ORIGINAL RESEARCH ARTICLE

Effectiveness of placental blood perfusion monitoring of nitroglycerin and labetalol in treatment of women with pregnancy-induced hypertension

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Abstract

This was an original study and elucidated the value of placental blood perfusion monitoring based on quantitative three-dimensional (3D) power Doppler ultrasound in evaluating the efficacy of nitroglycerin and labetalol in treating pregnancy-induced hypertension (PIH). Eighty PIH patients admitted in The Second Affiliated Hospital from October 2021 to October 2023 were divided into mild PIH group (Group A) and severe PIH group (Group B). Another 50 healthy pregnant women without PIH were selected as the control group (CG). Groups A and B received a combination treatment of nitroglycerin and labetalol. The TNF-α levels in Group A and B were higher relative to those in CG. Relative to before treatment, Group A and B had higher vascularization index (VFI), flow index (FI), and placental vascularization index (VI), higher middle cerebral artery pulsatility index (PI) and Apgar scores and lower left uterine artery PI and right uterine artery PI after treatment. After treatment, there was statistical significance in placental VI, FI, and VFI under different efficacy grades. We conclude that the application of quantitative 3D power Doppler ultrasound technology can accurately monitor the therapeutic effect of nitroglycerin and labetalol in treatment of pregnant women with PIH. *(Afr J Reprod Health 2025; 29 [2]: 61-68).*

Keywords: Pregnancy-induced hypertension; hypertensive disorders complicating pregnancy; placental blood perfusion; three-dimensional power Doppler ultrasound; drug therapy

Résumé

Il s'agissait d'une étude originale qui a élucidé la valeur de la surveillance de la perfusion sanguine placentaire basée sur l'échographie Doppler quantitative tridimensionnelle (3D) pour évaluer l'efficacité de la nitroglycérine et du labétalol dans le traitement de l'hypertension induite par la grossesse (PIH). Quatre-vingts patients PIH admis dans le deuxième hôpital affilié d'octobre 2021 à octobre 2023 ont été divisés en groupe PIH léger (groupe A) et groupe PIH sévère (groupe B). 50 autres femmes enceintes en bonne santé sans PIH ont été sélectionnées comme groupe témoin (CG). Les groupes A et B ont reçu un traitement combiné de nitroglycérine et de labétalol. Les niveaux de TNF-α dans les groupes A et B étaient plus élevés que ceux du groupe CG. Par rapport à avant le traitement, les groupes A et B présentaient un indice de vascularisation (VFI), un indice de débit (FI) et un indice de vascularisation placentaire (VI), un indice de pulsatilité de l'artère cérébrale moyenne (PI) et des scores d'Apgar plus élevés, ainsi qu'un PI de l'artère utérine gauche inférieure et un PI de l'artère utérine droite après le traitement. Après le traitement, il y avait une signification statistique des VI, FI et VFI placentaires sous différents niveaux d'efficacité. Nous concluons que l'application de la technologie quantitative d'échographie Doppler de puissance 3D peut surveiller avec précision l'effet thérapeutique de la nitroglycérine et du labétalol dans le traitement des femmes enceintes atteintes de PIH. *(Afr J Reprod Health 2025; 29 [2]: 61-68).*

Mots-clés: Hypertension induite par la grossesse ; troubles hypertensifs compliquant la grossesse ; perfusion sanguine placentaire; échographie Doppler de puissance tridimensionnelle ; thérapie médicamenteuse

Introduction

Hypertensive disorders complicating pregnancy (HDCP) are one of the common and serious complications of pregnancy[1,2]. In recent years, with opening of the two-child policy in China and increase of maternal age, incidence rate of HDCP has risen in China. HDCP, as a major reason for

maternal and perinatal morbidity and mortality, seriously impacts physical and mental health along with quality of life of mothers and infants[3,4].

Currently, drug therapy feature as management options for pregnancy-induced hypertension (PIH) in clinical practice[5]. Some of these include central antihypertensive drugs, B receptor and G receptor blockers, calcium channel blockers, direct vasodilators, diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor antagonists[6,7]. Nevertheless, the impact on embryonic and fetal growth and development must be considered when these drugs are applied during pregnancy. There are often significant differences in therapeutic effects and safety of different antihypertensive drugs, whereas there is currently a lack of effective evaluation methods for efficacy and safety[8,9].

