

## Efficacy of Magnesium Sulfate and Labetalol in the Treatment of Pregnancy-Induced Hypertension and Its Effect on Anxiety and Depression: A Retrospective Cohort Study

### ABSTRACT

**Background:** In this study, the effect of magnesium sulfate and labetalol in treating pregnancy-induced hypertension (PIH) and its influence on anxiety and depression in patients are observed, and new ideas for treating anxiety and depression in PIH are introduced.

**Methods:** A retrospective cohort study was conducted to select patients with PIH diagnosed from July 2020 to July 2023 from Affiliated Hospital of Electronic Science and Technology University and Chengdu Women's and Children's Central Hospital in Chengdu of Sichuan Province. The changes in blood pressure, Edinburgh Postnatal Depression Scale (EPDS), and generalized anxiety disorder 7 (GAD-7) in patients with hypertensive pregnancy were collected and analyzed.

**Results:** In our investigation, 219 patients completed the study, and 36.1% (79/219) of them developed anxiety and depression. According to whether the patients were treated with magnesium sulfate and labetalol, 49 cases were assigned to the magnesium sulfate and labetalol treatment (MSLT) group, and 30 cases were assigned to the conventional treatment (CT) group. Edinburgh Postnatal Depression Scale scores and GAD-7 scores in the MSLT group were significantly lower than those in the CT group, indicating that magnesium sulfate and labetalol can improve anxiety and depression in hypertensive patients during pregnancy. The difference was statistically significant ( $P < .05$ ). According to the changes in systolic blood pressure, the clinical efficacy of patients was evaluated, and no significant difference in efficacy existed between the MSLT and CT groups.







**Conclusion:** Magnesium sulfate and labetalol can control the blood pressure of patients with PIH and indirectly improve anxiety and depression in patients with PIH, thereby introducing new ideas for the treatment of PIH accompanied by anxiety and depression.

**Keywords:** Magnesium sulfate, labetalol, hypertension during pregnancy, anxiety, depressed mood

### Introduction

Pregnancy-induced hypertension (PIH), whose main clinical manifestations are hypertension and proteinuria, is a complication unique to pregnancy and one of the main causes of maternal and perinatal death, with an incidence of approximately 5%-10%.<sup>1</sup> Pregnancy-induced hypertension is a multifactorial disease, and its development is closely related to immunological and placental factors.<sup>2</sup> Previous studies have shown that renal diseases, diabetes mellitus, obesity, and chronic hypertension are risk factors for PIH.<sup>2</sup> In addition, psychological distress is an important factor which cannot be ignored.<sup>3</sup> Evidence shows that women with PIH experience more stress than healthy pregnant women and that women with preeclampsia generally experience higher levels of anxiety and stress than pregnant women without preeclampsia.<sup>4</sup> The symptoms of anxiety and depression are mainly characterized by remarkably low mood and decreased interest in activities in the past; they are also characterized



Siyi Wang   
Jiajia Zhang   
Tianying Zhu   
Xiaoxiao Xie   
Xin Xia   
Yan Li 

Department of Obstetrics, Affiliated Hospital of Electronic Science and Technology University, UESTC, Chengdu Women's and Children's Central Hospital, Sichuan, China

#### Corresponding author:

Yan Li  
✉ Liyanliyan2023@sina.com

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by substantial anxiety, depression, and loss of interest and sense of pleasure.<sup>5</sup> Anxiety and depression are mood disorders characterized by persistent and obvious depression, which seriously affects work, life, and the exercise of social functions and requires specialist treatment.<sup>6</sup> Anxiety and depression have different diagnoses as their severity increases. Although the clinical incidence of anxiety and depression is approximately 5%-10%, more than 30% of hypertensive patients during pregnancy have experienced different degrees of anxiety and depression.<sup>7</sup>

We found from the relevant literature that most patients with PIH are prone to anxiety and depression, which are highly unfavorable to blood pressure control.<sup>8</sup> Unfortunately, traditional antidepressants are associated with an increased risk of developing gestational hypertension.<sup>9</sup> Thus, finding a safe drug to fight depression is necessary. Magnesium sulfate, which can help patients relieve vasospasm, is a common drug used in the clinical treatment of PIH.<sup>10</sup> Magnesium deficiency may be observed in the bodies of people with depression.<sup>11</sup> Magnesium can directly induce depression for unclear reasons, which may be related to magnesium's effect on the neurotransmitter system.<sup>12</sup> Labetalol is mainly used to reduce blood pressure by blocking the expression of adrenergic receptors.<sup>13</sup> A long history of clinical practice has shown that magnesium sulfate and labetalol are dependable and effective drugs. Some studies reported that magnesium sulfate and labetalol may have a positive effect on improving anxiety and depression symptoms.<sup>14,15</sup> However, evidence in pregnant patients is insufficient. Therefore, we conducted a retrospective cohort study to investigate the effect of magnesium sulfate combined with labetalol in treating hypertensive pregnancy and, most importantly, to study its effect on anxiety and depression.

