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Short Communication

Effect of Labetalol Combined with Nifedipine on the Efficacy, Renal Function and Hemodynamics of Hypertension in Pregnancy

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ABSTRACT

The objective of this study was to investigate the efficacy of labetalol in combination with nifedipine and its impact, renal function and hemodynamics of pregnancy-induced hypertension (PIH). The sample of ninety-eight patients diagnosed with PIH and treated at Shanghai East Hospital Ji-an Hospital between August 2018 and July 2019 were included in this study and randomly assigned to an observation group (OG, n=49) and a control group (CG, n=49) using the random number table method. Patients in the CG were treated with intravenous labetalol injection, and patients in the OG were treated with oral nifedipine on the basis of the CG. The clinical efficacy, renal function and hemodynamic level changes of the two groups were compared. Following the administration of the treatment, the OG exhibited a total effective rate (TER) of 81.63%, while the CG displayed a TER of 63.27%. Notably, a significant difference was observed between the two groups; after the treatment, the MAP level of patients in the OG was reduced than that before the treatment and better than that of the CG, and the levels of CI, SI and LCWI were increased than that before the treatment and better than the CG; the total incidence of adverse reactions in patients in the OG during and after the treatment was 10.20%, and that of patients in the CG was 26.53%. It was concluded that labetalol combined with nifedipine has obvious clinical efficacy in hypertension in pregnancy, which helps to further regulate renal function, improve hemodynamic level, and increase the rate of remission, and is worthy of clinical promotion.

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XH, JG and ZF conducted the experiments in this study. YX, LL and YL contributed to the design and interpretation of the current study and wrote the article. All authors read, revised, and approved the final manuscript.

Key words
Labetalol, Nifedipine, Pregnancy-induced hypertension, Curative effect, Renal function, Hemodynamics

Pregnancy induced hypertension (PIH) is an important cause of preterm delivery, low birth weight and other adverse birth outcomes and perinatal deaths in pregnant women, with hypertension, oedema, proteinuria, nausea, and vomiting caused by pathological elevation of blood pressure as the main clinical symptoms, and it is transient, usually starting at about 20 weeks, and disappearing after delivery (Liu and Xu, 2022). Hyperemesis gravidarum is a unique and common disease in pregnancy, with a prevalence rate of 9.5% in China, accounting for the second cause of maternal death, which has a significant affects on maternal and fetal health and life safety (Innes *et al*., 2016). According to the severity of the disease, it can be classified as mild PIH, moderate PIH, and severe PIH, which is also known as eclampsia or pre-eclampsia in clinical practice. At present, the etiology of PIH is unknown and cannot be completely prevented. Clinically, it is believed that there are two main reasons for its occurrence: on the one hand, a certain substance from the placenta enters the mother's bloodstream and causes a change in the immune factor of the pregnant woman's body, resulting in asphyxiation, bone fracture, self-inflicted injuries, which leads to the occurrence of pulmonary oedema, acute cardiac failure, acute renal insufficiency, cerebral herniation, inhalation pneumonia, placenta previa, fetal distress and intrauterine fetal death. The other side of the coin is believed to be related to genetic factors (Qasim *et al*., 2016), such as a higher incidence of maternal morbidity in pregnant women whose mothers have a history of PIH compared to normal pregnant women (Qasim *et al*., 2016; Pohlabeln *et al*., 2017). Currently, the clinical treatment of PIH is mainly sedation, antispasmodic, hypotensive, dilatation, diuretic, etc., and termination of pregnancy if necessary to prevent eclampsia and serious complications (Lee *et al*., 2016). It has been found that labetalol, in combination

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with nifedipine, helps to improve the clinical efficacy of hypertension treatment in pregnancy, but its effects on renal function as well as hemodynamics have been less reported (Easterling *et al*., 2019). The present study was conducted on patients treated with labetalol combined with nifedipine with the aim of investigating its effects on renal function as well as hemodynamics.

Materials and methods

Ninety-eight cases of PIH patients, aged 24-39 years old, all with gestational weeks of 27-39 weeks, 63 cases of primigravida and 35 cases of menstruation, who attended Shanghai East Hospital Ji-an Hospital from August 2018 to July 2019, were selected and divided into an observation group (OG) and a control group (CG) according to the method of random numerical expression. According to the 8th edition of Obstetrics and Gynecology (American College of Obstetricians and Gynecologists, 2020), patients in both groups were eligible to join the study if they met the following inclusion criteria: (1) The condition of hypertension is defined as the occurrence of systolic blood pressure equal to or exceeding 140 mmHg and/or diastolic blood pressure equal to or exceeding 90 mmHg, occurring for the first time after the 20th week of gestation; (2) Sunken oedema of the lower limbs; (3) Proteinuria +++; (4) Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) was elevated, or platelet count <100×109 /L; (5) no recent acute infections, and no combination of cardiac, hepatic and renal diseases; (6) no primary hypertension, hepatic or renal insufficiency.

