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CLINICAL RESEARCH

Effects of Traditional Chinese Medicine as an Adjuvant Therapy on Inflammatory Factors, Vascular Endothelial Function and Growth Factors in Diabetic Retinopathy Patients

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Key words

Adjuvant therapy of traditional Chinese medicine, Diabetic retinopathy, Inflammatory factor, Vascular endothelial function, Growth factor

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Abstract

Objective To explore the effects of traditional Chinese medicine as an adjuvant therapy on inflammatory factors, vascular endothelial function and growth factors in diabetic retinopathy patients. **Methods** A total of 96 diabetic retinopathy patients were selected as the research subjects, and they were randomly divided into control group and observation group. The control group was treated with pan-retinal photocoagulation, while the observation group was treated with Chinese medicine as an adjuvant therapy combined with pan-retinal photocoagulation. The clinical efficacy, inflammatory factors, vascular endothelial function and growth factor levels of the two groups were compared before and after treatment. **Results** After treatment, the total effectiveness rate of the observation group was significantly higher. After treatment, the serum levels of interleukin, hypersensitive C-reactive protein and tumor necrosis factor-α in the two groups were significantly lower than those of before treatment, with the parameters in the observation group sharply lower. After treatment, the levels of endothelin-1, vascular endothelial growth factor and angiopoietin-2 in the two groups were noticeably lower than those of before treatment, and vascular endothelial diastolic function was significantly higher. Moreover, the levels of the ET-1, VEGF, Ang-2 in the observation group were significantly lower, and FMD was greatly higher. **Conclusion** The adjuvant treatment with traditional Chinese medicine can greatly improve the clinical efficacy of diabetic retinopathy, alleviate the inflammatory response, improve vascular endothelial function and inhibit the formation of new blood vessels.

Introduction

Diabetic retinopathy (DR), which is a common microvascular complication of diabetes, can cause serious vision loss, and even cause permanent vision damage [1,2]. Studies have shown [3,4] that factors such as long-term high-glycemic state, micro-inflammation and retinal vascular endothelial dysfunction in diabetic patients will contribute to the occurrence and development of DR. At present, the most commonly used method for the treatment of DR is panretinal laser photocoagulation, which could also easily damage the axon of the retinal ganglion of the patients, leading to complications such as high intraocular pressure and postoperative bleeding. Therefore, more effective treatment measures should be developed for the management of such a condition of DR [5]. Traditional Chinese medicine has accumulated rich experience in the treatment of ophthalmic diseases, and can effectively improve vascular endothelial function and inflammation [6]. This study explored the effects of Chinese medicine as an adjuvant therapy on inflammatory factors, vascular endothelial function and growth factors in patients with diabetic retinopathy. The reports are as follows:

Materials and methods

General information

A total of 96 patients with diabetic retinopathy admitted to our hospital from January 2019 to January 2020 were selected and divided into a control group and an observation group using a random number table method, with 48 cases in each group. 28 males and 20 females in the observation group aged 35-68 years, with an average of age (53.23±11.39) years old, a disease course of 2-10 years, and an average disease course of (3.72±0.83) years. In the control group, there were 25 males and 23 females aged from 32 to 72 years old, with an average age of (55.96±10.78) years, a disease course of 2 to 11 years, and an average disease course of (3.96±0.87) years. Inclusion criteria: patients aged 30 to 75 years old, and their symptoms were in line with the *Diagnostic Criteria and Staging Criteria for diabetic retinopathy* [7] and the Diagnosis and Treatment criteria of Traditional Chinese Medicine for Diabetic Retinopathy [8]. Exclusion criteria: those suffering from severe heart, liver, kidney and other organ dysfunctions, from cataracts, glaucoma, retinal detachment and other eye diseases were excluded. This study was approved by the Ethics Committee of our hospital, and informed consent was signed by the patients and their families. There was no significant difference in gender, age, or clinical stage, etc. between the two groups of patients ($P>0.05$), as shown in Table 1.

Method

The control group was treated with pan-retinal laser photocoagulation, tropikamide was used to fully dilate the pupils of the affected eyes before the operation, and oxybucaine hydrochloride eye drops were used for surface anesthetic. Panretinal laser photocoagulation was performed using the Australian Integer 532 therapeutic apparatus (spot diameter 200-500 μm, exposure time 0.1-0.3 s, total photocoagulation 1,000-1 600 points, completed in 3 to 4 times). Eyesight was regularly recorded after surgery, and fundus fluorescein angiography was followed up at 3 months after surgery. The observation group was given Chinese medicine as an adjuvant treatment on the basis of the control group. Chinese medicine prescriptions consisted of Pueraria lobata 20 g, Cassia seed 20 g, Rehmannia glutinosa 20 g, Puhuang 15 g, Astragalus 15 g, Lycium barbarum 10 g, Fu Weizi 10 g, leech 5 g, and was added with 500 mL of water and decocted to 300 mL. The decoction was taken at 150 mL a time, twice a day, for 6 months.