In recent years, with improvement of three-dimensional (3D) ultrasound colour sensitivity and advancement of related software technologies, ultrasound examination technology can quantitatively analyze placental blood perfusion to evaluate condition and prognosis of patients with preeclampsia (PE), a major component of PIH[10,11]. Based on this, the objective of this study was to assess the effectiveness of the application of placental blood perfusion monitoring based on 3D power Doppler ultrasound in evaluating the efficacy of nitroglycerin and labetalol in treatment of PIH. Our study indicated that quantitative 3D power Doppler ultrasound technology was effective to monitor the therapeutic effectiveness of nitroglycerin combined with labetolol in pregnant women with PIH, which may be provided for the clinical diagnosis, objective evaluation, and treatment of PIH.

Methods

Eighty PIH patients receiving treatment in The Second Affiliated Hospital from October 2021 to October 2023 were chosen for this study. According to the classification criteria for HDCP in the 8th edition of the *Obstetrics and Gynecology*[12], the patients were divided into the mild PIH group (Group A; 32 cases) and severe PIH group (Group B; 48 cases). Another 50 healthy pregnant women without PIH were selected as the control group (CG). As shown in Table 1, there were no statistical significant differences in the socio-demographic characteristics between the three groups ($P > 0.05$). The inclusion criteria included singleton pregnancies with normal and healthymenstruation before pregnancy, with history of other comorbidities or drug allergies. All completed routine prenatal examinations and all cases met the diagnostic criteria for PE.

The exclusion criteria were women with complicated high-risk pregnancy conditions such as placenta previa and placental abruption, those with with trauma and systemic infectious diseases, family histories of hereditary diseases, those without a history of allergic reactions to nitroglycerin or labetalol, and those with heart, liver, and kidney diseases.

Treatment methods

Both Group A and Group B received a combination treatment of nitroglycerin and labetalol. Both groups underwent administration with nitroglycerin injection (G. Y. Z. Zi. H44020569; Guangzhou Baiyunshan Ming Xing Pharmaceutical Co., Ltd.) for therapy. Nitroglycerin was diluted with 5% glucose, followed by intravenous infusion with an infusion pump at a constant rate of 5 ug/min. The dosage of medication was adjusted based on blood pressure control. If the patients' blood pressure did not decrease markedly, dosage was received increase by 5 ug/min every 3-5 min. The above process occurred once a day. Both groups also received treatment with labetalol (G. Y. Z. Zi. H32026120; Jiangsu Desano Pharmaceutical Co., Ltd.). Oral administration received conduction after meals, 100 mg each time, three times a day, for one week.

Examination methods

The GE VOLUSON 730 color Doppler ultrasound diagnostic instrument[13] and matching abdominal volume probe received application for examination, with a probe frequency of 4-8 MHz. Routine two-dimensional (2D) ultrasound examination received performance to measure fetal biparietal diameter, head circumference, femur length, abdominal girth, amniotic fluid, placental maturity, etc.

Table 1: General data in three groups

General data		CG	Group A	Group B	χ^2/F	P
N		**50**	**32**	**48**		
Age (mean±SD) years)		30.2±3.5	30.4±3.4	30.7±2.7	0.3	0.9
Gestational age (mean±SD) (weeks)		32.5±2.8	31.5±3.0	31.8±2.0	1.1	0.6
Gravidity (Mean±SD		1.4±0.4	1.5±0.2	1.4±0.5	5.2	0.1
Parity [n (%)]	Multipara	18 (36.0)	10 (31.3)	17 (35.4)	0.2	0.9
	Primipara	32 (64.0)	22 (68.7)	31 (64.6)		

Then umbilical artery systolic/diastolic ratio (S/D), fetal middle cerebral artery pulsatility index (PI), and bilateral uterine artery PI of the pregnant women was measured. After obtaining the 2D ultrasonic parameters, the instrument parameters were adjusted to achieve the best effect of displaying low speed blood flow in placenta. The examination was conducted using power Doppler mode and 3D vascular mode while the fetus was in an apnea-like or quiet state. The placental position vertically entered by umbilical cord received consideration was the region of interest in 3D data box as it can clearly display all vascular bundles in chorionic villus template and placental basement membrane. During process of imaging, it was necessary to minimize the amplitude of pregnant women's breathing and check while they are holding their breath.

