BMC Pregnancy and Childbirth

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The impact of aspirin combined with labetalol on coagulation function and pregnancy outcomes in pre-eclamptic pregnant women

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Abstract

Background This study aimed to analyze the impact of aspirin combined with labetalol on coagulation function and pregnancy outcomes in women with pre-eclampsia.

Methods A total of 98 pregnant women with pre-eclampsia admitted to our hospital from September 2019 to March 2021 were selected for the retrospective analysis. Patient records were reviewed and divided into a control group ($n=49$) who received labetalol and an observation group ($n=49$) who received aspirin combined with labetalol. Extracted from the case collection system and observed: clinical efficacy, occurrence of adverse pregnancy outcomes, and adverse reactions.

Results The total effective rate in the observation group was higher than that in the control group. After treatment, the observation group had lower systolic blood pressure, diastolic blood pressure, D-D, Scr, β2-MG, and MA levels compared to the control group, and higher TT, PT and APTT levels. The occurrence rate of adverse pregnancy outcomes such as preterm delivery, intrauterine distress, postpartum hemorrhage, and fetal heart abnormalities was lower in the observation group than in the control group. There were no statistically significant differences in adverse reactions such as nausea, vomiting, hypotension, ocular tremor, and facial flushing between the two groups.

Conclusion Aspirin combined with labetalol has ideal therapeutic efficacy in women with pre-eclampsia. It can enhance the antihypertensive effect, improve the coagulation status of the body, protect renal function, improve adverse pregnancy outcomes, and is considered safe and reliable, deserving adoption.

Keywords Aspirin, Labetalol, Pre-eclampsia, Coagulation function, Pregnancy outcomes

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Introduction

Pre-eclampsia is a pregnancy-specific disorder characterized by the development of new-onset hypertension, proteinuria, or end-organ dysfunction after 20 weeks of gestation [1] It is a progressive and unique condition that significantly affects the outcomes for both mothers and fetuses [2]. Pre-eclampsia can be categorized into with or without severe features based on clinical manifestations and early-onset or late-onset depending on the timing of onset [1, 3]. The pathogenesis of pre-eclampsia is believed to involve abnormalities in the uteroplacental vasculature, excessive activation of inflammatory and immune responses, endothelial cell damage, and genetic factors [4–6].

Clinical management of pre-eclampsia typically includes continue monitoring for patients without severe symptoms, while medication is administered to patients with severe symptoms [7]. Labetalol, which belongs to the class of adrenergic receptor antagonists, has been commonly used in the past [3]. It reduces peripheral vascular resistance and increases blood volume [8]. However, its effectiveness has shown limitations as the number of pre-eclampsia patients continues to rise [9]. Aspirin, a cyclooxygenase inhibitor, possesses anti-inflammatory, anticoagulant, and vasodilatory properties. It has demonstrated promising results in the prevention of pre-eclampsia [10]. To further enhance the clinical efficacy in pre-eclamptic pregnant women, our institution has adopted a treatment approach that combines aspirin with labetalol. We aim to analyze the impact of this combination therapy on coagulation function and pregnancy outcomes in order to provide insights and guidance for selecting appropriate medication regimens in clinical practice.

