Am J Transl Res 2025;17(3):2005-2013
www.ajtr.org /ISSN:1943-8141/AJTR0161531

Original Article

Effects of labetalol plus magnesium sulfate on brain symptoms and pregnancy outcomes in hypertensive disorders of pregnancy

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Received October 28, 2024; Accepted January 25, 2025; Epub March 15, 2025; Published March 30, 2025

Abstract: Objective: This study aimed to evaluate the clinical efficacy of labetalol (LBT) combined with magnesium sulfate ($MgSO_4$) in improving symptoms and pregnancy outcomes in patients with hypertensive disorders of pregnancy (HDP). Methods: A total of 122 HDP patients admitted between January 2020 and June 2024 were included. Among them, 56 patients (control group) received $MgSO_4$ alone, while 66 patients (research group) received a combination of LBT and $MgSO_4$. Comparative analyses were conducted to evaluate therapeutic effectiveness, symptom improvement (edema, hypertension, and proteinuria), brain-related symptoms (nausea and vomiting, sluggishness, blurred vision, dizziness, and headache), pregnancy outcomes (placental abruption, neonatal asphyxia, fetal distress, and postpartum hemorrhage), blood pressure indicators (systolic (SBP) and diastolic blood pressure (DBP)), fetal umbilical artery hemodynamics (systolic-to-diastolic flow velocity ratio (S/D) and pulsatility index (PI)), and high-sensitivity C-reactive protein (hs-CRP). Results: The research group demonstrated significantly better outcomes than the control group, including a higher overall therapeutic effectiveness rate, faster resolution of edema, hypertension, and proteinuria, a lower incidence of adverse pregnancy events, and more pronounced reductions in SBP, DBP, S/D, PI, and hs-CRP levels after treatment (all $P < 0.05$). Conclusion: The combination of LBT and $MgSO_4$ is highly effective in improving symptoms and pregnancy outcomes in HDP patients, outperforming $MgSO_4$ monotherapy. This approach has strong potential for broader clinical application.

Keywords: Labetalol, magnesium sulfate, hypertensive disorders of pregnancy, brain symptoms, pregnancy outcomes

Introduction

Hypertensive disorders of pregnancy (HDP) are among the most common cardiometabolic complications during pregnancy. These disorders include various types, such as chronic hypertension, gestational hypertension, and preeclampsia/eclampsia [1]. The pathogenesis of HDP is complex and may involve inflammation, oxidative stress, and vascular endothelial dysfunction. These mechanisms can lead to adverse clinical manifestations such as edema, hypertension, and proteinuria [2, 3]. Statistics show that HDP affects 5-10% of pregnancies and has a negative impact on fetal and neonatal outcomes [4]. Several factors significantly increase the risk of pregnant women developing HDP, including pre-pregnancy obesity, excessive weight gain during pregnancy, gestational diabetes, and maternal age over 40 years [5]. Currently, the primary treatment for HDP relies on antihypertensive drug therapy. However, there is no consensus on the optimal treatment regimen for managing HDP [6, 7]. Actively exploring effective treatment strategies that alleviate symptoms and optimize pregnancy outcomes in HDP patients is still of critical medical importance. Such advancements could improve the quality of life and prognosis in affected patients.

Current pharmacotherapy for patients with HDP primarily aims to alleviate vasospasm, lower bl-

https://doi.org/10.62347/TWVI9995

ood pressure, and reduce cardiac workload. However, some medications may pose risks to pregnancy outcomes, necessitating the careful selection of appropriate pharmacotherapy [8]. Magnesium sulfate ($MgSO_4$) is commonly employed in the treatment of HDP and exerts antispasmodic, diuretic, and pain-relieving effects. It helps relax vascular smooth muscles and dilate peripheral blood vessels, thereby relieving spasms [9]. Despite its ability to lower blood pressure, $MgSO_4$ is suboptimal in terms of blood pressure control efficacy [10]. To enhance therapeutic effectiveness, it is essential to consider combining $MgSO_4$ with other medications for the treatment of HDP [11]. Labetalol (LBT), a combined alpha-adrenergic and beta-adrenergic receptor blocker, is effective in treating HDP by blocking adrenergic receptors, slowing ventricular rhythm, and reducing peripheral vascular resistance [12]. Previous studies have utilized LBT in combination with $MgSO_4$ to reduce anxiety and depression in patients with HDP [13]. In a study conducted by Lan et al. [14], LBT was shown to effectively achieve blood pressure control in patients with severe HDP.