Observed indicators

The 2D ultrasound examination of umbilical artery S/D, bilateral uterine PI of pregnant women, and fetal central middle artery PI were measured.

The image depiction of 3D contours was shown through manual mode of VOCAL virtual organization computer-aided analysis software. Each section received rotation by 15° for a total of 12 depictions. The plane A received consideration as reference plane was used to draw a 3D power histogram. The ultrasound examination results were generated independently by analysis software 3 days before treatment and 2 weeks after treatment, including vascularization index (VFI), flow index (FI), and placental vascularization index (VI).

The therapeutic effect of drug therapy on HDCP was evaluated. Significant effectiveness: After treatment, the clinical signs and symptoms of patients disappeared, systolic and diastolic blood pressure decreased by more than 30 and 15 mmHg; Effectiveness: After treatment, the clinical signs and symptoms of patients were improved, systolic and diastolic blood pressure decreased within 10 mmHg; Ineffectiveness: After treatment, the patient's systolic and diastolic blood pressure did not meet the above criteria or increased. Fetal indexes and postpartum Apgar score were recorded and analyzed. All ultrasound measurement and analysis software were completed by two experienced imaging physicians.

The inflammatory cytokine TNF-α mRNA and protein levels in pregnant women were measured with the application of real-time q-PCR and enzyme-linked immunosorbent assay (ELISA) kits[14,15].

Statistical analysis

The research data were analysed using SPSS 27.0 statistical software. Quantitative data that conformed to normal distribution received determined by mean ± standard deviation, followed by nonparametric Kruskal Wallis test for intergroup comparisons. Count data is represented by N and %, followed by χ^2 test for intergroup comparisons. $P < 0.05$ meant a significant difference.

Ethical considerations

This research obtained approval by the Medical Ethics Committee of Jiangxi Maternal and Child Health Hospital in January 15, 2021, and the Ethics approval number was EC-KY-202127. All patients along with their family members signed informed consent.

Results

TNF-α protein and mRNA levels

Relative to the CG, the TNF-α protein and mRNA levels in patients with mild and severe PIH was higher ($P < 0.05$; Figure 1).

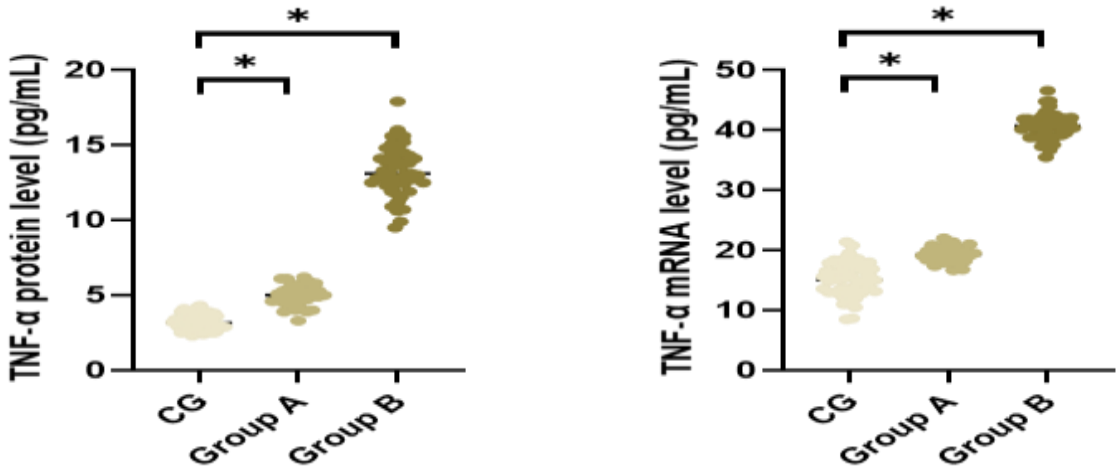

Figure 1: TNF-α protein and mRNA levels in three groups. *P < 0.05.