Materials and methods

Study design and population

The current study is a case-control study. Sample size was determined by the number of patients who met the inclusion criteria but did not meet the exclusion criteria admitted to our hospital from January 2021 to December 2022. Patient records were reviewed and divided into a control group who received labetalol and an observation group who received aspirin combined with labetalol. Inclusion criteria were as follows: [1] clinically diagnosed pre-eclampsia, defined as systolic blood pressure ≥ 140mmHg or diastolic blood pressure ≥ 90mmHg, accompanied by urinary protein ≥ 0.3 g/24 h, or positive random protein, or in the absence of proteinuria, but with any of the following: ①thrombocytopenia (platelet count < 100 × 10^9/L); ②liver function impairment (serum alanine aminotransferase level > 2 times the upper limit of normal); ③renal function impairment (serum creatinine level > 1.1 mg/L or > 2 times the upper limit of normal); ④pulmonary edema; ⑤new-onset central nervous system abnormalities or visual disturbances; [2] onset of symptoms before 34 weeks of gestation; [3] newly diagnosed patients without a history of special medication use prior to enrollment and during pregnancy; [4] age > 20 years; [5] patients and their families were aware of the benefits and risks of the study and signed an informed consent form. Exclusion criteria were: [1] comorbid malignant tumors or abnormal liver or kidney function; [2] comorbid hypertension, diabetes, or a history of nephritis with allergic reactions to any of the study medications; [3] severe psychiatric disorders or altered mental status; [4] coagulation dysfunction; [5] unclear examination results or poor compliance (incomplete information). A total of 105 pre-eclamptic pregnant women were screened and six cases were excluded. Finally, 98 were included in this retrospective study, among whom, 49 cases were assigned to observation group and 49 cases were assigned to the control group (Fig. 1).

Intervention methods

All patients received routine treatments, including antispasmodics, sedatives, and oxygen supplementation, while also receiving appropriate vitamin and nutrient supplementation. The control group was orally administered labetalol (Jiangsu Disino Pharmaceutical Co., Ltd., National Medical Products Administration [NMPA] approval number H32026120, 100 mg/tablet) at a dosage of 100 mg, 2–3 times a day. The observation group received aspirin (Shandong Xinhua Pharmaceutical Co., Ltd., NMPA approval number H20030396, 0.3 g/tablet) in addition to the labetalol used in the control group, at a dosage of 100 mg, once a day. The dose of labetalol in the observation group was the same as that of the control group. The occurrence of adverse reactions during the medication period was monitored in all patients and treated promptly, with continuous treatment until delivery.

Observational indicators

The following clinical efficacy and parameters were observed in both groups: clinical efficacy, blood pressure levels before and after treatment, coagulation function indicators including thrombin time (TT), prothrombin time (PT), activated partial thromboplastin time (APTT), and D-dimer (D-D) levels, renal function indicators including serum creatinine (Scr), blood urea nitrogen (BUN), microalbuminuria (MA), and beta-2-microglobulin (β2-MG) levels, as well as adverse pregnancy outcomes and adverse reaction occurrences.

(1) Clinical efficacy: The criteria for clinical efficacy were as follows: marked improvement - normalization of signs such as edema, hypertension, proteinuria,