This study suggests that the combination of LBT and $MgSO_4$ provides significant clinical benefits in terms of symptom alleviation and improved pregnancy outcomes in patients with HDP.

Clinical materials

General data

This retrospective study was approved by the Ethics Committee of Ji'an Central People's Hospital. The analysis included 122 patients with HDP treated at Ji'an Central People's Hospital between January 2020 and June 2024. Of these, 56 patients in the control group received $MgSO_4$ alone, while 66 patients in the research group were treated with LBT combined with $MgSO_4$. There were no statistically significant differences in the general data between the two groups ($P > 0.05$), indicating clinical comparability.

Inclusion and exclusion criteria

Inclusion criteria: meeting the diagnostic criteria for HDP [15]; regular menstruation before pregnancy; first onset of blood pressure >140/90 mmHg during pregnancy; singleton pregnancy; complete medical records.

Exclusion criteria: history of hypertension, diabetes, or abnormal liver and kidney function; abnormalities in fetal development; other pregnancy complications; allergies to study medications; concomitant bronchial asthma or conduction block; fetal developmental malformations.

Medication regimens

The same $MgSO_4$ administration protocol was applied to patients in both groups. In the research group, LBT was added as a combination treatment. $MgSO_4$ was administered intravenously. A loading dose of 4-6 g of $MgSO_4$ (Shanghai Aladdin Bio-Chem Technology Co., Ltd., M431166) was mixed with 20 mL of 25% glucose injection (Ronpharm (Shanghai) Co., Ltd., R004022) and given as an intravenous bolus over 15-20 minutes. This was followed by a maintenance intravenous drip at a rate of 1-2 g/h. The total daily dose of $MgSO_4$ within 24 hours did not exceed 25 g, and the treatment duration was generally limited to 5 days. In the research group, LBT (Shanghai Aladdin Bio-Chem Technology Co., Ltd., L336883) was administered in combination with the $MgSO_4$ regimen. LBT was given orally at a dose of 50-150 mg per administration, 3 times a day. For patients with severe hypertension, the dose was increased to 400 mg per administration, 3 times a day, with a maximum daily dose of 2400 mg.

Outcome measures

(1) Therapeutic effectiveness [16]: The criteria for evaluating therapeutic efficacy are as follows: Marked effectiveness: disappearance of symptoms such as edema and proteinuria after treatment, with blood pressure restored to within 140/90 mmHg; effectiveness: significant improvement in symptoms such as edema and proteinuria after treatment, with blood pressure restored to 140-150/90-100 mmHg; ineffectiveness: no change in symptoms such as edema and proteinuria after treatment, no improvement in blood pressure compared to baseline, or worsening symptoms. The overall effectiveness rate was calculated as the sum of the marked effectiveness rate and the effectiveness rate.

Table 1. Comparative analysis of general data

Data	Control group (n=56)	Research group (n=66)	χ^2/t	P
Age	30.45±5.76	29.02±4.86	1.487	0.140
Gestational age (weeks)	35.89±2.09	36.09±2.47	0.478	0.634
Body mass index (kg/m^2)	21.66±1.54	21.71±1.90	0.158	0.875
Parity			0.490	0.484
Primipara	39 (69.64)	42 (63.64)		
Multipara	17 (30.36)	24 (36.36)		
Abortion history			0.808	0.369
Without	44 (78.57)	56 (84.85)		
With	12 (21.43)	10 (15.15)		
Family history of hypertension			0.895	0.344
Without	50 (89.29)	55 (83.33)		
With	6 (10.71)	11 (16.67)		
Educational level			1.919	0.166
Senior high school or above	35 (62.50)	33 (50.00)		
Below senior high school	21 (37.50)	33 (50.00)		

(2) Symptom amelioration [17]: Symptom improvement in both groups was observed and recorded, including the time taken for relief of edema, hypertension, and proteinuria.

