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Effect of Salvia Miltiorrhiza Injection on Blood Pressure and Cardiac Function in Rats with Gestational Hypertension and Preeclampsia

Xia Zhang[1], Juan Li[2*], Ping Zhou[1], Qianqian Luo[1], Zhaojun Xiang[1], Hongying Wu[3*]

[1]Department of Neurosurgery, Taihe Hospital, Hubei University of Medical, Shiyan, China
[2]Department of Gynecology and Obstetrics, Taihe Hospital, Hubei University of Medical, Shiyan, China
[3]Department of Public Health, The First People's Hospital of Jingzhou, Jingzhou, China
*Email: 951777718@qq.com

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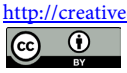

Abstract

Objective: This study is to observe the effects of Salvia miltiorrhiza injection on blood pressure and cardiac function in rats with pregnancy-induced hypertension and preeclampsia. **Methodology:** Syncytiotrophoblast microvilli (stbm) and l-arginine nitrosyl methyl ester were screened out via caudal vein injection. Twenty gestational hypertension-preeclampsia model SD (Sprague Dawley) rats successfully induced by L-NAME (L-arginine Nitrosyl methyl ester) were randomly divided into 2 groups (model group and Danshen injection group, n = 10). Then another 10 normal pregnant SD rats without model were selected as blank control group. The Salvia miltiorrhiza injection group was given Salvia miltiorrhiza injection (0.5 $g \cdot kg^{-1} \cdot d^{-1}$) through tail vein, and the control group and model group were given equal volume of normal saline through tail vein injection. All three groups were treated by tail vein injection once a day (d) for 7 days. After treatment, heart rate (HR), Systolic pressure (SP), diastolic pressure (DP) and mean arterial pressure (MAP) were measured by tail artery. Left ventricular end-diastolic diameter (LVDd) and Left ventricular end systolic diameter (LVDs) were recorded by echocardiography. Left ventricular end diastolic pressure (LVEDP), left ventricular systolic pressure (LVSP), left ventricular ejection fraction (left ventricular ejection) fraction, LVEF) and the maximum rate of increase/decrease of left ventricular pressure during isovolemic systole (+dp/dtmax/−dp/dtmax); Endothelin-1 (ET-1) levels in rat tail vein blood were detected by ELISA. **Results:** SP, DP, MP, HR, LVSP, LVDs and −dp/dtmaxx were all decreased, plasma ET-1 expression was low, and LVDd, LVEDP, LVEF, and +dp/dtmax were all increased in the Salvia miltiorroot injection group, with statistical significance compared to the model group ($p < 0.05$). **Conclusion:** Salvia miltiorrhiza injection can improve the cardiac function and reduce blood pressure in rats

*Corresponding author.

with pregnancy-induced hypertension and preeclampsia, and the mechanism may be related to alleviating systemic arteriolar spasm by regulating ET-1 level.

Keywords

Rat, Danshen Injection, Pregnancy-Induced Hypertension, Preeclampsia, Endothelin-1, Blood Pressure, Cardiac Function

1. Introduction

Hypertension during pregnancy is a common gynecological and obstetric disease closely related to maternal age, multiple births or previous medical history and other risk factors or immune factors. The prevalence rate is as high as 3% - 8%, and it is the main cause of perinatal and maternal death [1] [2]. Such patients have normal blood pressure before pregnancy, but have elevated blood pressure and urinary protein after 20 weeks of pregnancy. The etiology of pregnancy-induced hypertension is complex, and its main pathological basis is systemic small artery spasm and reduced blood perfusion of various organs, especially the kidney, which is the most seriously involved. When hypertension is accompanied by proteinuria or coagulation dysfunction, it is preeclampsia, and if not treated in time, it will eventually develop into severe preeclampsia or even eclampsia, which seriously threatens the life and health of mother and child [3] [4]. At present, the combination of Chinese and western medicine in the treatment of gestational hypertension and preeclampsia has achieved ideal clinical efficacy, and the fetal head descent rate, natural delivery rate, cesarean section rate and forceps assisted delivery rate are superior to the Western medicine treatment alone [5]. Currently, according to clinical reports, Danshen injection has a relatively prominent effect in the treatment of preeclampsia, which can significantly improve placental circulation, control blood pressure, significantly reduce the incidence of severe preeclampsia or even eclampsia in patients, reduce adverse pregnancy outcomes and promote the prognosis of newborns [6] [7]. At present, the clinical treatment of preeclampsia by Salvia miltiorrhiza injection is mostly based on the pharmacological properties of traditional Chinese medicine, while few targeted basic studies in animal experiments have revealed its possible mechanism. Therefore, this study observed the effects of Salvia miltiorrhiza injection on blood pressure and cardiac function of rats with pregnancy-induced hypertension and preeclampsia through the method of intravenous injection, analyzed its possible mechanism, and provided theoretical basis for clinical drug use.