Patients in the CG were treated with intravenous labetalol injection (Jiangsu Diseno Pharmaceutical Co., Ltd, State Drug Licence H32026121, specification 50mg/5ml), 100mg of labetalol injection was added to 250mL of 0.9% NaCl injection, the injection rate was 1~4mg per minute, and the effective dosage was about 50-200mg, while the patients with pheochromocytoma required 300mg or more. Patients in the OG were treated with oral nifedipine (Hunan Huana Pharmaceutical Co., Ltd., State Pharmaceutical Standard H20084558, 10mg*60 tablets) on top of the CG, orally 3 times a day, 10mg each time. Both groups received 4 weeks of the treatment.

The use of drugs was considered effective if there was decrease in systolic blood pressure >10mmHg, decrease in oedema, headache and abdominal discomfort, significant improvement in proteinuria. The drugs were considered ineffective when there was decrease in systolic blood pressure <10mmHg or no change, no improvement or even aggravation of oedema, dizziness, and abdominal discomfort, quantitative proteinuria >0.5g in 24h, and more serious complications in the postpartum period. Overall effective rate = (cure + obvious effect + effective) × 100%.

Before and after the treatment, 5 mL of blood of patients was drawn from the median vein of the elbow in the morning fasting. Serum was separated and stored in freezer for later examination. BUN and Scr were detected by ELISA (Shanghai Enzyme-linked Biotechnology Co;) Serum cystatin C (CysC) was detected by immunoturbidimetric transmission. Urine microalbumin (mALB) and 24-h urine protein were detected by latex-enhanced immunoturbidimetric transmission.

Mean arterial pressure (MAP), cardiac index (CI), stroke index (SI), and left ventricular work index (LVWI) were measured by Beckman Coulter CytoFLEX LX flow cytometer before and after treatment. Left ventricular work index (LCWI) (Lee *et al*., 2016).

Data analysis were carried out using the SPSS 22.0 statistical software, and the measurement information was expressed by (x±s), and the comparison was made by t-test, with statistically significant comparisons between data expressed as $P<0.05$.

Results and discussion

Table I shows general information of the study patients. As the table shows, there are no significant differences between the CG and the OG so it can be concluded that they are homogenous groups. After the treatment, the total effective rate (TER) of patients in the OG was 81.63%, and the TER of patients in the CG was 63.27%.

Table I. Comparing the two groups of general information ($\bar{x}$±s) and clinical efficacy [n (%)].

	CG (n=49)	OG (n=49)	χ^2/t	P
Maternity (primary/ menstrual)	29/20	24/25	-	-
Age (year)	28.27±2.68	28.22±2.70	0.092	0.927
Gestation period (week)	25.52±5.14	25.60±5.11	0.077	0.939
Pre-pregnancy BMI (kg/m2)	24.32±2.77	24.38±2.70	0.109	0.914
Cured	5(10.20)	1(2.04)		
Obvious effect	20(40.82)	18(36.73)		
Effective	15(30.61)	12(24.49)		
Ineffective	9(18.37)	18(36.73)		
TER	40(81.63)$^{\#}$	31(63.27)	4.141	0.042

BMI, body mass index.

Before the treatment, the differences in Cys C, mALB, 24h urinary protein, BUN and Scr were not significant in the two groups; after the treatment, the CysC, mALB, 24h urinary protein, BUN and Scr of the two groups were significantly reduced, and the degree of improvement in the OG was better than the CG (Table II).

Before the treatment, the differences in MAP, CI, SI and LCWI wre not significant in the two groups; after the treatment, the MAP of the two groups were significantly

Table II. Renal function and hemodynamic in both groups ($\bar{x}$±s).

Index	CG (n=49)		OG (n=49)	
	Before	After	Before	After
CysC (mg/L)	2.10±0.51	1.77±0.45*	2.09±0.46	1.05±0.33*#
mALB (mg /L)	40.48±6.55	14.27±2.61*	40.69±6.89	7.56±1.51*#
24-hurinary protein (mg)	1689.13±250.71	1098.43±43.18*	1685.29±251.80	689.91±35.17*#
BUN (mmol/L)	5.98±0.33	4.65±0.21*	5.97±0.31	4.12±0.14*#
Scr (μmol/L)	51.69±4.51	16.45±3.01*	51.48±4.41	11.23±2.32*#
MAP (mmHg)	91.36±6.59	83.63±5.56*	91.65±6.63	77.33±5.21*#
CI [L/(min·m2)]	2.13±0.59	2.96±0.71*	2.12±0.58	3.32±0.69*#
SI	27.65±3.58	30.77±4.65*	27.61±3.51	36.82±4.18*#
LCWI [kg/(m·m2)]	2.54±0.73	3.15±0.58*	2.55±0.72	3.75±0.62*#

(*), P<0.05 in comparison with the same group before treatment; (#), P<0.05 in comparison with CG after treatment.

lower, and the CI, SI and LCWI levels were higher (P<0.05), and the degree of improvement of the OG was better than the CG (P<0.05) (Table II).