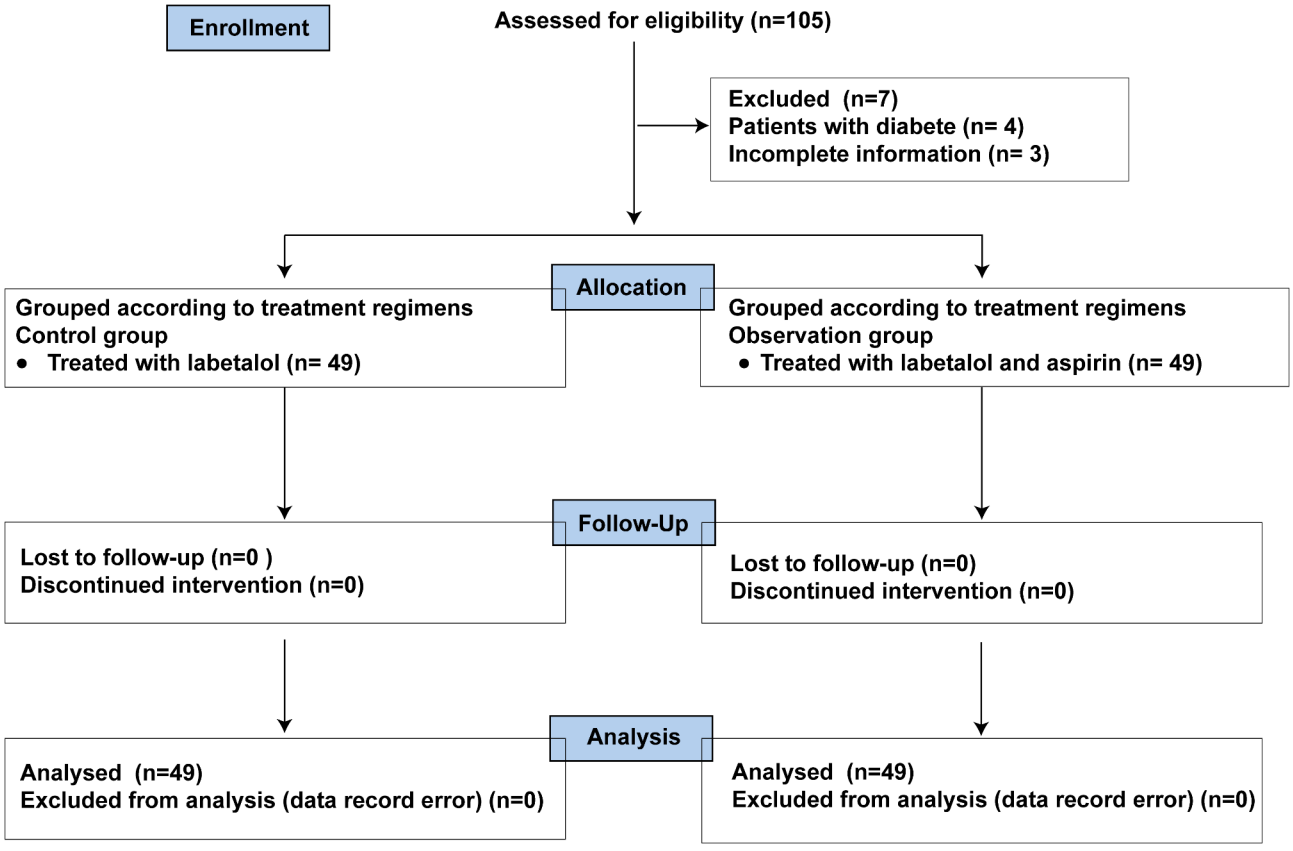

Fig. 1 Flow diagram of the patients included

headache, dizziness, or visual disturbances; effective improvement - improvement in signs such as edema, hypertension, proteinuria, but not reaching normal levels; ineffective - not meeting the above criteria. The total effective rate was calculated as the sum of the marked and effective rates.

(2) Blood pressure levels: Systolic and diastolic blood pressure in both groups were measured using the Dalian Omron (China) HEM1300 sphygmomanometer before and after treatment. Three measurements were taken, and the average was calculated.

(3) Coagulation function indicators: Peripheral venous blood samples (5 ml) were collected before and after treatment and analyzed using the Beckman-Coulter ACL-TOP automated coagulation analyzer to determine TT, PT, APTT, and D-D levels.

(4) Renal function indicators: Peripheral venous blood samples (10 ml) were collected before and after treatment for routine analysis of Scr and BUN levels. Urine samples were also collected to measure β2-MG and MA levels. Reagent kits were purchased from Shenzhen Ziko Biotechnology Co., Ltd.

(5) Adverse pregnancy outcomes: The incidence of adverse pregnancy outcomes, such as premature delivery, intrauterine distress, postpartum hemorrhage, and abnormal fetal heart rate, was recorded in both groups.

(6) Adverse reactions: The occurrence of adverse reactions, including nausea, vomiting, hypotension, nystagmus, and facial flushing, was recorded in both groups.

Statistical analysis

Data were analyzed using SPSS version 25.0. Count data were presented as [n (%)] and analyzed using the chi-square test. Normally distributed continuous data were presented as mean ± standard deviation (SD) and analyzed using the t-test. A p-value of less than 0.05 was considered statistically significant.

Results

Comparison of general data between the two groups

As shown in Table 1, there were no statistically significant differences in general data, such as age, gestational weeks, body mass index, parity, and severity of disease, between the two groups ($p > 0.05$), indicating comparability between the groups.