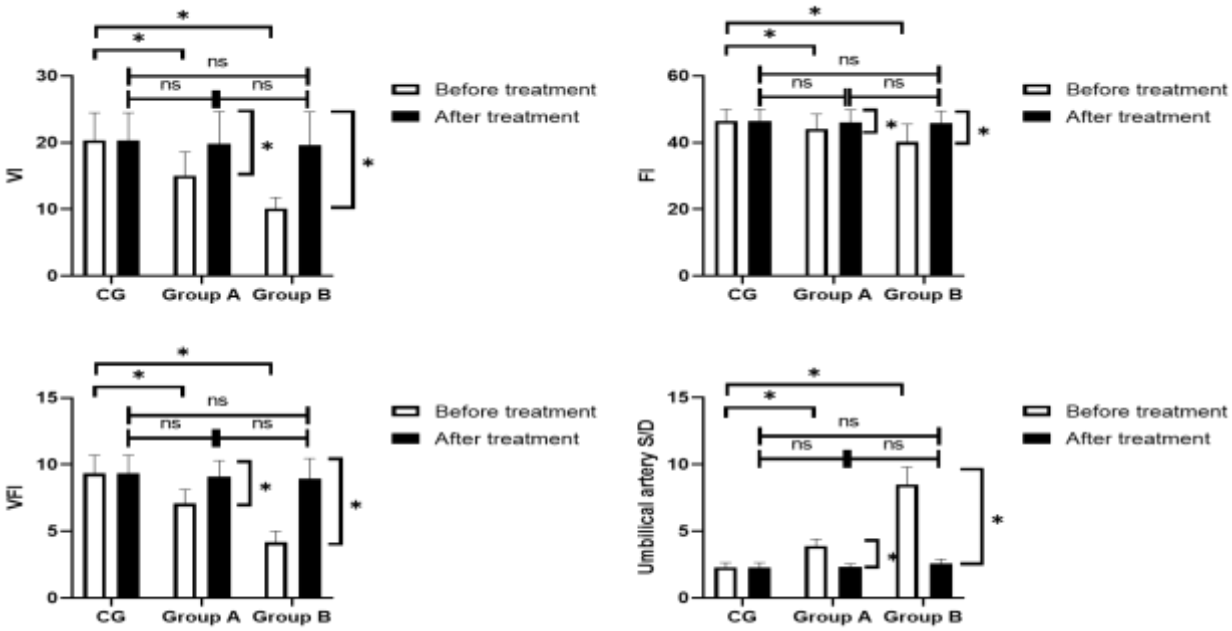

Figure 2: Test results of hemorheological indexes in three groups. *P < 0.05, ns meant P > 0.05.

Hemorheological indexes

Before treatment, VI, FI, and VFI in Group A and B were low relative to those in CG, while umbilical artery S/D in Group A and B were higher relative to that in CG (all P < 0.05). After treatment, VI, FI, and VFI in Group A and B were higher relative to those before treatment (P < 0.05). No statistical significance in hemorheological indexes were shown d between the three groups (P > 0.05; Figure 2).

2D ultrasound and 3D power index

Before treatment, the middle cerebral artery PI and Apgar scores in Group A and B exhibited were lower relative to those in CG, while the left uterine artery PI and right uterine artery PI in Group A and B were higher than those in CG (all P < 0.05).