2. Materials and Methods

2.1. Experimental Animals

A total of 80 10-week-old SPF (Specific pathogen Free)-grade SD rats, half male

and half female, with body weight of 265.5 g - 275.5 g, were purchased from Wuhan Jintangxin Culture Technology Co., LTD. [SCXK (Hubei) 2018-0015]. Feeding room temperature was 22˚C - 26˚C, relative humidity was 50% - 75%, the animals were allowed to feed freely. During the experiment, the female rats were caged 1:1 at 18:00 every night, and the vaginal secretions of female rats were taken at 8:00 am on the second day (d), and observed under the microscope. After pregnancy, the female mice were sorted out and fed intensively.

2.2. Reagents and Instruments

Salvia miltiorrhiza Injection (Zhengda Qingbao Pharmaceutical Co., Ltd., lot number: 180245); Sodium pentobarbital (Foshan Chemical Experiment Factory, batch number: 0180104); Endothelin-1 (ET-1) ELISA test kit for mice (Shanghai Guangrui Biotechnology Co., Ltd., lot No: EH1047); CODATM-2 Non-invasive Tail Arterial Blood Pressure Measurement and Analysis System (Kent, USA); Multifunctional enzyme marker (biotek); BL-420N integrated information signal acquisition and processing system (Chengdu Taimeng Software Co., Ltd.).

2.3. Methods

2.3.1. Preparation of Syncytiotrophoblast Microvilli (STBM)

STBM was prepared from 5 pregnant rats on 18 days of gestation. After decapitated, the rats were dissected and the placentas were quickly extracted. Washed with PBS and cut into 1 mm^3 tissue blocks, 2 g was put into 100 ml NaC1 solution containing 1% chlorine-streptomycin, and STBM was enriched after shaking at 40˚C overnight.

2.3.2. Establishment and Grouping of Pregnancy-Hypertension-Preeclampsia Model

The enriched STBM was diluted with PBS buffer to 0.14 mg/ml for use. On the 5th day of gestation, rats were injected with 2 ml STBM preparation from the tail vein and subcutaneously injected with L-arginine Nitrosyl methyl ester (L-NAME) at the injection dose of 125 mg/kg once a day for 7 consecutive days [8]. After the injection, urine was collected to detect urinary protein content, and the M2 non-invasive tail artery blood pressure measurement and analysis system was used to measure blood pressure, and the presence of urinary protein in pregnant rats with blood pressure ≥ 18 kPa was used as the model marker [9]. Then 20 pregnant rats meeting the model criteria of pregnancy-hypertension and preeclampsia were selected and divided into model group and Salvia miltiorrhiza injection group (n = 10) by random, controlled and blind method. Then another 10 normal SD rats at 20 days after conception (no treatment) were selected as blank control group.

2.3.3. Treatment

After L-NAME injection, the Salvia miltiorrhiza injection group was given Salvia miltiorrhiza injection (0.5 $g \cdot kg^{-1} \cdot d^{-1}$) through tail vein, while the blank control group and model group were given equal volume of normal saline through tail

vein injection. All three groups were treated by tail vein injection once a day for 7 days.