Table 1 Comparison of General characteristics between the two groups

Parameter	Observation Group ($n=49$)	Control Group ($n=49$)	χ^2/t	*P*
Age (years)	29.80 ± 4.10	29.45 ± 4.05	0.425	0.672
Gestational Weeks (weeks)	33.30 ± 3.15	33.54 ± 3.26	0.371	0.712
Body Mass Index (kg/m^2)	22.25 ± 1.10	22.30 ± 1.24	0.211	0.833
Puerpera [n (%)]				
Primipara	29 (59.18%)	28 (57.14%)	0.042	0.838
Multipara	20 (40.82%)	21 (42.86%)		
Severity [n (%)]				
Mild Disease Severity	35 (71.43%)	36 (73.44%)	0.051	0.821
Severe Disease Severity	14 (28.57%)	13 (26.56%)		

Table 2 Comparison of clinical efficacy between the two groups [n (%)]

Group	Marked Improvement	Effective Improvement	Ineffective	Total Effective Rate
Observation Group ($n=49$)	29 (59.18%)	19 (38.78%)	1 (2.04%)	48 (97.96%)
Control Group ($n=49$)	22 (44.90%)	20 (40.82%)	7 (14.29%)	42 (85.71%)
χ^2	-	-	-	4.900
P	-	-	-	0.027

Table 3 Comparison of blood pressure levels before and after treatment in the two groups (mmHg)

Group	Systolic Pressure		Diastolic Pressure	
	Before Treatment	After Treatment	Before Treatment	After Treatment
Observation Group ($n=49$)	155.65 ± 14.78	132.75 ± 11.45	110.72 ± 11.65	83.56 ± 10.24
Control Group ($n=49$)	156.10 ± 15.20	139.52 ± 12.40	109.98 ± 12.10	88.65 ± 9.75
χ^2	0.149	2.808	0.308	2.520
P	0.882	0.006	0.758	0.013

Table 4 Comparison of coagulation function parameters before and after treatment in the two groups

Parameter		Observation Group ($n=49$)	Control Group ($n=49$)	χ^2/t	*P*
TT (s)	Before Treatment	14.10 ± 3.25	14.62 ± 3.32	0.783	0.435
	After Treatment	18.30 ± 2.52	16.25 ± 2.40	4.124	0.001
PT (s)	Before Treatment	10.34 ± 1.25	10.28 ± 1.35	0.228	0.820
	After Treatment	13.08 ± 2.44	11.60 ± 1.65	3.517	0.001
APTT (s)	Before Treatment	26.30 ± 4.62	26.20 ± 5.54	0.097	0.923
	After Treatment	32.45 ± 6.32	29.35 ± 5.42	2.606	0.011
D-D (mg/L)	Before Treatment	1.37 ± 0.45	1.40 ± 0.42	0.341	0.734
	After Treatment	0.75 ± 0.12	1.06 ± 0.14	11.768	0.001

Clinical efficacy

As shown in Table 2, the total effective rate in the observation group was higher than that in the control group, with a statistically significant difference ($P<0.05$), indicating that the combination of aspirin and labetalol could improve the clinical efficacy of pregnant women with pre-eclampsia.

Blood pressure levels

As shown in Table 3, there were no statistically significant differences in systolic and diastolic blood pressure levels before treatment between the two groups ($P>0.05$). However, after treatment, the systolic and diastolic blood pressure levels in the observation group were lower than those in the control group, with a statistically significant difference ($P<0.05$), suggesting that the combination of aspirin and labetalol could better control the blood pressure levels of pregnant women with pre-eclampsia.

Coagulation function indexes

As shown in Table 4, there were no statistically significant differences in TT, PT, APTT, and D-D levels before treatment between the two groups ($P>0.05$). However, after treatment, the TT, PT, and APTT levels in the observation group were higher than those in the control group, while the D-D level was lower, with a statistically significant difference ($P<0.05$), suggesting that the combination of aspirin and labetalol could improve the coagulation function of pregnant women with pre-eclampsia.

