the control group for 3 d.

Observation index:

Clinical efficacy evaluation: Basic cure, either dizziness or edema, urine protein decreased ++, normal blood pressure, systolic blood pressure surpass 30 mmHg, diastolic blood pressure surpass 10 mmHg, pregnancy less than 37 w; Effective-dizziness or edema was significantly reduced, urine protein decreased +, blood pressure decreased to normal, diastolic or systolic blood pressure less than 10 mmHg, 36 to 37 w of gestation; invalid-gestational age <36 w, blood pressure or urine protein level did not decreased remarkably and clinical manifestation did not recover or deteriorate. Total effective rate=(Basic cure+effective)/Total effective rate×100 %.

Blood pressure monitoring and D-dimer detection: The systolic blood pressure, diastolic blood pressure and serum D-dimer of the two groups of patients before and after treatment were compared.

Pregnancy complications: The incidence of adverse pregnancy outcomes of complications (uterine contraction fatigue, fetal distress, neonatal asphyxia, placental abruption and postpartum hemorrhage) which were related to pregnancy hypertension were compared with both groups after treatment.

Other adverse reactions: The occurrence of adverse reactions such as palpitations, bradycardia, facial flushing and lower extremity edema after treatment were observed in the two groups.

Statistical methods:

Analysis is done using Statistical Package for the Social Sciences (SPSS) 19.0 software. Count data is compared in the form of percentage (%), using chi-square test and measurement data in ($\bar{x}\pm s$), using t test for comparison, $p<0.05$ indicates that the difference is statistically significant.

MATERIALS AND METHODS

General materials:

From December 2017 to December 2020, 180 patients with HDP were included as the research subjects and then divide them into observation group (90 cases) and control group (90 cases) randomly. The exclusion criteria were: The eligible patients took antihypertensive drugs within 1 w before cure; the eligible patients who had other pregnancy complications during admission; the eligible patients with mental disturbances or communication disorders.

RESULTS AND DISCUSSION

Clinical baseline data of two groups were compared. The intervention group has the characters of an average age (26.2±2.8), average pregnancy (34.8±4.2) w, the systolic blood pressure (159.2±7.7) mmHg and the diastolic blood pressure was (99.2±4.5) mmHg. The observation group was treated with a combination of nifedipine and LMWH. 90 patients in the control group average (27.2±2.1) y old, pregnancy (33.9±5.0) w, systolic blood pressure (158.1±8.0) mmHg, diastolic

blood pressure (98.4±4.8) mmHg, there was no statistically difference of baseline data for both groups (p>0.05) (Table 1).

Clinical efficacy after treatment of both groups was evaluated. After treatment, the mentioned observation group total clinical effective rate reached 90.0 %, which was remarkably higher than the 70.0 % in the other group (p<0.05), with an obvious statistical diversity. The efficacy evaluation results of the two groups of patients are shown in Table 2.

Systolic diastolic blood pressure, blood pressure and D-dimer before and after treatment in both groups were compared. Both groups systolic blood pressure and diastolic blood pressure lowered remarkably after treatment (p<0.05), but the observation group lowered more remarkably (p<0.05), as shown in Table 3 in detail. The observation group D-dimer decreased remarkably after treatment, while it did not decrease remarkably in the other group after treatment.

Incidence of pregnancy complications after treatment in both groups was compared. Uterine weakness and postpartum hemorrhage in the observation group occurred remarkably less than those the other (p<0.05), which was of statistical significance. Among them, fetal distress, placental abruption and neonatal asphyxia were not significantly different (p>0.05), which was not of statistical significance as shown in Table 4.

Incidence of adverse reactions after cure in both groups was compared. After cure, neither the observation group nor the control group incidence of adverse reactions is not different (p>0.05) and there was no statistical significance (Table 5).

TABLE 1: COMPARISON OF BOTH GROUPS CLINICAL BASELINE DATA

	Observation group (n=90)	Control group (n=90)	t/ χ^2	p
Age	26.2±2.8	27.2±2.1	-1.13	0.25
Gestational week	34.8±4.2	33.9±5.0	1.3	0.19
Systolic blood pressure (mmHg)	159.2±7.7	158.1±8.0	0.93	0.34
Diastolic blood pressure (mmHg)	99.2±4.5	98.4±4.8	1.15	0.25

TABLE 2: COMPARISON OF CLINICAL EFFICACY BETWEEN THE TWO GROUPS OF PATIENTS

	Cure	Effective	Ineffective	Total effective rate
Observation group	39 (43.3 %)	42 (46.7 %)	9 (10 %)	81 (90 %)
Control group	22 (24.4 %)	41 (45.5 %)	27 (30 %)	63 (70 %)
χ^2				11.25
p				0.003

