ORIGINAL RESEARCH

Labetalol, Low-dose Aspirin, and Vitamin E and Calcium for Gestational Hypertension and Influence on MicroRNA-126 and PLGF Levels

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ABSTRACT

Context • Hypertensive disorders in pregnancy (HDP) are common complications of pregnancy and the main cause of perinatal adverse outcomes. Clinicians mostly adopt comprehensive treatment strategies, including anticoagulants and micronutrients. At present, the clinical effects of a strategy combining labetalol + low-dose aspirin + vitamin E and calcium aren't completely clear.

Objective • The study intended to investigate the efficacy of a combined therapy of labetalol + low-dose aspirin + vitamin E and calcium for the treatment of HDP and the relationship of the levels of expression of microRNA-126 and placenta growth factor (PLGF) to outcomes, to provide better treatment strategies for patients.

Design • The research team performed a randomized controlled trial.

Setting • The study took place in the Department of Obstetrics and Gynecology at Jinan Maternity and Child Care Hospital in Jinan, China.

Participants • Participants were 130 HDP patients at the hospital between July 2020 and September 2022.

Intervention • The research team divided participants into two groups, with 65 participants each, using the random number table method: (1) a control group that received a combined therapy of labetalol + vitamin E and calcium and (2) an intervention group that received a combined therapy of labetalol + low-dose aspirin + vitamin E and calcium.

Outcome Measures • The research team measured clinical efficacy, blood pressure parameters, 24 h urinary protein, microRNA-126, PLGF, and drug-related adverse reactions.

Results • The intervention group's efficacy rate was 96.92%, which was significantly higher than that of the control group at 83.08% ($P = .009$). Postintervention, the intervention group's systolic blood pressure, diastolic blood pressure, and 24 h urinary protein levels were significantly lower than those of the control group (all $P < .05$), while the microRNA-126 and PLGF levels were significantly higher (both $P < .05$). No significant differences existed in the rate of drug-related adverse reactions between the groups, at 4.62% and 6.15%, respectively ($P > 0.05$).

Conclusions • The combined therapy of labetalol + low-dose aspirin + vitamin E and calcium had a high efficacy rate and could significantly reduce blood pressure and 24h urine protein and significantly increase microRNA-126 and PLGF levels, with a high safety profile. (*Altern Ther Health Med.* 2023;29(4):140-145).

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Hypertensive disorders in pregnancy (HDP) are common complications of pregnancy and the main cause of perinatal adverse outcomes. Garovic et al found that the rates of HDP and preeclampsia in pregnant women worldwide were 7.3% and 3.3%, respectively.[1] In recent years, with liberalization to the three-child policy, the prevalence of HDP has increased in China.

The situation around disease prevention and treatment is serious, and clinicians need to strengthen management of the disease's diagnosis and treatment. In addition, the disease is closely related to the risk of cardiovascular diseases in mothers and offspring. Determination of the pathological mechanism of HDP is also closely related to the ability to precisely diagnosis and treat patients, but currently, researchers haven't fully clarified the pathogenesis of HDP.

Clinicians believe that the pathogenesis may be closely related to placental ischemia, which is placental dysfunction

caused by maternal immune tolerance, and oxidative stress.[2] For treatment, due to the particularity of the pathological changes that can occur during pregnancy, medical practitioners need to pay attention to the protection of uterine and placental blood perfusion.

Also, the efficacy and safety of clinical medication strategies are very important. Active diagnosis, treatment, and management are of great significance.[3] If a timely intervention doesn't occur, the risk of maternal and fetal adverse outcomes can increase.[4]

HDP Treatments

Vitamin E and calcium. Clinicians mostly adopt comprehensive treatment strategies, including anticoagulants and micronutrients, among which the combination of vitamin E and calcium is common and can effectively prevent pre-eclampsia.[5] Vitamin E and calcium supplements, through exogenous vitamin and calcium elements, can effectively improve the nutritional status of and enhance the body's resistance at the same time.

