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Original Article

Therapeutic potential of Omega-3 polyunsaturated fatty acids on the immune function of patients with hypertensive disorder complicating pregnancy and preeclampsia

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Abstract: Background: This paper aims to explore the mechanism of Omega-3 polyunsaturated fatty acids (PUFA) on the immune function of patients having pregnancy induced hypertension (PIH). Methods: Through a retrospective study, 168 patients with PIH syndrome who were cured at the First Affiliated Hospital of Hebei North University (January 2020 to December 2021) were randomly divided into the Omega-3 treated group and the control group, with 84 cases in each group. The control group received treatment with magnesium sulfate. The other group was treated with PUFAs based on the magnesium sulfate treatment. To evaluate the differences in diastolic pressure, systolic pressure and inflammatory factors between the Omega-3 treated group and control group, statistical analysis was conducted using SPSS 23.0 software. The measurement data were subject to t-test, and x^2 test was adopted for counting data. Results: The treatment efficiency of the Omega-3 treated group and the control group was 95.24% and 80.95%, respectively, with a significant difference (P<0.05). Before receiving treatment, there was no difference in diastolic and systolic pressure, various inflammatory factors and various immune functions between these two groups (P>0.05). The group treated with omega-3 had lower CD3+, CD4+ and the CD4+/CD8+ ratio than the control group (P<0,05). The Omega-3 treated group had significantly higher IL-4 and CD8+ than those in the control group (P<0.05). Conclusion: Intravenous injection of Omega-3 can reduce blood pressure, improve immune function, and reduce inflammatory reactions in patients with gestational hypertension.

Keywords: Omega-3 polyunsaturated fatty acids preparation, immune function, mechanism, gestational hypertension

Introduction

Gestational hypertension is a common illness in women during pregnancy, being more common after 20 weeks of pregnancy [1]. Generally, the blood pressure of women aged 26-35 years old fluctuates around 112-114 mmHg for systolic pressure and 73-74 mmHg for diastolic pressure [2]. If the systolic and diastolic pressure during pregnancy are outweigh 140 mmHg and 90 mmHg respectively, gestational hypertension can be diagnosed. The disease affects both the fetus and the pregnant woman. Rational drugs are one of the effective tools to treat gestational hypertension. Among them, magnesium sulfate is a commonly used method for pregnancy induced hypertension (PIH). The mechanism of magnesium sulfate in PIH treatment is to cause vasodilation, thereby reducing blood pressure and ensuring blood supply [3]. It is helpful to improve the blood pressure and alleviate physical symptoms, but it is difficult to achieve expectations with only one medication [4]. However, some researches have suggested that hypertension in pregnant women is influenced by the immune system. Therefore, it is more effective to explore the mechanisms that affect the immune system of patients with hypertension. Polyunsaturated fatty acids (PUFA) are an immune enhancer that have been widely used clinically in recent years. The main reason is that Omega-3 can reduce

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Table 1. Comparison of clinical conditions

Group	*N*	Education level (*n*/*n*)	Age ($\overline{X}$±s, age)	Gestational week ($\overline{X}$±s, week)	Preeclampsia	Hypertensive pregnancy
		High school and above/High school and below				
Omega-3 treated group	84	44/40	28.51±2.46	27.72±2.21	58	26
Control group	84	45/39	28.39±2.52	27.80±2.24	57	27
Statistics		0.048	0.134	0.327	1.135	1.384
P		0.826	0.447	0.372	0.879	0.661

blood pressure for hypertensive patients. Some studies have confirmed that Omega-3 can effectively treat hyperlipidemia in pregnant women. It is an essential fatty acid in the body, including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), which are important for anti-atherosclerosis, blood pressure and inflammatory response control [5]. In previous clinical studies, it has been shown that Omega-3 has anti-inflammatory effects, which can up-regulate the activity of immune cells in the immune system, thereby affecting its immune function [6, 7]. In addition, some studies have proposed animal experiments to verify the application effectiveness of Omega-3. Research has found that Omega-3 can improve the host's resistance to pathogens and reduce the probability of the body being attacked by viruses [8-10]. However, the mechanism of PUFA preparation improving the immunity of patients with gestational hypertension still needs further exploration [11]. In view of this, this study selected 84 patients with gestational hypertension to explore the mechanism of PUFA preparations. The hypothesis was put forward that PUFA preparation could relieve hypertension by affecting immune function indexes during pregnancy.