Table 5 Comparison of renal function parameters before and after treatment in the two groups

Parameter		Observation Group ($n=49$)	Control Group ($n=49$)	t	*P*
SCr (μmol/L)	Before Treatment	67.48 ± 10.36	68.10 ± 11.24	0.284	0.777
	After Treatment	62.45 ± 9.22	66.78 ± 8.32	2.441	0.016
BUN (mmol/L)	Before Treatment	4.40 ± 1.20	4.35 ± 1.26	0.201	0.841
	After Treatment	4.32 ± 1.26	4.24 ± 1.14	0.330	0.742
β2-MG (mg/L)	Before Treatment	2.25 ± 0.38	2.20 ± 0.40	0.634	0.527
	After Treatment	1.37 ± 0.12	1.76 ± 0.34	7.572	0.001
MA (mg/L)	Before Treatment	208.35 ± 46.20	208.74 ± 47.25	0.041	0.967
	After Treatment	61.54 ± 6.32	102.25 ± 8.32	27.275	0.001

Table 6 Comparison of adverse pregnancy outcomes in the two groups

Group	Premature Birth	Intrauterine Distress	Postpartum Hemorrhage	Abnormal Fetal Heart Rate*	Occurrence Rate
Observation Group ($n=49$)	1 (2.04%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.04%)
Control Group ($n=49$)	3 (6.12%)	1 (2.04%)	2 (4.08%)	1 (2.04%)	7 (14.29%)
χ^2	-	-	-	-	4.900
P	-	-	-	-	0.027

Note:* A fetal heart rate of 110–180 bpm is considered normal fetal heart, while a rate outside of this range is considered abnormal fetal heart according to ACOG Practice

Table 7 Comparison of adverse reactions in the two groups

Group	Nausea/Vomiting	Hypotension	Nystagmus	Facial Flushing	Total
Observation Group ($n=49$)	1 (2.04%)	0 (0.00%)	1 (2.04%)	1 (2.04%)	3 (6.12%)
Control Group ($n=49$)	1 (2.04%)	1 (2.04%)	0 (0.00%)	0 (0.00%)	2 (4.08%)
χ^2	-	-	-	-	0.211
P	-	-	-	-	0.646

Renal function indexes

As shown in Table 5, there were no statistically significant differences in SCr, BUN, β2-MG, and MA levels before treatment between the two groups ($P>0.05$). However, after treatment, the SCr, β2-MG, and MA levels in the observation group were lower than those in the control group, with a statistically significant difference ($P<0.05$). There was no statistically significant difference in BUN levels between the two groups after treatment ($P>0.05$).

Adverse pregnancy

As shown in Table 6, the occurrence rates of adverse pregnancy outcomes, such as preterm delivery, intrauterine distress, postpartum hemorrhage, and fetal heart abnormalities, were lower in the observation group than in the control group, with a statistically significant difference ($P<0.05$), indicating that the combination of aspirin and labetalol could improve the pregnancy outcomes of pregnant women with pre-eclampsia.

Adverse reaction incidences

As shown in Table 7, there were no statistically significant differences in the incidences of adverse reactions, such as nausea/vomiting, hypotension, nystagmus, and facial flushing, between the two groups ($P>0.05$). This suggests that the treatment of pregnant women with pre-eclampsia using a combination of aspirin and labetalol does not significantly increase the occurrence of adverse reactions, and its safety remains relatively high.

Discussion

Pre-eclampsia is a severe and rapidly progressing condition that, if left untreated, can lead to adverse pregnancy outcomes and jeopardize the lives of both mother and baby [11]. Pre-eclampsia patients often experience systemic vasoconstriction, resulting in damage to nourishing cells, ischemia, and hypoxia. This stimulates oxidative stress response, leading to the production and release of inflammatory factors and inhibition of prostaglandin synthesis and release, resulting in elevated blood pressure [11]. Furthermore, these patients also suffer from widespread endothelial cell damage, leading to the release of procoagulant substances that disrupt the balance between the coagulation system and the fibrinolysis system. This increases the risk of thrombus formation, and in severe cases, can cause hyperfibrinolysis, leading to a series of serious complications [12, 13]. Literature reports indicate that approximately 10% of pregnant women in China experience gestational hypertension, with a mortality rate of 3-6% for newborns of mothers with gestational hypertension or mild pre-eclampsia, and a mortality rate of 17-21% for newborns of mothers with severe pre-eclampsia or eclampsia [14–16]. Therefore, it is of significant clinical importance to explore effective treatment strategies to improve the maternal and infant

outcomes of patients with pre-eclampsia without compromising fetal development.