(3) Brain symptoms and signs [18]: The number of cases of nausea and vomiting, sluggishness, blurred vision, dizziness, and headaches was recorded for both groups.

(4) Pregnancy outcomes [19]: Pregnancy outcomes, including placental abruption, neonatal asphyxia, fetal distress, and postpartum hemorrhage, were statistically analyzed.

(5) Blood pressure [20]: Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured for all patients before and after medication.

(6) Observation of fetal hemodynamics [21]: Before and after medication, a Doppler color ultrasound diagnostic apparatus was used to measure the systolic-to-diastolic flow velocity ratio (S/D), pulsatility index (PI), and fetal umbilical artery hemodynamics.

(7) Serum biochemical indexes [22]: Five milliliters of venous blood were collected from both groups before and after medication. The samples were centrifuged, and serum high-sensitivity C-reactive protein (hs-CRP) concentrations were determined using turbidimetry.

Statistical methods

In this study, the number of cases and percentages (n/%) were used to represent categorical data, and inter-group comparisons were conducted using χ^2 tests. Continuous data, expressed as mean ± standard deviation ($\bar{x}$±sd), were analyzed between groups using independent samples t-tests and within groups (before vs. after medication) using paired t-tests. Statistical analysis was performed using SPSS 19.0 software, with $P < 0.05$ indicating statistically significant differences. Additionally, the sample size for this study was determined using a sample size calculation formula, which established a minimum required sample size of 40 participants per group. The actual sample size in each group included in this study exceeded this minimum requirement. The specific formula used is presented below:

$$n = \frac{((Z_{1-\alpha/2} + Z_{\beta})^2 \times (p_t(1 - p_t) + p_c(1 - p_c)))}{(p_t - p_c)^2}$$

Results

Comparative analysis of general data

There were no statistically significant differences between the research group and the control group in terms of age, gestational age, body mass index (BMI), parity, abortion history, family history of hypertension, or educational level ($P > 0.05$). See **Table 1**.

Table 2. Comparative analysis of therapeutic effectiveness

Curative effect	Control group (n=56)	Research group (n=66)	χ^2	P
Marked effectiveness	25 (44.64)	35 (53.03)		
Effectiveness	21 (37.50)	28 (42.42)		
Ineffectiveness	10 (17.86)	3 (4.55)		
Overall effectiveness	46 (82.14)	63 (95.45)	5.639	0.018