TABLE 3: COMPARISON OF SYSTOLIC BLOOD PRESSURE, DIASTOLIC BLOOD PRESSURE AND D-DIMER IN BOTH GROUPS BEFORE AND AFTER TREATMENT

		Observation group	Control group	t	p
Systolic blood pressure (mmHg)	Before treatment	159.2±7.7	157.1±8.0	0.93	0.33
	After treatment	131.2±6.2	149.2±7.6	-17	0.00
Diastolic blood pressure (mmHg)	Before treatment	99.2±4.5	98.4±4.8	1.15	0.25
	After treatment	89.2±3.5	94.2±3.7	-9.71	0.005
D2 aggregate (mg/l)	Before treatment	2.48±0.59	2.50±0.56	-0.30	0.76
	After treatment	2.14±0.39	2.38±0.52	-4.11	0.001

TABLE 4: COMPARISON OF BOTH GROUPS INCIDENCE OF PREGNANCY-RELATED COMPLICATIONS

	Intervention group (n=90)	Control group (n=90)	χ^2	p
Uterine weakness	2 (2.2 %)	9 (10.0 %)	4.74	0.03
Postpartum hemorrhage	5 (5.6 %)	14 (15.6 %)	4.77	0.03
Fetal distress	3 (3.3 %)	7 (7.8 %)	1.69	0.19
Placental abruption	3 (3.3 %)	5 (5.6 %)	0.52	0.46
Neonatal asphyxia	2 (2.2 %)	5 (5.6 %)	1.34	0.24

TABLE 5: COMPARISON OF BOTH INCIDENCES OF ADVERSE REACTIONS AFTER TREATMENT

	Intervention group (n=90)	Control group (n=90)	χ^2	p
Palpitations	1 (1.1 %)	4 (4.4 %)	1.85	0.17
Bradycardia	3 (3.3 %)	6 (6.7 %)	1.05	0.31
Lower extremity edema	0 (0.0 %)	4 (4.4 %)	4.09	0.05
Facial flushing	2 (2.2 %)	6 (6.7 %)	1.34	0.24

Hypertension in pregnancy appears lumen stenosis by the reason of arteriole spasm, which manifests as obstruction of blood circulation and endothelial cell damage, which then evolves into multiple organ disease[8]. The clinical features of HDP include hypertension, urine protein, coma, edema and even multiple organ failure[9]. Because pregnancy-induced hypertension occurs frequently, if we meet some serious medical cases, it might lead to infant mortality during the puerperium or perinatal period[10]. As we all know, due to pregnancy physiological changes or hereditary thrombotic diseases, it can cause pregnant women to be in a hypercoagulable state, increasing Venous Thromboembolism (VTE), PE, early recurrence, late fetal loss, Intrauterine Growth Retardation (IUGR), placental abruption and other adverse pregnancy complications and their outcomes, especially in patients with pregnancy-induced hypertension[7].

Therefore, strengthening the monitoring during the puerperium can help us to discover the disease early and then we can accept an earlier HDP diagnosis and treatment, which is of great importance for ensuring mothers and babies' safety. In clinical treatment, the main principles of hypertension treatment during pregnancy are: to effectively relieve vasospasm, regulate blood circulation, maintain blood pressure at a normal level and prevent complications from occurring[11].

In this study, we found that the effective and antihypertensive efficiency of nifedipine and LMWH and adverse pregnancy outcomes occurrence were better than the other, it suggested that nifedipine plus LMWH has a synergistic effect and significantly reduces blood pressure in patients. There was no statistical significance in adverse drug reactions incidence ($p>0.05$). It is suggested that the combination of the two drugs has better safety, without any new adverse reactions. Nifedipine is a long-acting calcium antagonist. Its main function is to dilate the coronary arteries, increase the coronary blood flow of the patient, relax the smooth muscles in the blood vessels and achieve the purpose of stabilizing the drug concentration. It can also transfer calcium ions into the patient's myocardium and smooth muscle cells across the membrane, selectively inhibit the cells and relax the smooth muscles in the blood vessels, thereby reducing blood pressure and systolic blood pressure[12,13]. In the past two decades, LMWH has been increasingly used in the management of hypertensive patients during pregnancy[14]. Compared with heparin, LMWHs have a longer half-life and a more predictable anticoagulant reaction, no need to monitor the patient's laboratory parameters, significantly improve the hypercoagulable state of hypertensive patients during pregnancy. In addition, due to its large molecular weight, there is no transplacental metastasis, so there is no incidence of fetal bleeding or teratogenicity increase[15,16]. Studies have shown that among all patients treated with enoxaparin, the live birth rate is 89 %. It is a safe and effective alternative to heparin and warfarin. It can be used for various indications such as valve replacement, atrial fibrillation, thrombosis, thrombotic varices, repeated pregnancy loss and prevention or treatment of deep vein thrombosis, etc.,[17]. There are similarities between these studies and the results of this study. But this study also has some limitations. Since our research population is mainly for Chinese people, it is necessary to be cautious to interpret this result to other

populations; Secondly, the sample size of our research is too small and we do not rule out that it may bring some errors to the results of the study.