Maternal demand for calcium increases during pregnancy, and urinary calcium excretion also increases, resulting in a significant decrease in the body's calcium concentration. The supplementation of vitamin E and calcium can directly improve the symptoms of calcium and microbial deficiency and increase the absorption of calcium and nutrients in the fetus.[6]

Vitamin E can effectively inhibit phospholipid peroxidation and affect lipid metabolism, which can directly reduce vascular endothelial-cell injury and reduce the occurrence of proteinuria and other pathological states.[7]

Low-dose aspirin. Clinics also commonly use aspirin as an antiplatelet, with low-dose aspirin generally being used to prevent pregnancy-related vascular diseases. To ensure maternal and fetal safety, clinicians generally use low-dose aspirin.[8] Aspirin's pharmacological action through the placental barrier can effectively inhibit cyclooxygenase (COX) activity, acetylation activity, synthesis of thromboxane components, and fetal platelet aggregation.[9]

Siritharan et al found that women with HDP, compared with normal pregnant women, had a lower micronutrient intake and a higher risk of undernutrition.[10] Aspirin can reduce blood pressure by effectively inhibiting platelet aggregation and relieving blood-vessel pressure.

Labetalol. Labetalol is a common antihypertensive drug with good antihypertensive effect.[11] It's an adrenergic receptor blocker, the pharmacological effect of which is to lower blood pressure by blocking adrenergic receptors and effectively lowering vascular resistance. It also helps to stabilize blood pressure levels and prevents adverse effects.

Easterling et al found that early administration of labetalol as a single drug was effective in lowering blood pressure.[12] Greer et al found that aspirin combined with labetalol can effectively control blood pressure, improve the coagulation function and clinical efficacy, and ameliorate negative maternal and infant outcomes.[13]

Combined treatments. Zhang et al found that the combination of aspirin and labetalol had a significantly higher effective rate in treatment of HDP than did labetalol alone, which could effectively improve maternal and infant outcomes.[14]Those researchers also found that no significant difference existed in adverse reactions between the two treatments. Combinations of drugs can improve vascular endothelial function through different pathways and then affect the levels of microRNA-126 and PLGF.

MicroRNA-126 and PLGF

MicroRNA-126 has multiple functions, such as promoting angiogenesis and maintaining vascular and endothelial cell homeostasis, and its increased expression is closely related to the compensation mechanism of hypertensive patients, allowing its use as a target for the treatment of hypertension.[15]

PLGF is a glycoprotein involved in physiological effects, such as endothelial-cell proliferation and apoptosis, and can be a prognostic factor for HDP because it's closely related to adverse maternal outcomes and fetal complications.[16]

Current Study

At present, the clinical effects of a strategy combining labetalol + low-dose aspirin + vitamin E and calcium aren't completely clear.

The current study intended to investigate the efficacy of a combined therapy of labetalol + low-dose aspirin + vitamin E and calcium for the treatment of HDP and the relationship of the levels of expression of microRNA-126 and PLGF to outcomes, to provide better treatment strategies for patients.

METHODS

Participants

The research team performed a randomized controlled trial. The study took place in the Department of Obstetrics and Gynecology at Jinan Maternity and Child Care Hospital in Jinan, China. Potential participants were HDP patients at the hospital between July 2020 and September 2022. All enrolled patients were inpatients, and we screened the inpatients by screening them. We informed the patients who were eligible for enrollment about the informed consent related to the trial, and the patients agreed to be enrolled. We generally contacted the patients by phone or WeChat, and the patients were followed up regularly in the outpatient clinic after discharge. I am not the supervising physician for all patients enrolled.

The study included potential participants if they: (1) met the HDP diagnostic criteria as set by the Female Heart Health Group and the Hypertension Group of the Cardiovascular Branch of the Chinese Medical Association[14]—a systolic/diastolic blood pressure of ≥140/90 mmHg as measured twice after 20 weeks of gestation with an interval of ≥4 h—and (2) had no history of hypertension.

The study excluded potential participants if they: (1) had organ dysfunction or fetal growth restriction; (2) had diseases of the liver, kidney, blood system, or other primary diseases, or had had a cardiac pacemaker installed; or (3) had a history of allergies to the drugs in the study.

Participants' and their family members signed a consent form after being informed of the risks and benefits of treatment. The hospital's ethics committee approved the study's protocols. The study did comply with the Helsinki Declaration.

Procedures

Medications and supplements. The research team purchased: (1) the labetalol for injections and the labetalol tablets from Jiangsu Disainuo Pharmaceutical (Jiangsu, Zhejiang, China; specification: 10 ml : 50 mg, national drug approval: H32026121, and specification: 50 mg, national drug approval: H32026120, respectively; (2) the vitamin E from Shenzhen Aoruikang Biotechnology (Shenzhen, China; specification: 500 mg/tablet, national drug approval: G20080483); (3) the Caltrate from Wyeth Pharmaceutical (Suzhou, Jiangsu,China; specification: 600 mg, national drug approval: H10950029); and (4) the low-dose aspirin from Hebei Ruisen Pharmaceutical (Handan, Hebei, China; specification: 100 mg, national drug approval: H20173209).

