Original Research

Phytosterol enhances oral nifedipine treatment in pregnancy-induced preeclampsia: A placebo-controlled, double-blinded, randomized clinical trial

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Impact statement

There was no difference between the two groups regarding the adverse effects from infants and mothers. Findings in the study suggest that phytosterol is an effective and safe adjuvant of the oral nifedipine and can alleviate the hypertension symptoms in preeclampsia patients.

Abstract

Preeclampsia is a severe complication which influences pregnant women all around the world, the symptom of which is serious maternal hypertension. Phytosterol is a type of natural compound commonly found in plant products, and has been incorporated into various food vectors and natural drugs. In the paper, the curative effect on preeclampsia by combination of oral nifedipine and phytosterol was assessed. Random grouping was carried out, with 253 preeclampsia patients being registered and taking orally nifedipine+phytosterol or nifedipine+placebo. The time for controlling the blood pressure and the time needed for the occurrence of another hypertensive crisis were defined as primary endpoints. The dosage required for controlling blood pressure, and the adverse effects from infants and mothers were defined as secondary endpoints. The nifedipine+phytosterol group required a remarkably shorter time for controlling blood pressure than the nifedipine+placebo group, an obviously delayed time for the occurrence of new hypertensive crisis, and an obvious lower dosage for controlling blood pressure. There was no difference between the two groups regarding the adverse effects from infants and mothers. Findings in the study suggest that phytosterol is an effective and safe adjuvant of the oral nifedipine and can alleviate the hypertension symptoms in preeclampsia patients.

Keywords: Preeclampsia, phytosterol, nifedipine, hypertension, pregnancy

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Introduction

Preeclampsia is a serious condition that involves different systems. It usually can be observed during pregnancy, especially beyond 20 weeks of gestation.[1] Preeclampsia is still the main factor causing morbidity and mortality of pregnant women around the world, and the most harmful symptoms are serious increase in proteinuria and blood pressure. Therefore, monitoring and controlling patients' blood pressure play a pivotal role in managing preeclampsia;[2,3] thereinto, it is found that anti-hypertensive drug can be used to relieve hypertension in clinical practice.[4]

Nifedipine is one of the first-line anti-hypertensive drugs for preeclampsia women.[3,5,6] It acts as the Ca^{2+} channel inhibitor.[5] It is able to improve the renal blood flow to lower the vascular resistance and repress the anti-diuretic hormone release to increase the urine output, making it an appropriate anti-hypertensive drug to effectively control blood pressure during pregnancy.[7] It is important that nifedipine is proved to be a safe drug in clinical practice, specific for pregnant patients.[8] In the third trimester, applying nifedipine could contribute to an effective control on the high blood pressure, without leading to severe adverse effects on the development of both mother and fetus.[9] Besides, it is also applicable in the treatment of premature labor and meanwhile shows no adverse effects during perinatal stage.[10] Nifedipine has been reported to play a key role in improving the arterial pressure and increasing the urine output in the immediate puerperal state for patients with severe preeclampsia, which is of special relevance to our current study.[11]

A number of drugs shall not be used during pregnancy, making natural compounds safe candidate drugs for alleviating the preeclampsia symptoms. Phytosterol is a kind of

natural compound extracted from plant products, especially plant oils, grains, as well as some vegetables and fruits.[12] Phytosterol-based preparations are incorporated into various food vectors and natural drugs.[13] In fact, considerable amount of circulating phytosterols has been detected in normal females, as well as lactating mothers.[14] Two recent clinical studies reported that low-fat milk with rich phytosterol could make the total cholesterol, LDL-cholesterol, as well as diastolic blood pressure fall remarkably.[15,16] However, to date, there has been no investigation performed on the effect of phytosterol on preeclampsia patients.

The clinical experiments in the current trial aimed at applying phytosterol to assist the oral nifedipine treatment of serious preeclampsia during pregnancy, as well as observing its therapeutic effects and potential adverse effects.

Materials and methods

Ethical statement

The study adopts the intention-to-treat (ITT) analysis. The clinical experiment was designed in consistence with guidelines of the Declaration of Helsinki. The study protocol has obtained the approval from the Ethical Committee of Liaocheng People's Hospital. The study has obtained informed consents in written form from all participants.