Nifedipine and LMWH work together to treat patients with HDP can reduce blood pressure and reduce the incidence of uterine fatigue, postpartum hemorrhage and other related complications without increasing patient's adverse reactions. We think drugs combination is worthwhile clinical promotion.

Conflict of interests:

The authors declared no conflict of interest.

REFERENCES

1. Wang Y, Zhang X, Han Y, Yan F, Wu R. Efficacy of combined medication of nifedipine and magnesium sulfate on gestational hypertension and the effect on PAPP-A, VEGF, NO, Hcy and vWF. Saudi J Biol Sci 2019;26(8):2043-7.
2. Belovic DK, Plešinac S, Dotlić J, Radojević AS, Akšam S, Cvjetićanin MM, *et al.* Biochemical markers for prediction of hypertensive disorders of pregnancy. J Med Biochem 2019;38(1):71-82.
3. Wen L, Guo Z, Hu J. Epidemiology and pathogenesis of hypertensive disorder complicating pregnancy in Han nationality. J Med Res 2017;46(5):128-31.
4. Feng YL, Peng ZZ, Wang F, Su T, Yue F, Zhang L, *et al.* Impact of hypertensive disorder complicating pregnancy on birth outcomes and its potential risk factors. Chin J Dis Control Prev 2014;18(2):131-4.
5. Wu LL, Zhou X, Niu JM. Interpretation of 2018 ISSHP recommendations for hypertensive disorder of pregnancy classification, diagnosis and management. Chin J Pract Gynecol Obstet 2018;34(7):758-63.
6. Hu P, Chen JF. Coagulation function analysis in patients with gestational diabetes mellitus and gestational hypertension during the 3rd trimester pregnancy. Lab Med 2016;31(9):774-7.
7. Vucić N, Frleta M, Petrović D, Ostojić V. Thrombophilia, preeclampsia and other pregnancy complications. Acta Med Croatica 2009;63(4):297-305.
8. Wang YQ. Risk factors related to hypertensive disorders in pregnancy and effects of hypertension on pregnancy outcome. Appl J Gen Pract 2015;13(4):602-4.
9. Chen YI, Wang LJ, Shi WQ. Clinical analysis of the 379 patients with hypertensive disorders of pregnancy. Med Innov China 2017;14(22):51-5.
10. Chen FY, Xiao LJ, Huang S, Li ZJ. Epidemiological characteristics of hypertensive disorder complicating pregnancy complicated with multiple organ dysfunction syndrome and effect of plasma exchange combined with blood purification on its fatality rate. Mod Hosp 2018;18(7):999-1003.
11. Magee LA, Abalos E, von Dadelszen P, Sibai B, Easterling T, Walkinshaw S, *et al.* How to manage hypertension in pregnancy effectively. Br J Clin Pharmacol 2011;72(3):394-401.
12. Zhang GR, Liu HY, Zheng FP. Analysis of the effect of magnesium sulfate combined with nifedipine in the treatment of preeclampsia. J Lab Med Clin Sci 2018;15(5):703-4.
13. Professional Committee of Hypertension of Chinese Medical Doctor Association. Chinese expert consensus on blood pressure management of hypertension in pregnancy. Chin J Hypertens 2012;20(11):1023-7.
14. Yin JL, Chen H. Effect of enoxaparin sodium on pregnancy-induced hypertension and maternal and child prognosis. China Contin Med Educ 2019;11(29).
15. Ageno W, Crotti S, Turpie AG. The safety of antithrombotic therapy during pregnancy. Expert Opin Drug Saf 2004;3(2):113-8.
16. Zheng J, Chen Q, Fu J, Lu Y, Han T, He P. Critical appraisal of international guidelines for the prevention and treatment of pregnancy-associated venous thromboembolism: A systematic review. BMC Cardiovasc Disord 2019;19(1):1-10.
17. Singh N, Varshney P, Tripathi R, Mala YM, Tyagi S. Safety and efficacy of low molecular weight heparin therapy during pregnancy: Three year experience at a tertiary care center. J Obstet Gynaecol India 2013;63(6):373-7.

This article was originally published in a special issue, "Novel Therapeutic Approaches in Biomedicine and Pharmaceutical Sciences" Indian J Pharm Sci 2021:83(6) Spl Issue "79-83"