## Material and Methods

### Surveying the Scene

Patients with PIH from the Affiliated Hospital of Electronic Science and Technology University, UESTC, Chengdu Women's and Children's Central Hospital in Chengdu City of Sichuan Province were retrospectively included. The patients' exposure history, discovery mode, and treatment plan management mode were similar. For the ethics committee approval, the study was conducted following the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Affiliated Hospital of Electronic Science and Technology University, UESTC, Chengdu Women's and Children's Central Hospital (Approval Number: 202326; Date: February 23, 2023). In this retrospective observational study, we divided the patients into a magnesium sulfate and labetalol treatment (MSLT) group and a conventional treatment (CT) group based on whether the patients with PIH had used magnesium sulfate and labetalol during pregnancy. G-power, used to calculate sample size, effect size = 0.5,  $\alpha = 0.05$ ,  $1 - \beta = 0.8$ ,

and 2 tails, showed that the sample size is 40. Based on this result, we enrolled as many patients as possible.

The diagnostic criteria for PIH in this study were based on those stipulated in the national standard of the People's Republic of China and the Report of the Revision Committee of the Guidelines for the Prevention and Treatment of Hypertension.<sup>16</sup> The inclusion criteria of the survey subjects include (1)  $\geq 20$  years of age, (2) diagnosis of PIH, (3) singleton pregnancy, and (4) complete clinical data. The exclusion criteria of the survey objects include the following: (1) patients with PIH combined with diabetes, coronary heart disease, stroke, and other cardiovascular and cerebrovascular diseases; (2) clear diagnosis of secondary gestational hypertension, severe hepatic and renal insufficiency, and magnesium sulfate and labetalol drug allergy; (3) patients in critical condition, those who have difficulty evaluating the effectiveness and safety of drugs objectively, and those who cannot complete the self-rating scale because of factors such as educational level or comprehension barrier; (4) patients with mental illness.

### Retrospective Cohort Study Survey Method

The starting point of observation was the diagnosis time of hypertensive patients during pregnancy. The data from the observation period to the observation end were obtained from the field historical records. They included the follow-up data of case reports for hypertensive patients during pregnancy in Affiliated Hospital of Electronic Science and Technology University and Chengdu Women's and Children's Central Hospital in Chengdu of Sichuan Province, and the Edinburgh Postnatal Depression Scale (EPDS) scale and generalized anxiety disorder 7 (GAD-7) scale scoring data. The necessary information for missing or incorrect information was reviewed. We assessed the EPDS and GAD-7 of gravida at visits during the month before the expected date of confinement.

### Collected Content

**Key information:** Diagnosis date, treatment time, and treatment effect of hypertensive patients during pregnancy comprised the key information. The end states of observation included changes in blood pressure, EPDS score, and GAD-7 score in hypertensive patients during pregnancy. After subgrouping, the demographic information of gravida, the EPDS and GAD-7 data, and the treatment effectiveness between the 2 groups were compared.

**Demographic characteristics:** The demographic characteristics include age, body mass index (BMI), gestational hypertension incidence, gestational age during the survey, patients with pregnancy time, production time, patients' number of regular prenatal checkups, marital status, educational level, residential areas, and occupations.

**Clinical efficacy:** The main clinical efficacy index of magnesium sulfate and labetalol in treating hypertension during pregnancy is systolic blood pressure. The clinical efficacy was evaluated according to the following criteria in the Report of the Revision Committee of the Guidelines for Prevention and Treatment of Hypertension in China. Obvious effects: The clinical signs of pregnant women disappeared, the blood pressure dropped below the standard value (140/90 mmHg) and did not fluctuate, the urine protein decreased, and the pregnancy was safely maintained. Effective: The clinical symptoms of pregnant women were greatly improved, and the decrease in blood pressure was close to 90% of the standard value

## MAIN POINTS

- Of the patients with pregnancy-induced hypertension, 36.1% developed anxiety and depression.
- Magnesium sulfate and labetalol effectively controls the blood pressure of patients with pregnancy-induced hypertension.
- Magnesium sulfate and labetalol may improve anxiety and depression in patients with pregnancy-induced hypertension.

with small fluctuations. Ineffective: No change in blood pressure was observed in pregnant women, and clinical symptoms did not improve or aggravate. Total effective rate = (number of obvious effects cases + number of effective cases)/total number of cases per group  $\times$  100%.