Groups: The research team divided participants into two groups, with 65 participants each, using the random number table method: (1) a control group that received a combined therapy of labetalol + vitamin E and calcium and (2) an intervention group that received a combined therapy of labetalol + low-dose aspirin + vitamin E and calcium.

Outcome Measures. The research team measured: (1) clinical efficacy; (2) blood pressure parameters; (3) 24 h urinary protein, the level of which reflects renal function and regulates vascular endothelial cell dysfunction by activating metabolism of oxygen free radicals in renal tissue; (4) microRNA-126; (5) PLGF; and (6) drug-related adverse reactions.

Urine analysis. The research team collected participants' urine at 24 hours after participants emptied their bladders and detected the protein levels using a biuret assay (Delta Biology, Chengdu, Sichuan, China).

Serum analysis. The research team: (1) collected 10 ml of fasting venous blood from participants and placed it in an anticoagulant tube, (2) centrifuged 5 ml of it at 4°C and 3000 r/min of 10 min to obtain the upper serum, (3) placed the serum in a static environment of -800°C for testing.

For the microRNA-126 detection, the team: (1) centrifuged the serum again at 4°C and 16 000 r/min for 10 min), (2) completed the plasma RNA extraction, and (3) measured the expression level of microRNA-126 using real-time fluorescence quantitative polymerase chain reaction (PCR) with a 7500 type fluorescence quantitative PCR (Thermo Fisher Scientific, Waltham, MA, USA).

For the PLGF detection, the team used an enzyme-linked immunosorbent assay (ELISA) kit (Nanjing Biyuntian Technology, Nanjing, China) to detect the PLGF levels.

Interventions

Control group. Patients were started on vitamin E and calcium at enrollment. The group first received an injection intravenously once a day of 50 mg of labetalol mixed with 500 ml of 5% glucose, 100mg of vitamin E, and 300 mg of Caltrate.

The research team closely monitored the participants' vital signs until their blood pressures decreased to 140/90 mmHg. Participants then received a dose of labetalol orally as tablets, adjusted to 100 mg/time three times/day; 100 mg/time orally of vitamin E three times per day; and 300 mg/time of calcium two times per day, morning and evening.

Intervention group. The group received the same treatments of labetalol and vitamin E and calcium as the control group did. The groups also received 50 mg/time of low-dose aspirin once a day in the morning, until one week before the pregnancy's termination.

Outcome Measures

Clinical efficacy. The research team compared the clinical efficacy between the groups postintervention. According to the diagnostic criteria, the team divided each group's participants into efficacy groups: (1) significant effect—participants' blood pressure levels had returned to the normal range, with no abnormal organ function and a negative urinary protein result; (2) effective— participants' blood pressure levels and urinary protein had decreased but not to normal, with no abnormal organ function; and (3) ineffective—not reaching the above standards. Efficacy rate = (significant effect + effective)/number of samples in the group × 100%.

Blood pressure parameters. The research team compared the blood pressure parameters of the groups at baseline and postintervention. The team measured participants' blood pressure levels using an HBP9020 blood pressure meter (Omron, Kyoto, Japan) and used the average value of three measurements.

24h urinary protein. The research team compared the 24h urinary protein of the groups at baseline and postintervention. The comparison of 24-hour urine protein at baseline level was not statistically significant, suggesting that the two groups were located at the same baseline level and were comparable. 24-hour urine protein is an important indicator for evaluating renal function and injury, and its level reflects the permeability of the glomerular filtration membrane and the reabsorption function of the renal tubules. In patients with gestational hypertension, the level of 24-hour urine protein often increases, indicating the presence of renal injury. Therefore, if treatment can significantly or moderately reduce the level of 24-hour urine protein in patients, it indicates that the treatment plan has a certain effect on improving renal function and preventing renal injury, which helps to prevent the occurrence of renal complications.

Microrna-126 and PLGF levels. The research team compared the microrna-126 and PLGF levels of the two groups at baseline and postintervention. If the treatment can

significantly increase the level of microRNA-126 in patients, it indicates that the treatment may have a certain therapeutic effect on patients with gestational hypertension. MicroRNA-126 is a small molecule RNA related to endothelial cell function and angiogenesis, and plays an important role in the pathogenesis of gestational hypertension. Treatment that can increase the level of microRNA-126 may promote the recovery of endothelial cell function and enhance angiogenesis, thereby improving the disease condition of gestational hypertension.If the treatment can significantly increase the level of placental growth factor in patients, it indicates that the treatment may have a promoting effect on fetal growth and development in patients with gestational hypertension. Placental growth factor is a polypeptide molecule expressed in the placenta and maternal blood, which is essential for maintaining fetal growth and development. In patients with gestational hypertension, the level of placental growth factor is often low. Treatment that can increase the level of placental growth factor may promote fetal growth and development and reduce the risk of birth defects.