Materials and methods

General information

The research included 168 hypertensive patients during pregnancy who receiving treatment in the First Affiliated Hospital of Hebei North University (January 2020 to December 2021). Enrollment criteria: ① Patients cooperate to complete the detection and treatment of various indicators; ② The patient is aged between 20 and 48 years old; ③ The types of hypertension are gestational hypertension and pre-eclampsia. Exclusion criteria: ① The patient has a history of mental illness; ② Patients frequently miss medication or withdraw from taking their drugs without authorization; ③ The patient is accompanied by other pregnancy complications; ④ The patient has a miscarriage late in pregnancy; ⑤ Patient experiences fetal malformation induced abortion; ⑥ The patient is diagnosed with chronic hypertension before pregnancy. The study obtained approval of the Ethics Committee of the hospital. All patients were stochastically divided into two groups. There was no statistically significant difference in gender, course of disease and age between these two groups (**Table 1**) (all *P*>0.05).

Methods

Magnesium sulfate is the most widely applied antispasmodic drug for treating hypertensive disorders in pregnancy. For this reason, the control group received magnesium sulfate and magnesium sulfate (approved by Hebei Wuluo Co., Ltd., H13022977), intramuscular injection of 10 ml 25% magnesium sulfate and 5% glucose diluted to 1% concentration, intravenous injection, once a day, for 7 consecutive days [12]. The Omega-3 treatment group received - 3 polyunsaturated fatty acid drugs based on the treatment in the control group. The drugs are omega-3 fish oil soft capsule, 1 capsule/d, taken for 7 days. The drug contains DHA>20000 mg per tablet and DHA 200 mg per 100 g, EPA>30000 mg per tablet, and EPA 300 mg per 100 g. All reagents used have been tested to verify their feasibility and safety, and we evaluated the performance of each kit before using. During the medication period, we guided the patient to perform simple exercises to promote blood circulation and accelerate recovery [13].

Observation indicators

(1) Efficacy analysis: There are three efficacy stages: markedly effective (symptoms disappear, blood pressure ≤140/90 mmHg, normal), effective (symptom improvement, blood pres-

Table 2. Contrast of effective total rate between teams [n (%)]

Group	N	Prominent	Efficacious	Valid Invalid	Response rate
Omega-3 treated group	84	45 (59.52)	35 (35.71)	4 (4.76)	80 (95.24)
Control group	84	39 (52.38)	29 (28.57)	16 (19.05)	68 (80.95)
x^2	-				4.087
P	-	0.198	0.072	0.049	0.043

sure ≤150/100 mmHg), and ineffective (symptoms do not change or even worsen). The total response rate = marked response rate + response rate. (2) Blood pressure analysis: The diastolic and systolic pressure of all the patients before and 7 days after receiving treatment are determined by a desktop mercury sphygmomanometer. The average value is taken. (3) Inflammatory factor analysis: All patients have 3 mL of peripheral blood drawn. After centrifugation (3420 r/min, 15 min), serum is collected. Then the enzyme-linked immunosorbent assay was used to measure interleukin levels 7 days before and after treatment, including interleukin 4 (IL-4), γ interferon (IFN-γ), and IL-2 indicators. (4) Comparison of immune function: 5 mL of whole blood was extracted to measure the serum T lymphocyte subsets through flow cytometry.

The disease progression was monitored by weekly follow-up and routine tests were performed to observe the changes of hemoglobin, platelet, 24-hour urine protein, alanine aminotransferase, aspartate aminotransferase, uric acid, creatinine and lactic acid levels.

ELISA kit was used to detect IL-4, IFN-γ and IL-2 in patients' serum. Firstly, patient serum samples were added to the orifice plate strip and placed at room temperature of 25°C. When the color of the control tube was appropriate, the reaction was stopped. The counting method of lymphocytes is to dilute blood to a certain amount with lymphocyte dilution solution, while destroying the red blood cells and staining the white blood cell cytoplasm light red, so that the nucleus and cytoplasm can be clearly distinguished. Combined with the morphological characteristics of lymphocytes, it is easy to differentiate with the medium under a low power microscope. After dilution, it was dropped into a counting plate to count the number of lymphocytes within a certain range.

The patients with preeclampsia were diagnosed by detecting the expression of PlGF, VEGF and sFlt-1 in serum samples based on immunohistochemical SP method. The results of sFlt-1, VEGF and PLGF staining as follows. (-): 0%-5% of the cytoplasm is stained. (+): 5%-25% of the cytoplasm is stained. (++): 50% of the cytoplasm is stained. (+++): >50% of the cytoplasm is stained. (-) (+) are negative, and (++) (++) are positive.

Statistical methods

SPSS 23.0 software was adopted for data statistical analysis. The measurement data are indicated with ($\bar{x} \pm s$). The data were analyzed by t-test. The count data were indicated with examples or percentages. The x^2 test was used to analyze the data. The difference was considered significant when $P<0.05$.