**Anxiety and depression:** The method we use to evaluate depression is EPDS scale score. Edinburgh Postnatal Depression Scale is a psychological scale developed by Cox in 1987 and it is widely used in the West.<sup>17</sup> The total score of the EPDS scale ranges from 0 to 30 points. The higher the total score is, the more severe the depressive symptoms are. Ten questions exist, among which the forward score is 1.2.4, and the reverse score is 3.5.6.7.8.9.10. A score of 0 to 9 indicates no depression. A score of 10 to 12 indicates possible mild depression. A score of 13 or higher indicates moderate to severe depression. The reliability coefficient of EPDS was 0.94, and the content validity index was 0.98.

The method we use to evaluate anxiety is GAD-7. Generalized anxiety disorder 7 was developed by Spitzer et al. to screen generalized anxiety and assess symptom severity.<sup>18</sup> The GAD-7 scale score consists of 7 items, and the description of each item is divided into 4 levels, assigned 0 to 3 points in that order. A score of 0 means none at all, a score of 1 means it happens on a few days, a score of 2 means it happens on more than half of the days, and a score of 3 means it happens almost every day. The total score ranges from 0 to 21, with a high score indicating severe anxiety symptoms. A score of 0 to 4 indicates no anxiety disorder. A score of 5 to 9 indicates mild anxiety. A score of 10 to 14 indicates possible moderate anxiety. A score of 15 to 21 indicates severe anxiety. The reliability coefficient of GAD-7 was 0.96, and the content validity index was 0.92.

We assessed the EPDS and GAD-7 scores of gravida at visits during the month before the expected date of confinement. We were the first to obtain their scores and, therefore, determine the presence of anxiety or depressive symptoms. The obstetrician responsible for regular follow-up during pregnancy was the first to diagnose PIH.

### Quality Control

All the data collected by the retrospective cohort study was collected by 3 postgraduate students who had been uniformly trained. The requirements for filling in the questionnaire were explained using uniform guidelines. The principles of informed consent and voluntary participation were followed, and the quality of the questionnaire was ensured. All questionnaires were collected and verified on the spot if the contents of the questionnaire were filled in with the investigator's assistance. Before data entry, questionnaires with items missing more than 10% were excluded. The data of qualified questionnaires was recorded into Excel software in 2 pairs, the value range was set, and multiple checks were conducted to ensure the accuracy of data entry. We used uniform criteria for data collection and controlled the inclusion and exclusion criteria for study participants to reduce selection bias. The information was collected by 3 researchers to reduce detection bias. We tried to keep the data as complete as possible. Missing data should not exceed 5% of the total items. Thus, we do not handle missing data.

### Statistical Analysis

The data of all the hypertensive patients during pregnancy included in our study were established using Microsoft Excel 2016 software (Microsoft, Seattle, WA, USA). After logical verification, the data were imported into Statistical Package for the Social Sciences (SPSS)

version 26.0 (IBM SPSS Corp.; Armonk, NY, USA) software for data analysis. The mean (SD) or quartiles were used to describe continuous data, and percentages were used to describe categorical data. Categorical data were compared using the chi-square test. Student's *t*-test was used to compare normally distributed data. The significance level of statistical tests with a *P*-value of  $<.05$  indicated a significant statistical difference.

## Results

### General Comparison of Survey Results

During the investigation and follow-up, 11 patients had missing questionnaire items and were lost to follow-up. The remaining 219 patients with anxiety depression were 36.1% (79/219). Out of 219 patients with depression and anxiety, 79 were investigated. The patients were grouped according to whether they were treated with magnesium sulfate and labetalol: 49 cases were in the MSLT group, and 30 cases were in the CT group. The average age at diagnosis of gestational hypertension, BMI, gestational age at onset, gestational age at the time of investigation, gestational times, parity, patients' access to regular antenatal examination, marital status, education level, residential area, and occupation were analyzed (Table 1).