Drug-related adverse reactions The research team compared the rates of drug-related adverse reactions for the groups, including dizziness, chest tightness, and upper abdominal discomfort.

Statistical Analysis

The research team analyzed the data using SPSS 23.0 software (IBM, Armonk, NY, USA). The research team: (1) expressed measurement data as means ± standard deviations (SDs) if the data were normally distributed and compared the groups using a t-test for independent samples, (2) expressed nonnormally distributed data as medians and compared the groups using the Mann-Whitney U test, (2) expressed count data as numbers and percentages (%) and compared the groups using the χ^2 or Fisher test. $P < .05$ statistically significant differences.

RESULTS

Participants

The study included and analyzed the data of 130 participants, 65 in each group (Table 1). The intervention group's ages ranged from 24 to 37 years, with a mean age of 29.44 ± 7.42 years. The control group's ages ranged from 23 to 38, with a mean age of 29.35 ± 7.46 years.

The intervention group's gestational age ranged from 21 to 34 weeks, with a mean number of weeks of 29.58 ± 1.62. That group's number of deliveries ranged from 1 to 3, with a mean of 1.29 ± 0.32. The control group's gestational age ranged from 21 to 34, with a mean number of weeks of 29.13 ± 1.68. That group's number of deliveries ranged from 1 to 3, with a mean of 1.26 ± 0.35.

Table 1. Participants' Demographic and Clinical Characteristics at Baseline (N = 130)

Characteristics	Intervention Group n = 65	Control Group n = 65	*P* value
Age, y			
Range	24-37	23-38	
Mean ± SD	29.44 ± 7.42	29.35 ± 7.46	.945
Gestational age, wks			
Range	21-34	21-34	
Mean ± SD	29.58 ± 1.62	29.13 ± 1.68	.123
Deliveries, n			
Range	1-3	1-3	
Mean ± SD	1.29 ± 0.32	1.26 ± 0.35	.611

Table 2. Comparison of the Clinical Efficacy in the Intervention and Control Groups (N = 130)

Groups	n	Significant Effect n (%)	Effective n (%)	Ineffective n (%)	Efficacy Rate n (%)
Intervention	65	39 (60.00)	24 (36.92)	2 (3.08)	63 (96.92)
Control	65	25 (38.46)	29 (44.62)	11 (16.92)	54 (83.08)
χ^2					6.923
P value					.009[a]

[a]$P < .009$, indicating that the intervention group's efficacy rate was significantly higher than that of the control group

Clinical Efficacy

Table 2 shows that 39 participants in the intervention group had a significant effect (60.00%), and 24 had an effective result ((36.92%), for a total efficacy rate of 96.92%. In the control group, 25 participants had a significant effect (38.46%), and 29 had an effective result (44.62%), for an efficacy rate was 83.08%. The intervention group's rate was significantly higher than that of the control group ($P = .009$).

Blood Pressure and Urinary Protein

Table 3 shows that no significant differences existed between the groups at baseline in systolic blood pressure, diastolic blood pressure, or 24h urinary protein levels ($P > .05$). Between baseline and postintervention, both groups systolic blood pressure ($P = .000$), diastolic blood pressure ($P = .000$), and 24h urinary protein ($P = .000$) decreased significantly.

Also, postintervention, the intervention group's levels of systolic blood pressure ($P = .014$), diastolic blood pressure ($P = .003$), and 24h urinary protein ($P = .000$) were significantly lower than those of the control group.

MicrorNA-126 and PLGF Levels

Table 4 shows that no significant differences existed between the groups at baseline in microRNA-126 and PLGF levels ($P > .05$). Between baseline and postintervention, both groups microRNA-126 ($P = .000$) and PLGF ($P = .000$) increased significantly.

Postintervention, the intervention group's levels of microRNA-126 ($P = .003$) and PLGF ($P = .021$) were significantly higher than those in the control group.