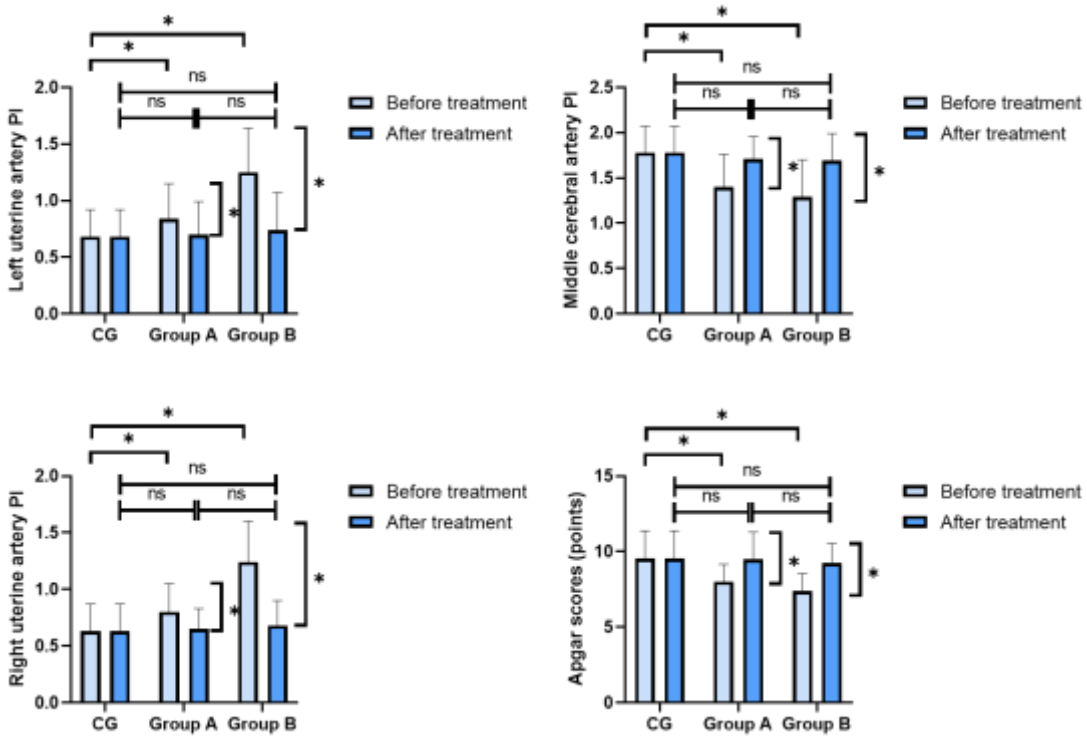

Figure 3: 2D ultrasound and 3D power index in three groups. *P < 0.05, ns meant P > 0.05.

Table 2: Total effective rate in both groups

Groups	N	Significant effectiveness	Effectiveness	Ineffectiveness	Total effective rate [n (%)]
Group A	32	18 (56.3)	12 (37.5)	2 (6.2)	30 (93.8)
Group B	48	30 (62.5)	14 (29.2)	4 (8.3)	44 (91.7)
χ^2					0.1
P					0.7

Table 3: Placental VI, FI, and VFI under different efficacy grades after drug therapy

Groups	Grading	N	VI	FI	VFI
Group A	Significant effectiveness	18	20.1±2.3	46.8±1.6	9.5±1.4
	Effectiveness	12	19.1±1.2	43.8±1.8	9.0±1.2
	Ineffectiveness	2	17.3±1.4	42.0±3.3	7.5±1.0
F			7.3	21.0	16.5
P			0.0	<0.001	<0.001
Group B	Significant effectiveness	30	19.2±2.1	45.8±2.0	9.0±1.1
	Effectiveness	14	16.8±1.3	43.2±2.3	7.9±1.2
	Ineffectiveness	4	12.2±1.9	41.1±2.8	5.7±1.0
F			25.2	15.6	20.0
P					

After treatment, the middle cerebral artery PI and Apgar scores in Group A and B were higher relative to those before treatment, while the left uterine artery PI and right uterine artery PI in Group A and B were lower as compared to those before treatment (all $P < 0.05$). There was no statistical significance in ultrasonic parameters between the three groups ($P > 0.05$; Figure 3).

Analysis on association of ultrasonic parameters and treatment efficacy

During treatment process, neither group experienced any serious adverse drug reactions or complications. The total treatment effective rate in Group A was slightly higher than Group B, but the difference was not statistically significant ($P > 0.05$; Table 2). After drug therapy, there was statistical significance in placental VI, FI, and VFI under different efficacy grades ($P < 0.05$; Table 3)

Discussion

Hypertension is the most common medical problem during pregnancy, seriously threatening the life and health of pregnant women and fetuses[16]. Currently, actively and quickly controlling blood pressure and maintaining good hemodynamic level can effectively avoid the occurrence of severe complications such as cerebral hemorrhage, eclampsia, and acute renal failure. Since the treatment of PIH needs to consider the effects and safety of acute blood pressure reduction in pregnant women and the fetus (or newborn), the choice of antihypertensive drugs and the timing of drug treatment should weigh the advantages and disadvantages of both.