Patients

During August 2015 and August 2018, 295 women with singleton pregnancy and aged from 25 to 35 were diagnosed with severe preeclampsia in the Liaocheng People's Hospital, and then agreed to be participants of the study. All of them needed to receive treatment for controlling blood pressure, with 42 being excluded following these exclusion criteria: (1) with history of being treated with the anti-hypertensive drugs; (2) with history of cardiac failure during pregnancy.

Randomization and treatment

Two hundred and fifty-three patients meeting the randomization condition were selected at last, and they were randomly divided into two groups of treatment with a permuted-block design which was stratified based on their baseline diastolic blood pressure: (1) nifedipine+phytosterol group ($n = 127$), orally took nifedipine capsules (10 mg each dosage, and up to five dosages) and phytosterol capsules (300 mg each dosage, and up to five dosages) every 15 min until the blood pressure was below 150/100 mmHg; (2) nifedipine+placebo group ($n = 126$), orally took nifedipine capsules (10 mg each dosage, and up to five dosages) and starch capsules (300 mg each dosage, and up to five dosages) as placebo every 15 min until the blood pressure was below 150/100 mmHg. The dosage was stopped once patients' blood pressure was lower than 150/100 mmHg. Investigators blind to the group assignment prepared the placebo and phytosterol capsules with the same appearance to make its content blind to patients as well. Each phytosterol capsule contained 50% β-sitosterol, 0.5% sitostanol, 35% campesterol, 8% brassicasterol, 1.5% stigmasterol, 1% campestanol and 4% other sterols, all of which were from natural food source.

Endpoints

Primary endpoints of the study were: (1) time required for controlling blood pressure to $\leq$ 150/100 mmHg; (2) time until the occurrence of another hypertensive crisis. Secondary endpoints were: (1) dosage required for controlling blood pressure to $\leq$ 150/100 mmHg; (2) adverse effects from infants and mothers.

Anthropometrics

A digital scale with accuracy of 0.1 kg and a stadiometer with accuracy of 0.1 cm were used to measure the body weight and height, respectively, of patients standing straight, dressed in light clothing and wearing no shoes. Body mass index (BMI) was calculated by the formula of body weight/(body height)^2 in kg/m^2. A digital monitor of blood pressure with accuracy of 0.1 mmHg was used to measure the blood pressure.

Adverse effects

Investigators continuously monitored the heart rates of the mother and fetus in the course of treatment. At the endpoint of experiments, investigators also required all the patients to finish a designed questionnaire about symptoms they might have suffered during the treatment, such as emesis, nausea, tachycardia, light headedness, dizziness, pectoralgia, hypotension, and polypnea.

Statistical analysis

The data differences exhibited by the two groups were measured by Pearson's Chi-square test together with Student t test, with 95% confidence interval (CI). Effect-size of the study, by Cohen's d method, was calculated to be 0.79 using "Time to control blood pressure" as the measurement. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 18.0 (SPSS Inc., USA).

Results

According to Figure 1, the study enrolled 295 women with singleton pregnancy and aged from 25 to 35 who were diagnosed with severe preeclampsia from August 2015 to August 2018. After excluding 42 patients following the exclusion standard, investigators randomly divided the other qualified participants ($n = 253$) into two groups of treatment, with 127 patients in the nifedipine+phytosterol group, and 126 patients in the nifedipine+placebo group, respectively. They were orally administered one dose every 15 min before the blood pressure was decreased below 150/100 mmHg. Anthropometrics of all 253 participants in the two groups are listed in Table 1 for comparison, such as the age of mother, the age of gestation, the systolic blood pressure, the diastolic blood pressure, the body weight, the body height, the BIM and the heart rate.

No significant differences were observed between patients in the two groups.

The primary endpoints regarding the two groups are listed in Table 2. Firstly, the nifedipine+phytosterol group could achieve an effective control on patients' blood pressure within 41.1 ± 13.5 min, whereas for the nifedipine+placebo group, the time was 53.7 ± 18.2 min, which was significantly longer than the former ($P = 0.02$; 95% CI 5.2–9.8). Secondly, in the nifedipine+phytosterol group, the time before the occurrence of another hypertensive crisis after the effective control of blood pressure was 8.3 ± 1.7 h, whereas in the nifedipine+placebo group, the time was 6.1 ± 1.9 h, remarkably shorter than the nifedipine+phytosterol group ($P = 0.01$; 95% CI 0.4–2.3).