Results

Efficacy analysis

The difference in treatment effects between the two groups is shown in **Table 2**. According to **Table 2**, the treatment response rate of patients in the Omega-3 treated group was 95.24%, and the control group was 80.95% ($P<0.05$).

Blood pressure analysis

Table 3 shows the difference in blood pressure performance. According to **Table 3**, no significant difference in systolic and diastolic pressure was found before receiving treatment ($P>0.05$). After receiving the treatment, significant difference was found in systolic pressure and diastolic pressure between these two groups. The Omega-3 treated group had lower systolic pressure and diastolic pressure ($P<0.05$).

Blood index analysis

Table 4 shows the difference analysis of blood related indexes between these two groups.

Table 3. Contrast of blood pressure levels between teams ($\bar{x}\pm s$, n=84, mmHg)

Group	Diastolic pressure		Systolic pressure	
	Before cure	After cure	Before cure	After cure
Omega-3 treated group	92.27±9.35	81.34±7.17*	147.18±12.49	120.21±10.31*
Control group	92.30±9.36	86.20±7.13*	147.16±12.48	132.95±11.18*
t	0.064	11.231	0.029	15.959
P	0.475	0.000	0.489	0.000

Note: *indicates *P*<0.05 compared with that before cure.

Table 4. Blood index difference between groups

Index	Omega-3 treated group		Control group	
	Before cure	After cure	Before cure	After cure
Hemoglobin (g/L)	106.37±8.01	109.90±12.77	104.51±9.03	106.68±10.27
Platelet ($\times10^9$/L)	255.17±41.69	289.74±54.67	264.22±30.39	278.03±41.55
24 h urine protein (mg)	77.96±19.57	102.27±28.39	86.73±16.08	111.33±22.45*
Alanine aminotransferase (U/L)	25.33±3.21	29.07±5.41	32.55±5.71	30.61±4.66
Aspartate aminotransferase (U/L)	24.60±5.45	28.22±3.31	28.10±4.29	30.39±2.28
Uric acid (μmol/L)	218.22±55.17	336.07±71.12	239.77±50.51	374.65±67.44*
Creatinine (μmol/L)	41.23±10.05	55.11±9.23	48.55±12.49	67.19±7.62*
Lactic acid (mmol/L)	1.41±0.39	1.87±0.25	1.40±0.25	2.01±0.35*

Note: *indicates a significant difference compared with before receiving treatment (*P*<0.05).

Table 5. Contrast of inflammatory factor index between teams ($\bar{x}\pm s$, n=84)

Group	IL-4 (ng/L)		IFN-γ (ng/l)		IL-2 (ng/L)	
	Before cure	After cure	Before cure	After cure	Before cure	After cure
Omega-3 treated group	23.62±2.18	40.12±1.20*	406.39±28.30	260.36±22.42*	68.72±6.29	47.27±4.21*
Control group	23.68±2.19	32.65±1.59*	407.61±28.39	318.70±27.69*	68.76±6.30	60.38±4.40*
t	0.137	8.981	0.215	6.201	0.559	10.529
P	0.446	0.000	0.415	0.000	0.289	0.000

Note: *indicates *P*<0.05 compared with before cure.

Although no significant difference was found before receiving treatment, the differences in 24 h urine protein, creatinine, uric acid and lactic acid were statistically significant after receiving treatment (*P*<0.05).

Inflammatory factor analysis

Table 5 shows the difference in the inflammatory factors between these two groups. According to **Table 4**, no significant difference in the inflammatory factor was found before receiving treatment. However, there were significant changes in inflammatory factors in both groups after treatment. Besides, there was significant difference in the inflammation level between the two (*P*<0.05).

Growth factor analysis

Table 6 shows the difference in growth factors between these two groups. According to **Table 6**, there were significant differences in growth factors between the two groups (*P*<0.05).

Comparison of immune function

The differences in immune function indicators between the two groups are shown in **Table 7**. According to **Table 7**, before receiving treatment, no significant difference was found between these two groups in terms of immune function indicators (*P*>0.05). After receiving treatment, the immune function indexes of patients in the two groups changed sharply (*P*<0.05).