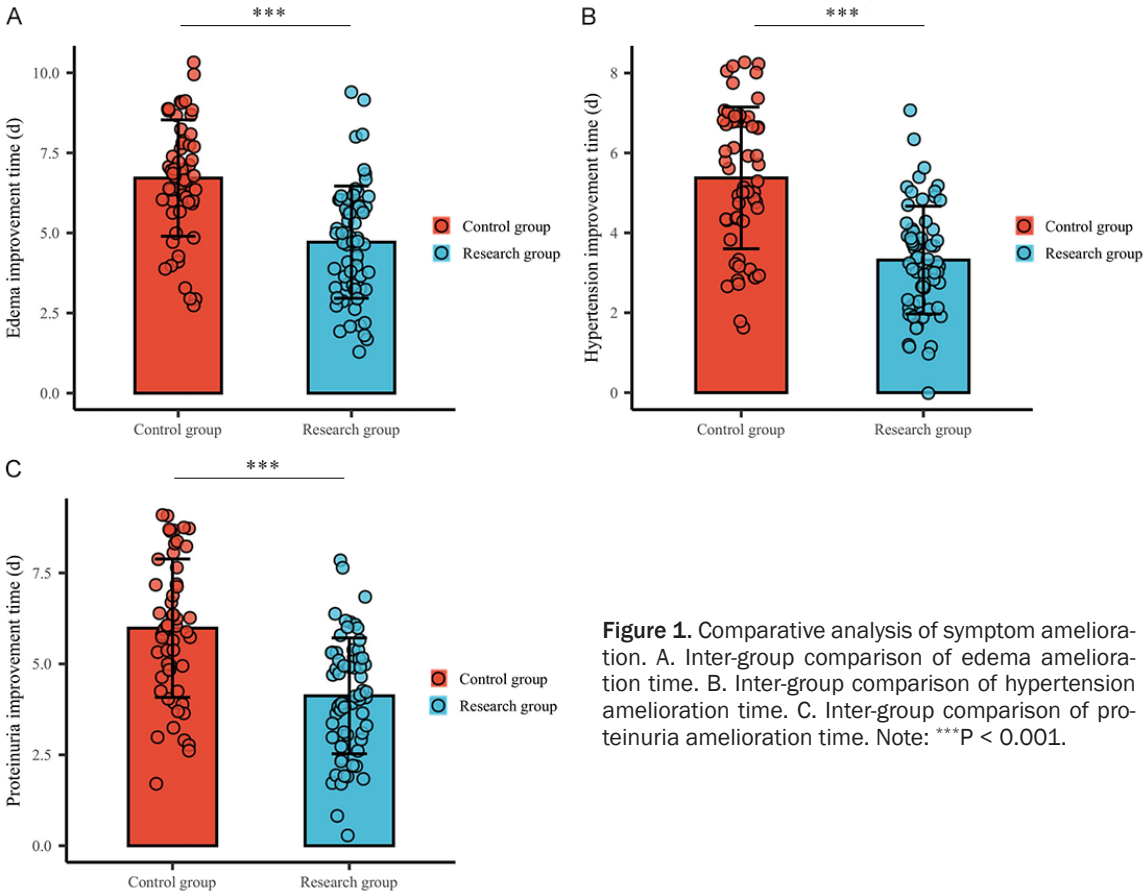

Figure 1. Comparative analysis of symptom amelioration. A. Inter-group comparison of edema amelioration time. B. Inter-group comparison of hypertension amelioration time. C. Inter-group comparison of proteinuria amelioration time. Note: ***P < 0.001.

Comparative analysis of therapeutic effectiveness

The overall effectiveness rates were 82.14% in the control group and 95.45% in the research group, indicating a significantly superior therapeutic effectiveness in the research group (P < 0.05). See **Table 2**.

Comparative analysis of symptom amelioration

Statistical analysis of symptom improvement time (edema, hypertension, and proteinuria) revealed that the research group experienced significantly shorter time to symptom amelioration in all measured aspects (P < 0.05). See **Figure 1**.

Comparative analysis of brain symptoms and signs

The overall incidence of brain symptoms and signs, including nausea and vomiting, sluggishness, blurred vision, and dizziness or headache, was significantly lower in the research group than that in the control group (P < 0.05). See **Table 3**.

Contrastive analysis of pregnancy outcomes

The analysis of pregnancy outcomes revealed that the total incidence of adverse events-such as placental abruption, neonatal asphyxia, fetal distress, and postpartum hemorrhage-was significantly lower in the research group than that

Table 3. Comparative analysis of brain symptoms and signs

Brain symptoms and signs	Control group (n=56)	Research group (n=66)	χ^2	P
Nausea and vomiting	3 (5.36)	1 (1.52)		
Sluggishness	1 (1.79)	0 (0.00)		
Blurred vision	2 (3.57)	1 (1.52)		
Dizziness and headache	2 (3.57)	0 (0.00)		
Total	8 (14.29)	2 (3.03)	5.100	0.024

Table 4. Comparative analysis of pregnancy outcomes

Pregnancy outcomes	Control group (n=56)	Research group (n=66)	χ^2	P
Placental abruption	1 (1.79)	0 (0.00)		
Neonatal asphyxia	2 (3.57)	0 (0.00)		
Fetal distress	2 (3.57)	0 (0.00)		
Postpartum hemorrhage	2 (3.57)	1 (1.52)		
Total	7 (12.50)	1 (1.52)	5.966	0.015

in the control group (1.52% vs. 12.50%, $P < 0.05$). See **Table 4**.