2.3.4. Determination of Rat Tail Arterial Blood Pressure

After treatment, the rats in each group were disinfected with 75% alcohol and then connected with CODATM (COVID-19 Data and Surveillance Toolkit)-2 non-invasive tail arterial blood pressure measurement and analysis system. Heart rate (HR), Systolic pressure (SP), diastolic pressure (DP) and mean arterial pressure (MAP) were measured, and each rat was measured 3 times.

2.3.5. Echocardiographic Recording of Cardiac Function in Rats

Rats were anesthetized with 2% isoflurane and fixed. LVDd and LVDD were recorded by echocardiography.

2.3.6. Cardiac Function Recording Methods

Cardiac function was recorded by inserting arterial catheter into the right ventricle after treatment. After anesthesia, the right common carotid artery was separated and an arterial catheter was inserted into the heart to record the intraventricular pressure. LVEDP, Left ventricular systolic pressure (LVSP), Left ventricular ejection fraction (Left ventricular ejection) fraction, LVEF) and the maximum increase/decrease rate of left ventricular pressure during isovolemic systole (+dp/dtmax/−dp/dtmax).

2.3.7. Detection of Rat Tail Venous Blood Plasma by ET-1 ELISA

1 ml of rat tail venous blood was taken and placed in an anticoagulant test tube without pyrogen and endotoxin, centrifuged at 1000 ×g for 20 min, the haemorrhagic clearance and red blood cells were separated, and the supernatant was collected for later use (the sample to be measured). Then prepare the standard, according to the number of samples to be tested plus the number of standards to determine the number of slats required, each standard and blank hole is recommended to do multiple holes. Add the diluted standard 50 μl into the reaction hole and the sample to be measured 50 μl into the reaction hole. Immediately add 50 μl of biotin-labeled antibody. Cover the film plate, gently shake and mix, and incubate at 37˚C for 1 h. Shake off the liquid in the hole, fill each hole with washing liquid, shake for 30 s, shake off the washing liquid, pat dry with absorbent paper. Repeat this operation three times. Add 80 μl of affinity strepsin-HRP to each well, gently shake and mix, and incubate at 37˚C for 30 min. Shake off the liquid in the hole, fill each hole with washing liquid, shake for 30 s, shake off the washing liquid, pat dry with absorbent paper. Repeat this operation three times. Add 50 μl of substrate A and B to each well, gently shake and mix, and incubate at 37˚C for 10 min. Avoid light. Remove the enzyme label plate and quickly add 50 μl termination solution. OD values of each hole should be measured at 450 nm wavelength immediately after adding the termination solution. Then, the absorbance OD value is taken as the vertical coordinate (Y), and the corresponding ET-1 standard concentration is taken as the horizontal coordi-

nate (X), and the corresponding curve is made. The ET-1 content of the sample can be converted from the standard curve to the corresponding concentration according to its OD value.

2.3.8. Statistical Processing

SPSS (Statistical Package for the Social Sciences) 22.0 statistical software was used to analyze the data, and normal test was performed on all measurement data. The normal measurement data were represented by mean ± standard ($\overline{X} \pm SD$), and comparison between groups was performed by t test. $p < 0.05$ was considered statistically significant.

3. Results

3.1. Blood Pressure and ET-1 Results

HR, SP, DP, MAP and ET-1 were all increased in the model group, and the difference was statistically significant compared to the blank control group ($p < 0.05$). HR, SP, DP, MAP and ET-1 in Danshen injection group were significantly decreased, and the difference was statistically significant compared with model group ($p < 0.05$). See Table 1.

3.2. Cardiac Function Results

LVSP, LVDs and −dp/dtmax were increased in model group, while LVDd, LVEDP, LVEF and +dp/dtmax were decreased, and the differences were statistically significant compared to blank control group ($p < 0.05$). LVSP, LVDs and −dp/dtmax decreased in Salvia miltiorrhiza injection group, while LVDd, LVEDP, LVEF and +dp/dtmax increased, with statistical significance compared to model group ($p < 0.05$). See Table 2.

Table 1. Comparison of blood pressure and ET-1 test results among the 3 groups ($\overline{x} \pm SD$, $n = 10$).