**Table 1.** General Comparison of Survey Results

	MSLT Group (n = 49)	CT Group (n = 30)	t/x <sup>2</sup>	P
Average age (years)	29.8 (SD = 3.3)	29.8 (SD = 4.9)	0.634	.756
BMI (kg/m <sup>2</sup> )	31.5 (SD = 3.5)	31.8 (SD = 3.3)	0.527	.265
Gestational age at onset (week)	23.0 (SD = 2.6)	23.6 (SD = 2.8)	0.818	.834
Gestational age during the survey (week)	32.5 (SD = 2.9)	32.8 (SD = 3.5)	0.068	.067
Number of pregnancies	3.3 (SD = 0.7)	3.3 (SD = 0.8)	0.539	.099
Number of production	3.5 (SD = 0.6)	3.5 (SD = 0.5)	0.235	.495
Regular prenatal examination (n)	-	-	0.315	.574
Yes	33	22	-	-
No	16	8	-	-
Marital status (n)	-	-	0.546	.460
Married	45	26	-	-
Divorced	0	0	-	-
Widowed	0	0	-	-
Unmarried	4	4	-	-
Cultural degree (n)	-	-	0.626	.429
High school and the following	30	21	-	-
More than a high school	19	9	-	-
Professional (n)	-	-	0.262	.609
Mental work	35	23	-	-
Manual labor	14	7	-	-
Area of residence (n)	-	-	0.000	.989
Towns	36	22	-	-
Villages	13	8	-	-

CT, conventional treatment; MSLT, magnesium sulfate and labetalol treatment; BMI, Body Mass Index.

**Table 2.** Comparison of Anxiety and Depression ( $\pm$  SD Score)

	EPDS Score	GAD-7 Score
MSLT group (n = 49)	9.1 (SD = 2.6)	7.9 (SD = 1.8)
CT group (n = 30)	10.3 (SD = 1.6)	9.8 (SD = 1.2)
<i>t</i>	2.275	3.234
<i>P</i>	.026	.002

CT, conventional treatment; EPDS, Edinburgh Postnatal Depression Scale; GAD-7, generalized anxiety disorder 7; MSLT, magnesium sulfate and labetalol treatment.

### Comparison of Anxiety and Depression

According to statistical calculation, the EPDS and GAD-7 scores of patients in the MSLT group were significantly lower than those of patients in the CT group, indicating that magnesium sulfate and labetalol could improve anxiety and depression in hypertensive patients during pregnancy. The difference was statistically significant ( $P < .05$ ; Table 2).

### Clinical Curative Effect Comparison

According to the change in systolic blood pressure, no significant difference existed between the total effective rate (83.6%) in the MSLT group and that (80%) in the CT group (Table 3).

### Discussion

Our study found that treating PIH using magnesium sulfate and labetalol has the same effect on blood pressure control as CT. The reasons are as follows. Labetalol can significantly dilate, increase volume, and reduce the resistance of blood vessels in hypertensive patients during pregnancy.<sup>19</sup> Patients with gestational hypertension can also have a certain delay effect on the typical sinus rhythm in gestational hypertension.<sup>20</sup> Magnesium sulfate has a drug mechanism of inhibiting chemical transmission between nerve and neuromuscular tubercle synapses and has a significant effect on vasospasm and neurosis of hypertensive patients during pregnancy.<sup>21</sup> However, magnesium sulfate has side effects; thus, the dosage of drugs used in treating hypertensive patients during pregnancy is limited to a certain extent, resulting in unsatisfactory effects.<sup>22</sup> However, the drug force can be exerted well by combining labetalol and magnesium sulfate; the combination of labetalol and magnesium sulfate has good clinical effects for controlling blood pressure, improving vasospasm, reducing heart rhythm, and preventing anxiety and depression in patients with gestational hypertension.<sup>23</sup>

We conducted a retrospective cohort study and found that 36.1% of patients with gestational hypertension in the MSLT group have anxiety and depression; this finding is consistent with previous literature reports.<sup>24</sup> Although the pathogenesis and clinical manifestations of hypertension during pregnancy are different, the main characteristics include elevated blood pressure and damage to the heart, brain,

liver, and kidney.<sup>25</sup> Therefore, a series of pathophysiological or psychological changes in hypertensive patients during pregnancy may lead to anxiety, depression, and other adverse emotional states.<sup>26</sup> Anxiety and depression are common adverse emotions during pregnancy, and such psychological changes have negative effects on the mother and the fetus.<sup>27</sup> Relevant studies have shown that the incidence of hypertension and depression during pregnancy is 21.7%, and anxiety has a similar prevalence of approximately 21.5%, which tends to worsen with the progress of pregnancy.<sup>28</sup> The prevalence of moderate-to-severe depression in pregnant women with preeclampsia is 31.2%.<sup>29</sup> The above literature reports are similar to our findings. Our research results and related literature reports show that the EPDS and GAD-7 scores of patients in the MSLT group were significantly lower than those of patients in the CT group, indicating that magnesium sulfate and labetalol can improve anxiety and depression in hypertensive patients during pregnancy. The specific mechanism is analyzed as follows. The action mechanism of magnesium sulfate is to reduce the blood pressure of patients with gestational hypertension by inhibiting the secretion of acetylcholine in nerve tissue and muscle, reducing muscle contraction, soothing vascular smooth muscle, keeping skeletal muscle smooth and relaxed, and expanding peripheral blood vessels.<sup>30</sup> Labetalol antagonizes the production of  $\alpha$  and  $\beta$  receptors in patients with gestational hypertension, thereby increasing vascular blood volume and reducing peripheral vascular resistance in patients with gestational hypertension.<sup>31</sup> Magnesium sulfate and labetalol have synergistic properties. Thus, the combined administration can improve the antihypertensive effect. Magnesium sulfate is a kind of N-methyl-D-aspartate receptor antagonist, which may have antidepressant effects.<sup>32</sup> These findings may explain our result. Other studies also found a similar effect of magnesium sulfate.<sup>33</sup>