Table 6. Growth factor difference between groups

Group	VEGF		PIGF		sFlt-1	
	Negative	Positive	Negative	Positive	Negative	Positive
Omega-3 treated group	10	74	8	76	49	35
Control group	55	29	32	52	9	75
x^2	0.465	2.458	0.177	1.386	0.488	1.550
P	0.000	0.000	0.000	0.000	0.000	0.000

Table 7. Contrast of immune function between teams ($\bar{x}\pm s$, n=84)

Group	CD3+		CD4+		CD8+		CD4+/CD8+ ratio	
	Before receiving treatment	After receiving treatment	Before receiving treatment	After receiving treatment	Before receiving treatment	After receiving treatment	Before receiving treatment	After receiving treatment
Omega-3 treated group	53.11±5.45	65.22±5.68*	32.65±3.10	39.23±3.33*	44.55±3.56	30.85±4.40*	1.05±0.16	1.98±0.24
Control group	53.13±5.40	59.10±5.67*	32.63±3.15	36.10±3.45*	44.56±3.53	37.45±3.39*	1.07±2.17	1.63±0.22
t	0.039	19.643	0.023	9.460	0.013	6.522	0.171	0.039
P	>0.05	<0.05	>0.05	<0.05	>0.05	<0.05	>0.05	>0.05

Note: *indicates *P*<0.05 compared with that before cure.

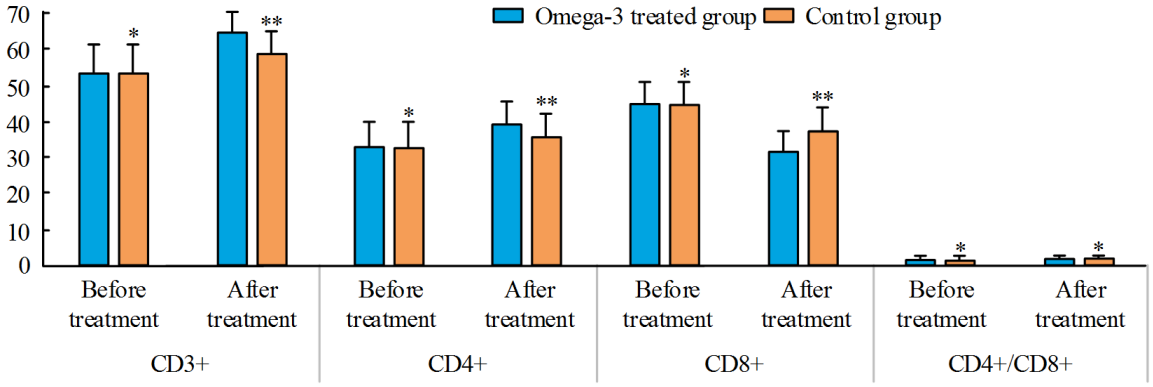

Figure 1. Contrast of immune function between groups. Note: * indicates no difference compared with before receiving treatment. ** indicates significantly different from before receiving treatment.

Figure 1 shows the changes and differences in immune function indexes between these two groups. In **Figure 1**, the Omega-3 treated group showed significant changes in various functional indicators.

Discussion

Gestational hypertension is a complication of pregnancy that requires different treatments based on blood pressure measurements [14]. Today, magnesium sulfate is often employed for treating patients with gestational hypertension. As a widely used drug for treating hypertension, it is mostly adopted for catharsis, choleretic, anticonvulsant, hypertension and other symptoms. However, this product may cause stomach pain and vomiting. Drugs with low toxicity such as symptoms must be injected intravenously according to the specifications. Excessive doses are dangerous to the fetus and pregnant women [15, 16]. Some studies show that Omega-3 plays a significant clinical role in the treatment of hypertension. Its mechanism is to reduce cholesterol and triglycerides in the blood, repair damaged cells, and reduce the incidence of tumors [17]. For this reason, this study delves into the therapeutic effect of Omega-3 on preeclampsia, providing ideas for clinical application.

The research results showed that the hypothesis put forward by the study is valid. Omega-3 can significantly affect the immune function