Group	HR (time/min)	SP (kPa)	DP (kPa)	MAP (kPa)	ET-1 (ng/ml)
Blank	260.52 ± 7.41	13.98 ± 0.92	10.57 ± 1.14	11.97 ± 0.87	12.04 ± 1.90
Model	281.29 ± 10.94[a]	20.83 ± 1.58[a]	15.40 ± 0.92[a]	17.65 ± 2.02[a]	46.54 ± 2.17[a]
Danshen	262.10 ± 12.87[b]	14.57 ± 1.15[b]	11.01 ± 1.27[b]	12.14 ± 1.02[b]	12.63 ± 1.46[b]

Note: Compared with blank control group, [a]$p < 0.05$; Compared with the model group, [b]$p < 0.05$.

Table 2. Comparison of cardiac function results in 3 groups ($\overline{x} \pm SD$, $n = 10$).

Group	LVSP (mmHg)	LVEDP (mmHg)	LVEF (%)	LVDd (mm)	LVDs (mm)	+dp/dt$_{max}$ (mm·Hg/sec)	−dp/dt$_{max}$ (mm·Hg/sec)
Blank	109.50 ± 4.52	−13.30 ± 3.09	75.30 ± 6.77	5.63 ± 0.30	4.23 ± 0.45	7482.57 ± 537.16	−6521.37 ± 357.24
Model	147.21 ± 7.75[a]	−7.57 ± 1.81[a]	66.57 ± 4.81[a]	4.59 ± 0.21[a]	6.61 ± 0.56[a]	6113.63 ± 441.51[a]	−7737.92 ± 401.65[a]
Danshen	110.24 ± 5.52[b]	−12.65 ± 2.68[b]	74.70 ± 5.68[b]	5.84 ± 0.239[b]	4.90 ± 0.32[b]	7117.93 ± 512.14[b]	−6561.29 ± 459.96[b]

Note: Compared with blank control group, [a]$p < 0.05$; Compared with the model group, [b]$p < 0.05$.

4. Discussion

Hypertension-preeclampsia during pregnancy is the main cause of maternal morbidity, perinatal poor prognosis and even death, and the maternal death is second only to hemorrhage and embolism [10] [11]. If not treated in time, complications such as hypertension, liver and kidney injury, pulmonary edema, respiratory distress syndrome, cardiomyopathy, stroke and central nervous system injury may occur in pregnant women [12]. The fetus may suffer complications such as placental abruption, intrauterine growth restriction, premature birth, retinopathy of prematurity, neonatal respiratory distress syndrome, and even stillbirth [13].

Traditional Chinese medicine believes that "blood stasis" is the fundamental pathogenesis of preeclampsia. Women's essence is based on blood, and the deficiency of Yin blood due to the deficiency of zang fu organs. Coupled with the interference of wind, fire and dampness, qi and blood are not blocked and blood deficiency is induced, which leads to "child swelling", "child fainting" and "eclampsia" [14]. Modern medicine believes that hypertension-preeclampsia during pregnancy is caused by multi-factor induced systemic arteriolar spasm resulting in hemodynamic abnormalities leading to hypoxia and ischemia of tissues and organs, among which utero-placenta hypoxia and ischemia is particularly serious, because with the continuation of pregnancy, the contradiction between the increasing demand for oxygen and energy of the embryo and the decreasing supply of placenta perfusion is increasingly intensified. Hypoxia and ischemia in utero-placenta will act on the body in turn, inducing a series of oxidative stress and inflammation, resulting in changes in vascular permeability and cytotoxic damage, and ultimately aggravating the patient's condition, which also provides an objective basis for the "blood stasis theory" in traditional Chinese medicine [15] [16]. Salvia miltiorrhiza is slightly cold and bitter. Salvia miltiorrhiza injection is its extract, which has the functions of promoting blood circulation and removing blood stasis, nourishing blood and calming nerves, regulating pulse and nourishing heart, stopping bleeding and reducing swelling, etc. It can expand peripheral blood vessels, strengthen myocardial contraction, improve heart function and blood stagnation [17]. It can also reduce the synthesis of cholisoalcohol and improve the disorder of lipid metabolism in the body, which is conducive to the recovery of blood pressure and kidney function, and promote the normal function of the body [18].