Table 3. Comparison of the Changes in Blood Pressure Parameters and 24h Urinary Protein Between Baseline and Postintervention for the Intervention and Control Groups (N = 130)

Group	n	Systolic Blood Pressure mmHg		Baseline to Postintervention	
		Baseline Mean ± SD	Postintervention Mean ± SD	*t*	*P* value
Intervention	65	146.34 ± 25.17	109.14 ± 11.25	10.878	.000[a]
Control	65	145.69 ± 26.32	114.29 ± 12.35	8.707	.000[a]
t		0.144	2.485		
P value Between Groups		.886	.014[b]		
Group	**n**	**Diastolic Pressure mmHg**		**Baseline to Postintervention**	
		Baseline Mean ± SD	**Postintervention Mean ± SD**	***t***	***P* value**
Intervention	65	96.17 ± 8.44	83.45 ± 6.17	9.809	.000[a]
Control	65	96.21 ± 8.39	86.79 ± 6.22	7.272	.000[a]
t		0.027	3.074		
P value Between Groups		.978	.003[b]		
Group	**n**	**24 h Urine Protein g/24 h**		**Baseline to Postintervention**	
		Baseline Mean ± SD	**Postintervention Mean ± SD**	***t***	***P* value**
Intervention	65	0.36 ± 0.15	0.09 ± 0.02	14.385	.000[a]
Control	65	0.37 ± 0.12	0.13 ± 0.03	15.643	.000[a]
t		0.420	8.944		
P value Between Groups		.675	.000[b]		

[a]$P < .05$, indicating that both groups systolic blood pressure, diastolic blood pressure, and 24h urinary protein decreased significantly between baseline and postintervention
[b]$P < .05$, indicating that postintervention the intervention group's levels of systolic blood pressure, diastolic blood pressure, and 24h urinary protein were significantly lower than those of the control group

Table 4. Comparison of Changes in Microrna-126 and PLGF Levels Between Baseline and Postintervention for the Intervention and Control Groups (N = 130)

Group	n	MicrorNA-126		Baseline to Postintervention	
		Baseline Mean ± SD	Postintervention Mean ± SD	*t*	*P* value
Intervention	65	0.17 ± 0.04	1.42 ± 0.26	38.310	.000[a]
Control	65	0.18 ± 0.02	1.29 ± 0.22	40.511	.000[a]
t		1.803	3.077		
P value Between Groups		0.074	.003[b]		
Group	**n**	**PLGF pg/ml**		**Baseline to Postintervention**	
		Baseline Mean ± SD	**Postintervention Mean ± SD**	***t***	***P* value**
Intervention	65	41.27 ± 10.36	51.25 ± 11.37	5.231	.000[a]
Control	65	41.29 ± 10.31	46.78 ± 10.43	3.018	.003[a]
t		0.011	2.336		
P value Between Groups		0.991	.021[b]		

[a]$P < .05$, indicating that both groups microRNA-126 and PLGF levels increased significantly between baseline and postintervention
[b]$P < .05$, indicating that postintervention the intervention group's levels of microRNA-126 and PLGF were significantly higher than those of the control group

Abbreviations: PLGF, placenta growth factor

Table 5. Comparison of Drug-related Adverse Reactions Between the Intervention and Control Groups (N = 130)

Group	n	Dizziness n (%)	Chest Tightness n (%)	Upper Abdominal Discomfort n (%)	Incidence Rate n (%)
Intervention	65	2 (3.08)	1 (1.54)	0 (0.00)	3 (4.62)
Control	65	1 (1.54)	2 (3.08)	1 (1.54)	4 (6.15)
χ^2					0.151
P value					.698

Drug-related Adverse Reactions

Table 5 shows that no significant differences existed between the groups in the rate of drug-related adverse reactions, at 4.62% and 6.15%, respectively ($P > .05$).

DISCUSSION

The current study showed that the efficacy rate of the treatment for the intervention group was significantly higher than that of the control group. Postintervention, the intervention group's systolic blood pressure, diastolic blood pressure, and 24 h urinary protein levels had decreased significantly, and the microrNA-126 and PLGF levels had increased significantly. The rate of drug-related adverse reactions in the two groups wasn't significantly different ($P < .05$).

The current study, had some limitations including a lack of diversity in participants' baseline information, the lack of study by age group, and the lack of clarity on the efficacy the treatments for HDP patients in different age groups.

CONCLUSIONS

The combined therapy of labetalol + low-dose aspirin + vitamin E calcium for HDP patients had a high efficacy rate and could significantly reduce blood pressure and 24h urine protein and significantly increase microRNA-126 and PLGF levels, with a high safety profile.

AUTHORS' DISCLOSURE STATEMENT

The authors have no potential conflicts of interest to report relevant to this study.

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