Anxiety and depression are common psychiatric conditions that are burdensome to the general population and require considerable attention when diagnosed in a pregnant woman. Anxiety and depression have several risk factors.<sup>34</sup> The high prevalence of anxiety and depression in patients with PIH indicates that PIH and anxiety and depression are interrelated. First, anxiety and depression have overlapping risk factors with PIH.<sup>35</sup> Abnormal hypercoagulability and platelet activation have been observed in pregnant hypertensive patients with severe anxiety and depressive symptoms. This scenario is also observed in a common pathophysiological process among hypertensive patients during pregnancy.<sup>36</sup> Relevant studies have confirmed that the activity of coagulation factors II, VI, VII, IX, and X in hypertensive patients during pregnancy increases, and plasminase significantly increases.<sup>37</sup> The pathophysiological processes shared by PIH patients and the symptoms of anxiety and depression may be parts of the potential mechanisms of their correlation.<sup>38</sup> Second, anxiety, depression, and PIH are involved in the abnormal activation of the sympathetic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis.<sup>39</sup> High stress in patients with anxiety and depression can activate the sympathetic nervous system and the HPA axis, and the levels of corticotropin-releasing hormone and catecholamine in the body can be increased.<sup>23</sup> In previous studies, elevated levels of corticotropin-releasing hormone and increased sympathetic nerve activity were also observed in preeclampsia patients.<sup>40</sup> Therefore, we speculate that the abnormal activation of the sympathetic nervous system and HPA axis is one of the reasons for the increased prevalence of anxiety and depression in hypertensive patients during

**Table 3.** Clinical Curative Effect Comparison

	Obvious Effect			Total Effective Rate (%)
	Effective	Ineffective		
MSLT group (n = 49)	19	22	8	83.6 (41/49)
CT group (n = 30)	15	9	6	80.0 (24/30)
$\chi^2$	–	–	–	0.172
<i>P</i>	–	–	–	.678

CT, conventional treatment; MSLT, magnesium sulfate and labetalol treatment.



pregnancy.<sup>41</sup> Finally, the disease itself and the treatment process of PIH can cause anxiety and depression.<sup>42</sup> Long-term blood pressure monitoring, frequent outpatient visits, and oral antihypertensive drugs should be taken before admission. These measures can lead to a psychological pressure for patients to be admitted at any time. Therefore, these preventive and therapeutic measures may instead lead to high blood pressure, anxiety, and depression during pregnancy.

Our study still has some shortcomings. Firstly, the retrospective study design is less persuasive than prospective. Secondly, the single-center study limits the further generalization of our findings to the whole country and the world. Lastly, our study fails to show how magnesium sulfate improves depressive symptoms at the mechanistic level. In summary, we collected and analyzed the data of hypertensive patients during pregnancy through a retrospective cohort study and found that magnesium sulfate and labetalol can improve anxiety and depression in hypertensive patients during pregnancy. Moreover, magnesium sulfate and labetalol can control blood pressure and indirectly improve anxiety and depression, thereby introducing new ideas for treating PIH accompanied by anxiety and depression.

Magnesium sulfate with labetalol is effective in controlling PIH. It may have a positive effect on relieving symptoms of depression or anxiety caused by PIH. In addition to controlling blood pressure, magnesium sulfate and labetalol treatment also relieves anxiety and depression.

**Availability of Data and Materials:** The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

**Ethics Committee Approval:** This study was approved by the Ethics Committee of the Affiliated Hospital of Electronic Science and Technology University, UESTC, Chengdu Women's and Children's Central Hospital (Approval Number: 202326; Date: February 23, 2023).

**Informed Consent:** Informed consent was obtained from the patients who agreed to take part in the study.

**Peer-review:** Externally peer-reviewed.

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