Comparative analysis of blood pressure and fetal umbilical artery hemodynamics

A comparative analysis of blood pressure indicators (SBP and DBP) and fetal umbilical artery hemodynamic indicators (S/D and PI) showed no significant inter-group differences in these indicators prior to medication ($P > 0.05$). However, all indicators in both groups were significantly reduced after medication ($P < 0.001$), with the research group achieving even lower levels ($P < 0.05$). See **Figure 2**.

Comparative analysis of serum biochemical indicators

The hs-CRP levels were similar in both groups prior to medication ($P > 0.05$). After medication, hs-CRP levels showed a significant decline in both groups ($P < 0.001$), with the research group displaying even lower levels ($P < 0.01$). See **Figure 3**.

Discussion

HDP, as the most common complication during pregnancy, not only impairs the antioxidant capacity and immunity of pregnant women but also results in insufficient blood supply to the fetus, contributing to adverse pregnancy outcomes [23]. Furthermore, HDP has long-term negative effects on health, increasing the risk of hypertension and other cardiovascular diseases in both patients and their newborns later in life [24]. To mitigate the detrimental effects of HDP, identifying an effective and clinically safe treatment regimen is essential.

After evaluating the curative effects, the overall effectiveness rate was found to be significantly higher in the research group compared to the control group (95.45% vs. 82.14%). This demonstrates that treating HDP with a combination of LBT and $MgSO_4$ can maximize therapeutic effectiveness. This effect may be attributed to the promotion of endogenous kallikrein expression under the combined action of LBT and $MgSO_4$, along with the effective downregulation of pregnancy-related hypertension predictors such as pregnancy-associated plasma protein A (PAPP-A), pregnancy-specific β1-glycoprotein (SP1), placental growth factor (PLGF), human placental lactogen (HPL), transforming growth factor β1 (TGF-β1), and vascular cell adhesion molecule-1 (VCAM-1) [25]. In terms of symptom amelioration, statistical analysis revealed that the LBT + $MgSO_4$ treatment significantly shortened the time required for the improvement of symptoms such as edema, hypertension, and proteinuria. This highlights the efficacy of LBT + $MgSO_4$ in alleviating clinical manifestations in HDP patients.

Furthermore, the total incidence of brain symptoms and signs, including nausea and vomiting, sluggishness, blurred vision, and dizziness or headache, was significantly lower in the research group than that in the control group. This suggests that LBT + $MgSO_4$ is effective in re-