Currently, clinical management of pre-eclampsia often involves the use of antispasmodics, antihypertensives, diuretics, and other measures [17]. KATE N et al. [18] conducted a study that found a more desirable hypotensive effect in women with pre-eclampsia treated with aspirin and labetalol. The study showed that the overall effective rate in the observation group was higher than that in the control group, and the levels of systolic and diastolic blood pressure after treatment were lower than those in the control group ($P<0.05$), which is consistent with the results of previous studies. The analysis suggests that the combination of aspirin and labetalol has a coordinating effect. It can inhibit platelet cyclooxygenase, reduce thromboxane, thus inhibiting microcirculation, decreasing vascular resistance, promoting blood flow, and facilitating blood pressure recovery. Labetalol has been shown to have good blood pressure control effects, can reduce urinary protein levels, suppress sympathetic nervous system excitatory conduction, and rapidly lower blood pressure [19]. Additionally, labetalol achieves long-term blood pressure reduction by selectively blocking α and β-adrenergic receptors in the kidneys, increasing catecholamine levels, decreasing vascular resistance, and increasing blood volume [20]. We inferred that the association of aspirin and labetalol may improves maternal hemodynamics and therefore improving the outcomes. The potential synergistic effect between aspirin and labetalol in improving hemodynamics may involve their complementary effects on blood pressure and vascular function. Asiprin reduces platelet aggregation and enhances vasodilation through its anti-inflammatory effects, improving microcirculation. Labetalol, by blocking α1 receptors, reduces peripheral vascular resistance, and through β-blockade, lowers heart rate and cardiac output [21]. Together, they may provide enhanced blood pressure control and reduce cardiac workload, leading to improved overall hemodynamics [22]. PARK F et al. [23]. found that labetalol has a certain diuretic effect, and when used in combination with aspirin, it can significantly increase the permeability of the glomerulus, thereby reducing urinary protein levels and protecting kidney function. In our study, after treatment, the levels of SCr, β2-MG, and MA in the observation group were lower than those in the control group ($P<0.05$), suggesting that the combination of aspirin and labetalol could protect the renal function of pregnant women with pre-eclampsia, which is consistent with the above research results. The levels of TT, PT, and APTT in the observation group were higher than those in the control group, while the D-D level was lower than that in the control group ($P<0.05$). This can be attributed to the addition of aspirin to labetalol, which is a commonly used antiplatelet aggregator. Aspirin can significantly inhibit platelet cyclooxygenase, reduce the production of thromboxane A2, and platelet aggregation and thrombus formation, improving coagulation function [24]. KATE N et al. [25] also found that the use of aspirin and labetalol in women with pre-eclampsia can reduce adverse pregnancy outcomes. The incidence of premature birth, intrauterine distress, postpartum hemorrhage, and abnormal fetal heart rate in the observation group was lower than that in the control group ($P<0.05$), which is consistent with the results of clinical reports. This is because the combination of aspirin and labetalol for the treatment of pre-eclampsia can achieve good blood pressure control, improve fetal oxygen and nutrient supply, and reduce adverse pregnancy outcomes [26, 27]. Furthermore, there was no statistically significant difference in the occurrence of adverse reactions such as nausea, vomiting, hypotension, nystagmus, and facial flushing between the two groups ($P>0.05$). This suggests that the combination of labetalol and aspirin significantly improves efficacy without increasing the risk of adverse reactions. Clinical studies have shown that both labetalol and aspirin may induce gastrointestinal dysfunction. Therefore, when using labetalol in combination with aspirin to treat women with pre-eclampsia, attention should be paid to the occurrence of gastrointestinal adverse reactions and timely intervention [28].