indicators, thereby alleviating PIH. PUFA is a long-chain unsaturated fatty acid that can improve endothelial cell function, which is a core substance for maintaining human health [18]. Increased intake may reduce the risk of PIH [19]. In this research, it was found that the total response rates of the Omega-3 treated group and the control group were 95.24% and 80.95%, respectively, with a statistically prominent difference ($P<0.05$). Seven days after receiving treatment, diastolic and systolic pressure of all patients reduced, while the Omega-3 treated group had lower systolic pressure and diastolic pressure. IL-4 was elevated and higher in the Omega-3 treated group, and the discrepancy was statistically prominent ($P<0.05$). Research showed that Omega-3 can help reduce blood pressure and inflammatory reaction in patients with gestational hypertension, with significant effects. The inflammatory reaction was negatively correlated with blood pressure level. From the research results, the main principle of this drug in treating PIH is to regulate the composition of fatty acids in cell membrane phospholipids, improve endothelial function and vascular compliance, and reduce blood pressure. It can also repair the inflammatory cell membrane structure locally, slow down inflammation and immune response, and improve blood pressure indicators. CD3+, CD4+, CD8+ and CD4+/CD8+ ratio are common immune indicators, which can reflect the degree of immune regulation disorder. The results showed that CD3+, CD4+ and CD4+/CD8+ increased in all patients after receiving treatment. Besides, the Omega-3 treated group had lower CD8+ in patients than the control group, with significant difference ($P<0.05$). This certificates that the PUFAs are helpful to improve immunity in patients with gestational hypertension. Omega-3 PUFA have anti-inflammatory effects, which may improve the immune status of patients with gestational hypertension by regulating the proliferation and differentiation of CD3+ T cells, reducing inflammatory responses. CD4+ T cells mainly participate in cellular immunity, and Omega-3 therapy may reduce the proportion of CD4+ T cells, lower the cellular immune function in patients, thus alleviating inflammatory reactions. Therefore, the CD4+/CD8+ ratio decreases, thereby affecting the proportion of regulatory T cell subsets. Meanwhile, Omega-3 therapy may reduce immune function by promoting the differentiation and proliferation of regulatory T cell subsets, increasing T cells with immune suppressive effects in the body. Therefore, Omega-3 may indirectly affect the cytotoxic killing function of CD8+ T cells. Cause analysis shows that after the PUFA preparation enters the human body, it can significantly inhibit inflammatory factors, improve the body's internal environment to the greatest extent, remove free radicals in the body, and prevent the production of Omega-3 PUFA. It can also support the immune response by regulating the membrane lipid mediator of immune cells, promote the proliferation of CD3+ and CD4+ T lymphocytes, increase the secretion of various cytokines and chemokines, decline the risk of disease infection, and enhance the body's systemic immunity [20].

Tita AT and other scholars explored the safety of the treatment for gestational hypertension. Blood pressure not exceeding 140/90 mmHg is proposed as an evaluation indicator to assess the health of patients. The analysis demonstrate that this method effectively reduces premature birth and fetal death, and improves the safety of childbirth for pregnant women [21]. The retrospective study of Sisti G et al. have similar results as the above study. They also found that when the critical value of blood pressure is 130/80 mmHg, hypertensive pregnant women are most suitable for delivery [22]. Rezk M et al. conducted clinical observation and comparison on the efficacy of methyldopa and other drugs for the treatment of gestational hypertension. Compared with non-drug treatment and methyldopa treatment, both the ability of neonates to convert bilirubin and liver metabolism in patients treated with labetalol decrease [23]. Guglielminotti J et al. carried out a retrospective analysis on the incidence and time patterns of pulmonary arterial hypertension during pregnancy. The data display that patients with obesity and elevated arterial blood pressure have a higher prevalence of PH. They are more likely to have a premature birth and miscarriage. Therefore, they emphasize the importance of premarital examinations, especially pulmonary hypertension screening [24]. According to the research of Chandrasekaran S and other scholars, PIH poses a significant risk, such as stroke, pulmonary edema, and death. Meanwhile, newborns also face adverse symptoms such as stillbirth

and congenital malformations. Therefore, it is essential to diagnose and treat hypertension in pregnant mothers and infants during pregnancy [25]. Cornelius DC et al. discussed the pathological relationship between PE and PIH. Pregnant women with PE have an imbalance in their immune system, causing damage to the placenta. However, the reduction of inflammatory cells during PE offers a new way for the treatment of PIH [26, 27]. Most of the discussions on PIH focus on treatment and prevention. In general, there are few studies on drug treatment for PIH, especially on Omega-3 Polyunsaturated fatty acid treatment. Therefore, this study provides a new direction and reference for treatment of PIH.

Advantages and limitations of research

The study focuses on the treatment of PIH, innovatively using PUFA. The clinical efficacy of this treatment for PIH, including blood pressure indicators, inflammation, and immune responses of patients, is compared and analyzed, providing assistance for the clinical treatment of PIH. Although the research has made some achievements, there are still some deficiencies in this study. Due to the limitations of equipment and other conditions, the number of samples selected in the study is small, which needs further exploration.

Conclusion

In summary, intravenous Omega-3 application reduced blood pressure levels, improved immune function, and reduced inflammatory reactions of patients with gestational hypertension. This can be popularized in the clinical cure of gestational hypertension and can promote the development of drug treatment. In future research, the sample size should be expanded to observe the clinical treatment effects of more patients with gestational hypertension to further enrich this exploratory result.

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Informed consent was obtained from all the study subjects before enrollment.

Disclosure of conflict of interest

None.

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