The pathogenesis of pregnancy-hypertension—preeclampsia is not fully understood, but there is increasing evidence that abnormal ET-1 levels are the main cause of the disease. ET-1 is synthesized by vascular endothelial cells and is the strongest vasoconstricting polypeptide known so far. It not only exists in vascular endothelium, but also widely exists in various tissues and cells. Et-1 is an important factor regulating cardiovascular function, plays an important role in maintaining basic vascular tension and cardiovascular system homeostasis, and plays an important role in various hypertension-related pathogenesis [19].

Although the role and influence of ET-1 in hypertensive diseases during pregnancy are still not very clear, as an endogenous long-term vasoconstriction regulator, endothelin also has a strong positive myokinetic effect, and may even induce calcium overload of cardiomyocytes, arrhythmia and myocardial energy metabolism disorders, which undoubtedly have a correlation in the pathogenesis of hypertension-preeclampsia during pregnancy: Endothelial cell activation—increased endothelin levels—systemic vasospasm—increased blood pressure—preeclampsia. Studies have shown that ET-1 is positively correlated with the severity of the disease, and the expression of ET-1 in peripheral blood of patients is significantly increased, and high expression is an independent risk factor for poor prognosis of pregnant women with preeclampsia [20] [21]. Pregnant women with preeclampsia are a major risk factor for long-term cardiovascular complications and have the risk of heart failure. However, due to the hidden onset of cardiac insufficiency, early clinical symptoms are easy to be ignored. Therefore, timely detection and correction of cardiac insufficiency and active control of preeclampsia are important measures to prevent adverse pregnancy outcomes and improve delivery safety for patients with pregnancy-induced hypertension syndrome [22]. In this study, the low expression of ET-1 in the salvia miltiorrhiza injection group suggested that the injection could inhibit the synthesis of ET-1 by vascular endothelial cells, and with the decrease of ET-1 level, its vasoconstriction effect on systemic blood vessels would also be reduced, which would have a hypotensive effect and significantly decrease SP, DP and MP in the Salviorrhiza Miltiorrhiza injection group. While producing vasoconstriction and blood pressure increase, ET-1 can also reflexively cause HR increase and accelerate the pathological process of pregnational hypertension—preeclampsia, which is reflected in increased blood pressure (SP, DP, MP), HR increase, and reduced cardiac work (such as decreased LVEF, LVSP and +dp/dtmax in the model group). LVEDP, LVDd, LVDs, and -dp/dtmax were all elevated). After treatment, LVEDP, LVDd, LVDs and −dp/dtmax all decreased in the Salviorrhiza injection group, while LVEF, LVSP and +dp/dtmax all increased, suggesting that myocardial diastolic function and cardiac pumping function were restored in the Salviorrhiza injection group. SP, DP and MP all decreased significantly, and hypertension symptoms were controlled.

5. Conclusion

It has been confirmed that ET-1 receptor blockers can prevent the progression of the disease in animal model experiments of hypertension-preeclampsia during pregnancy, and ET-1 itself has pro-inflammatory and pro-proteinuria properties and strong vasoconstriction activity, which undoubtedly leads to the conclusion that ET-1 is the main factor mediating hypertension-preeclampsia during pregnancy [23]. However, uterine artery stenosis in hypertensive patients during pregnancy leads to increased placental circulation resistance, relatively inhibited cardiac function, abnormal hemodynamic parameters, and relatively low cardiac output. It is entirely possible that this phenomenon is caused by excessive syn-

thesis of ET-1, and by its exciting effect, systemic vasospasm will cause blood pressure to rise, resulting in multiple organ damage. This study also found that Danshen injection may mainly act on the link of ET-1, reducing its vasoconstriction effect by inhibiting the synthesis of ET-1, thereby improving the heart function of pregnancy-hypertension-preeclampsia rats and reducing the risk of eclampsia.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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