The secondary endpoints regarding the two groups were assessed. According to Figure 2, nifedipine+phytosterol group required a lower number of dosages for controlling blood pressure than the nifedipine+placebo group. Finally, when the experiment ended, investigators summarized the adverse effects from mothers and fetus, as shown in Table 3. No significant difference was seen in the two groups regarding the adverse effects from mother, such as emesis, nausea, tachycardia, light headedness, dizziness, pectoralgia, hypotension, and polypnea. Also, no significant difference was seen in the two groups regarding the adverse effects from the newborns, such as Apgar score and birth weight.

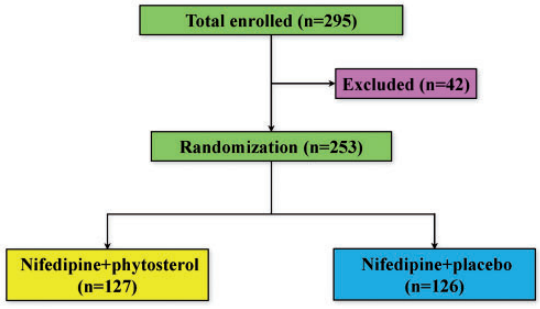

Figure 1. Illustration of study design. (A color version of this figure is available in the online journal.)

Table 1. Characteristics of patients from the two treatment groups.

Characteristics	Nifedipine+ phytosterol (*n*=127)	Nifedipine+ placebo (*n*=126)	*P*
Maternal age (year)	31.3±3.7	30.8±4.1	0.52
Gestation age (week)	33.6±2.9	33.8±3.6	0.48
Systolic blood pressure (mmHg)	170.3±16.0	169.8±15.7	0.29
Diastolic blood pressure (mmHg)	109.2±10.3	107.8±9.2	0.37
Heart rate (/min)	85.4±9.5	87.3±8.7	0.16
Body weight (kg)	63.2±4.1	64.1±3.9	0.38
Body height (m)	1.62±0.10	1.61±0.13	0.11
BMI (kg/m^2)	23.2±2.9	23.8±2.7	0.20

BMI: body mass index.

Table 2. Efficacy of the two treatments in controlling blood pressure among preeclampsia patients.

Primary endpoints	Nifedipine+ phytosterol (*n*=127)	Nifedipine+ placebo (*n*=126)	*P*
Time to control blood pressure (min)	41.1±13.5	53.7±18.2	0.02
Time before a new hypertensive crisis (h)	8.3±1.7	6.1±1.9	0.01

Discussion

Anti-hypertensive treatment can control the hypertension in an effective manner during preeclampsia triggered by pregnancy.[17] It also plays an important role in decreasing the rate of incidence for maternal and fetal complications.[18,19] At present, the appropriate application of drugs to manage hypertension in patients with preeclampsia in clinical practice is mainly based on the experience of

Table 3. Adverse effects and neonatal complications of the two treatments.

Secondary endpoints	Nifedipine+ phytosterol (*n*=127)	Nifedipine+ placebo (*n*=126)	*P*
No adverse effect	110 (86.6%)	112 (88.9%)	
Nausea	6 (4.7%)	7 (5.6%)	
Vomiting	3 (2.4%)	2 (1.6%)	
Maternal tachycardia	2 (1.6%)	2 (1.6%)	
Mild headache	2 (1.6%)	1 (0.8%)	
Dizziness	2 (1.6%)	1 (0.8%)	
Chest pain	1 (0.8%)	0 (0%)	
Hypotension	1 (0.8%)	0 (0%)	
Shortness of breath	0 (0%)	1 (0.8%)	
Birth weight (kg)	3.04±0.52	2.96±0.47	0.29
Apgar scores			
>6	103 (81.1%)	98 (77.8%)	
4–6	24 (18.9%)	28 (22.2%)	