Previous reports have depicted that application of 3D power Doppler ultrasound technology to detect maternal hemorheological indicators, effectively monitoring the patient's condition and evaluating treatment outcomes[17]. The selected 3D power Doppler ultrasound indicators include VFI, FI, and placental FI[18]. VFI is an indicator that reflects combination of vascular information and blood flow information, FI is an indicator that reflects the ability of blood perfusion, and placental VI is an indicator that reflects the fetal growth. Normal placental blood vessels are 3D dendritic. With fetal growth and maturity, the number of villous branches and tertiary villous arteries increases, blood vessels gradually thickens, blood flow velocity accelerates, and blood perfusion volume increases[19]. Quantitative 3D power Doppler ultrasound technology can monitor placental blood perfusion accurately, intuitively and dynamically, and in practical applications, it can monitor blood flow from multiple angles and sides[20].

Nitroglycerin can enter the fetal circulation through the placenta, but the therapeutic dose does not affect the fetal umbilical-placental blood circulation. On the contrary, it reduces the resistance of fetal placenta circulation, improves the intrauterine environment of the fetus, and is an ideal drug for the treatment of PIH[21]. However, when nitroglycerin is used to control PIH, increased doses can cause significant adverse effects, such as reflex tachycardia and severe headache[22], and large doses of nitroglycerin may affect fetal circulation. Labetalol is a competitive blocker with non-selective β receptor blockade. Labetalolol is associated with decreased heart rate and decreased myocardial oxygen consumption at the same time, and the antihypertensive effect is strong and rapid, which can reduce the complications of fetuses and newborns[23]. It has been reported that the combination of nitroglycerin and labetolol can achieve satisfactory hypotensive control effect [24,25]. Therefore, this study determined whether the combination of nitroglycerin and labetolol could effectively improve patients' blood flow, and used 3D Doppler ultrasound technology to monitor the changes of patients' data before and after treatment.

Domestic and foreign experts believe that quantitative 3D energy Doppler ultrasound technology is highly sensitive to the information of patients with different blood flow directions, which can effectively reduce the influence of vascular cross, blood flow velocity and vascular curvature on blood flow direction information, and display blood perfusion in different directions, which is conducive to accurate clinical understanding of patient information[26]. The growth and development of the fetus itself is closely related to uterine artery and placental blood supply[27].

In our study, the results suggested that hemorheology indexes in both group A and group B showed an upward trend after treatment, and there was no significant difference in the

improvement effect between the two groups. At the same time, the ultrasonic parameters of group A and group B changed significantly, but the improvement effect between the two groups was not significantly different. Furthermore, there was no significant difference in the total effective rate between the two groups, but there was statistical significance in placental VI, FI, and VFI under different efficacy grades. The above findings suggest that the combination of drugs can achieve good therapeutic effect on different severity of HDCP. The combination of nitroglycerin and labetolol in the treatment regimen can inevitably affect the hemorheological indicators and ultrasound parameters of patients, while quantitative 3D power Doppler ultrasound can dynamically monitor placental blood perfusion, and objectively and accurately evaluate the changes of placental blood perfusion of patients by comparing the changes of relevant indicators before and after treatment, which is of great significance to evaluate the therapeutic effect and prognosis of patients[28]. Consistently, Liu *et al*. suggested that the parameters of 3D power Doppler ultrasonography can reflect the perfusion status of the placenta and predict the outcome of pregnancy in patients with hypertensive disorders complicating pregnancy[29].

Study strengths and weaknesses

The main strength of our study was that we used quantitative 3D power Doppler ultrasound technology to monitor therapeutic effectiveness of nitroglycerin combined with labetolol in pregnant women with PIH, which can be provided for the clinical diagnosis, objective evaluation, and treatment of PIH. However, the sample size of this study is small, and the objectivity of the research results is insufficient. Further analysis will be conducted in subsequent studies.

Conclusion

Nitroglycerin combined with labetolol is effective in the treatment of PIH. At the same time, the application of quantitative 3D power Doppler ultrasound technology can accurately monitor the placenta and fetal blood perfusion, which is worthy of further promotion.

Acknowledgement

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Contribution of authors

Yang ZL, Zhao JH: conceived and designed the study, collected and analysed the data, and prepared the manuscript. All authors mentioned in the article approved the manuscript.

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