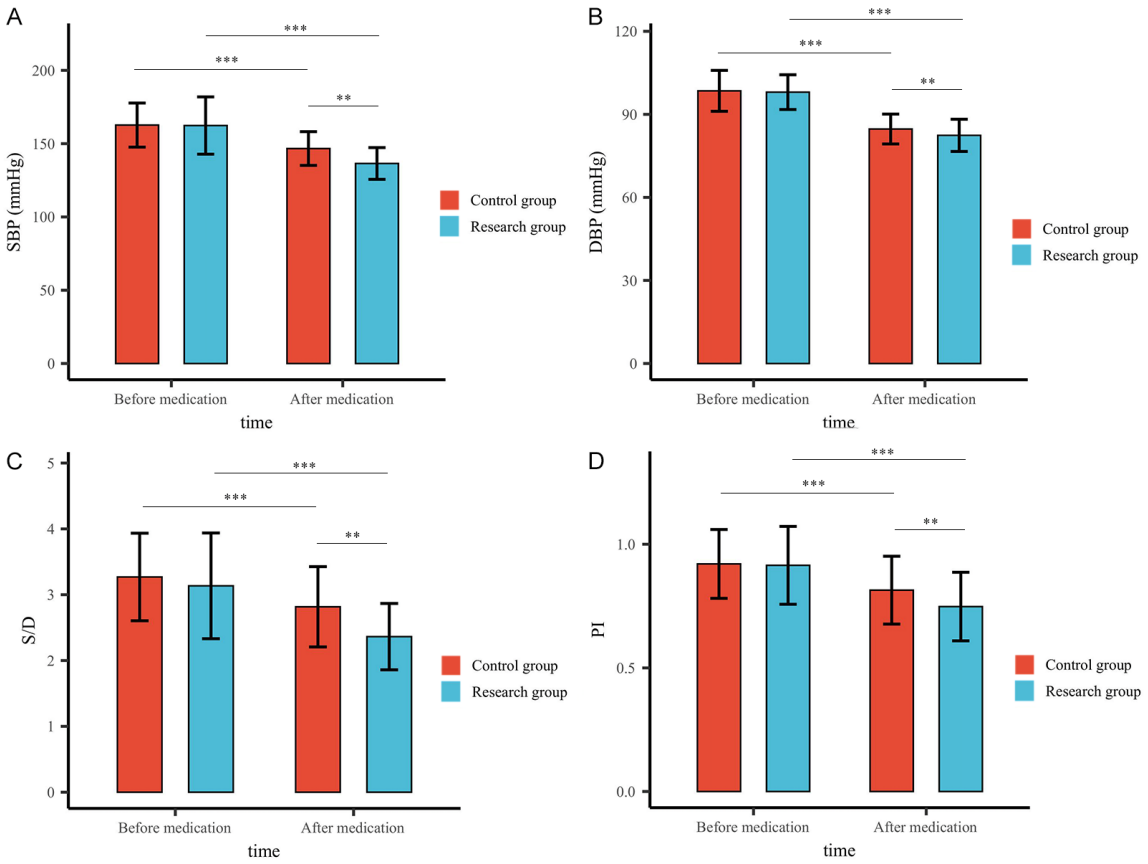

Figure 2. Comparative analysis of blood pressure and fetal umbilical artery hemodynamics. A. Inter-group comparison of systolic blood pressure (SBP). B. Inter-group comparison of diastolic blood pressure (DBP). C. Inter-group comparison of systolic-to-diastolic flow velocity ratio (S/D). D. Inter-group comparison of pulsatility index (PI). Note: $^{**}P < 0.01$; $^{***}P < 0.001$.

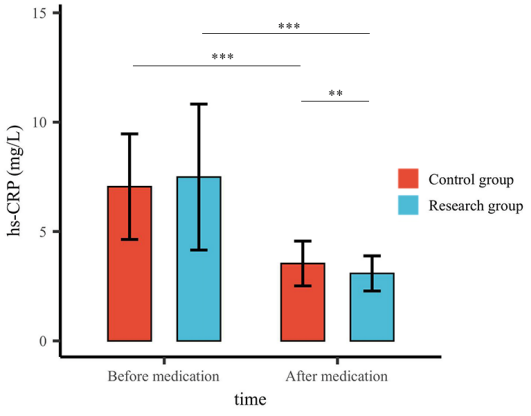

Figure 3. Comparative analysis of high-sensitivity C-reactive protein (hs-CRP). Note: $^{**}P < 0.01$; $^{***}P < 0.001$.

ducing the risk of cerebral symptoms and signs in HDP patients. It has been established that these brain symptoms in HDP patients are partially associated with factors such as an abrupt decline in estrogen levels, postpartum depression, sleep deprivation, and the emotional stress of adapting to new maternal roles [26, 27]. In the research conducted by Wang et al. [13], it was demonstrated that the application of LBT combined with $MgSO_4$ in the treatment of HDP effectively regulates blood pressure while alleviating anxiety and depressive moods. This partially explains the positive impact of this therapeutic regimen on cerebral symptoms and related manifestations.