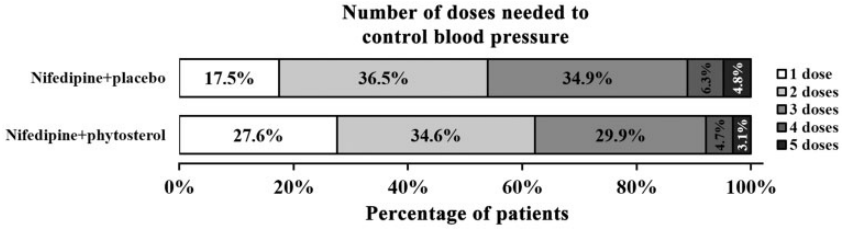

Figure 2. Number of doses needed to control blood pressure in two groups of patients. Percentages do not add up to 100 dues to rounding.

physicians, and nifedipine acts as one of common first-line drugs to control the high blood pressure of patients during pregnancy.[3,6] Compared with other anti-hypertensive alternatives, oral nifedipine holds the advantages of low cost, safety, and effectiveness over other anti-hypertensive drugs, while achieving similar efficacy in reducing blood pressure during preeclampsia triggered by pregnancy.[5,20]

Although pregnancy is of great consideration and interest in the society, it is difficult for preeclampsia patients to find available anti-hypertensive drugs, as these drugs are only limited to non-pregnant hypertension patients. Hence, it is necessary to develop a safe and novel drug to effectively complement oral nifedipine, aiming at significantly benefiting preeclampsia patients. On that account, phytosterol is a type of natural compound commonly found in plant products, and have been incorporated into various food vectors and natural drugs. As the source is safe and natural, many researches have proved that phytosterol can be used to treat the complications of patients during and after pregnancy.[13,21] Therefore, phytosterol is applied in the current clinical trial for treating preeclampsia-affected pregnant women, with the hypothesis that phytosterol is beneficial to relieve hypertension in preeclampsia induced by pregnancy.

According to the results of our clinical trial, combining oral nifedipine with phytosterol contributed to obvious improvements on both the primary and secondary endpoints, in comparison to nifedipine+placebo treatment. Nifedipine+phytosterol group required an obviously shorter time for controlling the blood pressure than nifedipine+placebo group, and exhibited a remarkably delayed time for the occurrence of another hypertensive crisis. The nifedipine+phytosterol group needed an obviously lower dosage for controlling the blood pressure. Above all, pregnant preeclampsia patients showed no severe adverse effects related to the phytosterol administration, regardless of maternal or neonatal, demonstrating that phytosterol is very safe in clinical practice for pregnant women.

Although phytosterol is proved to be effective to complement the oral nifedipine clinically, the mechanism underlying phytosterol effect to relieve hypertension remains unknown. It was reported that, matrix metalloproteinase (MMP)-3 expression was abnormally upregulated by TNF-α in decidual cells, which could disturb the regular stepwise invasion of decidua by human extravillous trophoblast cells.[22] On the other hand, MMP-13 was reported to be highly expressed in preeclamptic placenta.[23] Moreover, in a recent clinical study, MMP-13 level was also found to be higher in preeclamptic pregnant women.[24] Taken together, these studies have implicated both MMP-3 and MMP-13 in the pathology of preeclampsia. Interestingly, phytosterol was found to be able to decrease the productions of both MMP-3 and MMP-13 in human cells.[25] Therefore, these two MMPs may be implicated in the property of phytosterol for the relieve of hypertension observed in preeclampsia patients. It is necessary to perform further studies for assessing the abovementioned potential mechanism, therefore a multi-center trial in larger scale is warranted, especially since results obtained in the current study strongly supports the efficacy and safety of the combinational treatment.

In conclusion, the current placebo-controlled, double-blinded, randomized clinical trial has reported that phytosterol is a safe and potent adjuvant to assist the treatment of oral nifedipine. Phytosterol can contribute to an obvious enhancement on the treatment outcome of hypertension exhibited by serious preeclampsia during pregnancy. The conclusion is, however, limited by a relatively small number of participating preeclampsia patients, and therefore further investigations, such as a multi-center trial in larger scale, are needed to verify our current findings.

Authors' contributions: All authors participated in the design, interpretation of the studies and analysis of the data and review of the manuscript; MZ and HRF conducted the experiments, MZ wrote the manuscript.

DECLARATION OF CONFLICTING INTERESTS

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