During and after the treatment, the total incidence of adverse reactions in patients in the OG was 10.20%, and the total incidence of adverse reactions in the CG was 26.53% (P<0.05) (Table III).

Table III. Adverse reactions in two groups of patients [n (%)].

	CG (n=49)	OG (n=49)	χ^2	P
Headache	4(8.16)	1(2.04)		
Nausea	2(4.08)	2(4.08)		
Throw up	4(8.16)	1(2.04)		
Fever	3(6.12)	1(2.04)		
Total incidence	13(26.53)	5(10.20)	4.356	0.037

PIH is a pathological state that occurs with spasm of small arteries throughout the body and impaired function of multiple organ systems, which is a disease unique to pregnancy and could cause maternal and fetal death. Ying and Yang (2021) found that hormone level disorders in patients with PIH can lead to abnormal coagulation function, and blood that has been in an abnormally high coagulation state for a long time is maybe to cause the occurrence of hypertension in patients. At present, the clinical treatment of PIH mainly uses adrenergic receptor blockers, calcium channel blockers, etc., but the clinical therapeutic effect of a single drug is poor. Nifedipine is a calcium channel antagonist with high drug safety, and can suppresscalcium inward flow, impede the release of calcium in the cell wall, activate the calcium ion pump, reduce the loss of calcium in the patient's blood, promote coronary artery and peripheral arterial vasodilatation, inhibit vasospasm, improve the microcirculation of blood vessels, and reduce the patient's blood pressure (Xiang *et al*., 2020). However, its sustained blood pressure reduction level is poor. Labetalol, a salicylamide derivative, belongs to the alpha-adrenoceptor blocker or beta-adrenoceptor blocker, which can expand peripheral vasculature, reduce peripheral resistance, increase blood volume, reduce cardiac load, eliminate radiological tachycardia due to lowered blood pressure, and reduce myocardial oxygen consumption, so as to reduce the incidence of intrauterine distress syndrome (Do *et al*., 2022). A study found that labetalol with nifedipine in the treatment of PIH could provide significant clinical efficacy, which is the same as the results of our study.

The kidney is an important organ for metabolic regulation, excretion of metabolites and some endocrine functions of the organism. It has been found that hypertension, diabetes mellitus and other systemic diseases can cause different degrees of renal damage, and CysC, mALB, 24h urinary protein, BUN and Scr are important indicators commonly used in clinical practice to evaluate renal function (Hall, 2016). Among them, serum CysC is a small-molecule protein that is normally produced by nucleated cells, reabsorbed in the proximal tubule, and then completely metabolized and broken down. CysC can be used as an endogenous marker reflecting changes in glomerular filtration rate (Ebert *et al*., 2016). Urinary mALB and 24h urine protein quantitative test is an important indicator of the occurrence of early nephropathy, the body in the normal metabolic conditions, the urine mALB and 24h urine protein quantitative content is very small, and when the patient occurs renal hypoplasia, its content is significantly increased (Dong *et al*., 2018). Blood Scr is a product of muscle metabolism, which can be filtered through the glomerulus, and creatinine produced in the body on a daily basis, almost all of which is excreted in the urine, generally independent of urine output. Relevant studies have confirmed that under normal conditions, the ratio of BUN to Scr is about 10,

which increases significantly when certain diseases occur in the kidney (Bartal *et al*., 2022). The research shows that labetalol with nifedipine can significantly regulate renal function and reduce the degree of renal damage in patients.

The heart pumps blood with content and nutrients into the blood vessels, which in turn transports it to all tissues. The dual action of the heart and blood vessels constitutes the circulation of blood. During pregnancy, the cardiovascular system undergoes some adaptive changes in total blood volume, blood composition and cardiac function in order to fulfil its special period role. It has been reported that blood flow science can functionally reflect the contractility and diastolic capacity of the myocardium, as well as the level of anterior and posterior loads during the cardiac cycleand can more accurately respond to the pathophysiological processes of the heart (Stott *et al*., 2017). Among them, decreased SI can increase the resistance of small peripheral blood vessels, while increased MAP can overload the heart and blood vessels, increasing the burden on the patient's heart and decreasing contractility (Spaan *et al*., 2013). The results revealed that labetalol with nifedipine can improve the level of cardiac function, dilate blood vessels, reduce blood pressure, and improving clinical outcomes.

Labetalol with nifedipine has remark clinical efficacy in patients with hypertension during pregnancy, can effectively stabilize the renal function, increase the level of blood flow science, and the occurrence of adverse effects is low, the drug is safe, and can be promoted for use in the clinic.

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IRB approval

This study was approved by the Advanced Studies Research Board of Shanghai East Hospital Ji-an Hospital, Tongji University, Jiangxi Province, China.

Ethical approval

The study was carried out in compliance with guidelines issued by ethical review board committee of Shanghai East Hospital Ji-an Hospital, Tongji University, China. The official letter would be available on fair request to corresponding author.

Statement of conflict of interest

The authors have declared no conflict of interest.

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