Regarding pregnancy outcomes, the research group exhibited a significantly lower overall incidence of adverse events such as placental abruption, neonatal asphyxia, fetal distress, and postpartum hemorrhage. These findings highlight the clinical safety of LBT + $MgSO_4$ in reducing the risk of such complications. The manifestation of these adverse conditions in HDP patients is often linked to elevated blood pressure and insufficient uterine and placental

blood supply, which negatively impact fetal oxygen and nutrient absorption in utero [28]. LBT exerts its therapeutic effects by dilating blood vessels, reducing cardiac load and myocardial oxygen consumption, and increasing cardiac output, thereby stabilizing blood pressure, controlling symptoms, and preventing adverse events [29, 30]. Additionally, $MgSO_4$, through its antagonistic action on calcium ions (Ca^{2+}), not only counteracts convulsions but also facilitates blood pressure reduction via vascular dilation. This action enhances microcirculation and helps avert hypertensive crises [31, 32]. In a study by Wang et al. [33], the use of LBT + $MgSO_4$ in patients with early-onset severe preeclampsia was shown to significantly improve treatment effectiveness and pregnancy outcomes, aligning with our findings. Similarly, study of Liu et al. [34] suggests that the combination of $MgSO_4$ and LBT for HDP patients maximizes therapeutic effects, reduces adverse birth outcomes, and improves uterine artery hemodynamics, further supporting our results.

In this study's analysis, significant reductions in SBP, DBP, S/D, PI, and hs-CRP levels were observed in the research group following the treatment, with these reductions being significantly greater than those in the control group. This indicates that LBT + $MgSO_4$ not only lowers blood pressure and enhances uterine-placental-fetal circulation but also inhibits excessive inflammatory responses. As an inflammatory cytokine, hs-CRP can predict the severity of preeclampsia and, to some extent, forecast SBP levels and adverse fetal outcomes in HDP patients [35, 36]. In the study conducted by Gu et al. [37], the combination of LBT and $MgSO_4$ in HDP patients significantly reduced SBP, DBP, whole blood viscosity, plasma viscosity, hematocrit, and homocysteine levels. These findings suggest that this combination not only helps control blood pressure and improve hemodynamics but also significantly alleviates inflammation and stress, aligning with our observations. Additionally, Patel et al. [30] found that LBT was effective in controlling blood pressure in cases of severe HDP, demonstrating a higher efficiency in blood pressure control compared to hydralazine, which further validates our results. Similarly, research by Mowafy et al. [38] showed that LBT treatment in preeclampsia patients with severe features significantly lowered cerebral perfusion pressure, blood pressure, and heart rate, thereby improving cerebral blood flow, a finding consistent with our study outcomes. Regarding mechanisms, the improvement of umbilical artery hemodynamics in HDP patients treated with LBT may be partly attributed to its role in inhibiting platelet aggregation and reducing thromboxane levels. Furthermore, LBT has been found to accelerate fetal lung maturation, which adds to its therapeutic benefits [39].

The innovation of this research lies in its comprehensive validation of the clinical efficacy, safety, and various other clinical benefits of LBT combined with $MgSO_4$ in treating patients with HDP. This evaluation encompasses multiple perspectives, including therapeutic effectiveness, symptom amelioration, brain symptoms and signs, pregnancy outcomes, blood pressure indices, fetal hemodynamics, and serum hs-CRP. The results consistently demonstrate that LBT + $MgSO_4$ offers more pronounced clinical advantages across all these aspects compared to $MgSO_4$ alone, positioning it as a preferred treatment option for patients with HDP.

In conclusion, the combination of LBT and $MgSO_4$ significantly improves umbilical artery hemodynamics, reduces serum inflammatory responses, and enhances neurological function. Furthermore, it markedly increases therapeutic effectiveness, alleviates symptoms, prevents brain symptoms, and reduces the incidence of adverse pregnancy outcomes and excessive blood pressure levels.

Disclosure of conflict of interest

None.

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