It should be noted that labetalol is a combined α- and β-adrenergic blocker with distinct effects on cardiovascular function. Its β-blocking properties reduce myocardial contractility and heart rate, which can lead to a reduction in cardiac output (CO) and stroke volume (SV) [8]. Preeclampsia is a highly heterogeneous condition, with patients exhibiting varying hemodynamic profiles. Some women with preeclampsia may present with high CO and high SV, particularly in the early stages [29]. In these patients, the β-blocking effect of labetalol may help control blood pressure without significantly compromising stroke volume. However, other patients, especially those with more severe preeclampsia or underlying cardiovascular disease, may have low CO and low SV, which can worsen in response to labetalol's β-blocking effects. In such cases, labetalol may further reduce myocardial contractility, leading to significant hypotension and impaired organ perfusion. Therefore, it is crucial to consider the individual hemodynamic status of each patient when selecting labetalol for the management of preeclampsia. In case of a hypodynamic circulation during hypertensive disorders of pregnancies other drugs might be more appropriate, such as dihydropyridine calcium channel blockers (i.e. Nifedipine, Amlodipine, etc.) [30, 31].

In the current study, we found that ineffective treatment was present in a greater proportion of patients treated with labetalol alone vs. labetalol + aspirin (14.29%

vs. 2.04%). The power of the current study is about 62%. In fact, the sample size needed to detect a reduction of efficacy from 14 to 2% is 80 patients per group, for a Type 1 (alpha) error 0.05 and a Type 2 (beta) error 0.20. Although this study found that the efficacy of combination therapy was better than labetalol alone, the power of this study is limited. What's more, it is a non-randomized, retrospective, and non-blinded design, which may introduce several biases. These include selection bias, as patients were not randomly assigned, and information bias, due to the retrospective nature of data collection. Observer bias may have occurred since the study was not blinded, potentially influencing data recording and interpretation. Confounding factors could have affected the results, as randomization was not employed to control for baseline differences between groups. Therefore, prospective randomized controlled trials are needed to further validate the results of this study.

Conclusions

In summary, the combination of aspirin and labetalol in the treatment of pregnant women with pre-eclampsia may be a treatment regimen with higher efficacy than labetalol monotherapy. It enhances the hypotensive effect, improves the coagulation state of the body, protects kidney function, and improves adverse pregnancy outcomes. The treatment approach is considered safe and reliable, and thus, it is worthy of adoption. However, it is important to acknowledge the limitations of this study. For instance, the sample size included in this study was relatively small, the samples were obtained from a single hospital, and the follow-up duration was extensive. Therefore, future studies should consider conducting large-scale, multi-center, and long-term randomized controlled trials to further validate the aforementioned conclusions.

Acknowledgements
The authors express their appreciation to staff in Tianjin Nankai Hospital and The Second Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, for their technical assistance.

Author contributions
Min Zhang, Xiaoxuan Ren: data collection and analysis, drafting the manuscript, investigation. Dianrong Song: study design, data analysis, drafting the manuscript and revision of the manuscript. All authors read and approved the final version of the manuscript.

Funding
This study was supported by Research project on the integration of traditional Chinese medicine and Western medicine in Tianjin (No. 2019042).

Data availability
All data generated or analyzed in this study are included in the present manuscript.

Declarations

Ethics approval and consent to participate
This study was approved by the Ethics Committee of The Second Affiliated Hospital of Tianjin University of Traditional Chinese Medicine in accordance with regulatory and ethical guidelines. Participate consent was obtained from all participants. Informed consent was obtained from all subjects. The procedures were conducted in accordance with the ethical standards set forth by the Committee on Human Experimentation and the Helsinki Declaration of 1975, as revised in 2013.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Clinical trial
Not applicable.

Received: 6 November 2024 / Accepted: 10 February 2025
Published online: 27 February 2025

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