Evaluation criteria for clinical effectiveness

The clinical effectiveness of the two groups of patients after treatment was compared. Markedly effective: the patient's visual acuity was improved by more than 2 lines, the visual field was enlarged by more than 10 degrees, and the symptoms such as fundus microangioma all or partly disappeared; effective: the patient's visual acuity was improved by 1 to 2 lines, the visual field was enlarged by 5-10 degrees, and the symptoms of fundus microangioma

were attenuated; ineffective: after treatment, the patient has no obvious changes in symptoms or showed worsening of symptoms. The total effectiveness rate = (markedly effective + effective) number of cases/total number of cases × 100

Table 1 Comparison of general information of the two groups of patients (cases)

Groups	Cases	Gender (male/female)	Average age (years old)	Average disease course (years)	Diabetic retinopathy		
					Stage I	Stage II	Stage III
Observation group	48	28/20	53.23±11.39	3.72±0.83	27	14	7
Control group	48	25/23	55.96±10.78	3.96±0.87	25	14	9
$t/\chi^2/Z$		0.379	0.119	-1.283		-0.504	
P		0.538	0.231	0.170		0.614	

Observation indicators

The fasting venous blood (4 mL) was collected before and after treatment, and the serum was separated by centrifugation. Inflammatory factors, vascular endothelial function, and growth factor indexes of the two groups of patients were detected before and after treatment. For the detection of inflammatory factors, Hitachi 7600 automatic biochemical analyzer was used for determining the levels of interleukin (IL-6), high-sensitivity C-reactive protein (hs-CRP), tumor necrosis factor-α (TNF-α). IL-6 and TNF-α were determined by Enzyme-linked immunoassay, and hs-CPR was detected by immunoturbidimetric method. For the detection of vascular endothelial function, an automatic biochemical instrument was used to detect endothelin-1 (ET-1); American General Company LOGIO-500 color ultrasound was applied to detect and calculate vascular endothelium-dependent diastolic function (FMD), and record the basic inner diameter of the brachial artery (D0) and brachial artery congestion inner diameter (D1). FMD=(D1-D0)/D0×100%, when FMD<10%, it is defined as an endothelial damage. For the detection of growth factors, an automatic biochemical analyzer was used to detect vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang-2) by performing enzyme-linked immunoassay.

Statistical methods

Statistical analysis was performed using SPSS 20.0. The count data were compared with the $\chi 2$ test. The measurement data were expressed as mean ± standard deviation（$\bar{x}\pm s$）. The t test was used for comparison. The rank data was compared with the rank sum test Z. $P<0.05$ was considered as a statistically significant difference.

Results

Comparison of clinical effectiveness between the two groups

After treatment, the total effectiveness rate of the observation group was 87.50%, and that of the control group was 70.83%. Obviously, the total effectiveness rate of the observation group was significantly higher than that of the control group ($P<0.05$), see Table 2.

Comparison of serum levels of inflammatory factors between the two groups

Before treatment, there was no significant difference in serum levels of IL-6, hs-CRP, or TNF-αbetween the two groups of patients ($P>0.05$). After treatment, the serum levels of IL-6, hs-CRP, and TNF-α between the

two groups of patient were significantly lower than before treatment (P<0.05), with the parameters in the observation group sharply lower than those in the control group (P<0.05), see Table 3.

Table 2 Comparison of clinical effectiveness between the two groups [cases (%)]

Groups	Cases	Markedly effective	Effective	Ineffective	Total effectiveness rate (%)
Observation group	96	26	58	12	84（87.50）
Control group	96	18	50	28	68（70.83）
χ^2					9.084
P					0.004

Table 3 Comparison of serum levels of inflammatory factors between the two groups （ $\bar{x}\pm s$）

Groups	Cases	IL-6 (ng/L)		hs-CRP (mg/L)		TNF-α (ng/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	48	26.94±5.27	13.16±2.92[a]	6.23±0.86	2.98±0.43[a]	45.37±4.85	24.89±2.96[a]
Control group	48	26.78±5.19	19.81±2.18[a]	6.19±0.91	4.45±0.59[a]	45.20±4.82	32.25±3.88[a]
t		0.150	-12.643	0.221	-13.950	0.172	-10.449
P		0.881	0.000	0.825	0.000	0.864	0.000

Note: compared with before treatment, [a]*P*<0.05.

Comparison of vascular endothelial function and growth factor levels between the two groups

Before treatment, there was no significant difference in the levels of ET-1, VEGF, Ang-2, and FMD between the two groups of patients (P>0.05). After treatment, the levels of ET-1, VEGF, and Ang-2 of the two groups were sharply lower than those of before treatment (P<0.05), and FMD was significantly higher than before treatment (P<0.05). Moreover, the levels of ET-1, VEGF and Ang-2 in the observation group were greatly lower than those in the control group (P<0.05), and FMD was significantly higher than the control group (P<0.05), see Table 4.

Table 4 Comparison of vascular endothelial function and growth factor levels between the two groups

Groups	Cases	ET-1 (ng/L)		FMD (%)		VEGF (ng/L)		Ang-2 (ng/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	48	192.82±12.72	112.22±9.72[a]	8.18±0.92	12.75±1.67[a]	493.10±85.42	321.55±65.42[a]	6.64±0.53	3.89±0.33[a]
Control group	48	198.10±14.99	163.56±11.99[a]	8.27±0.87	9.79±1.36[a]	477.16±90.21	391.59±66.15[a]	6.59±0.56	4.45±0.47[a]
t		-1.861	-23.045	-0.492	9.522	0.889	-5.216	0.449	-6.756
P		0.066	0.000	0.624	0.000	0.376	0.000	0.654	0.000

Note: compared with before treatment, [a]*P*<0.05.

Discussion

DR is the most common and serious ocular complication of diabetes. In recent years, the increase in the number of diabetic patients is accompanied with the increasing incidence of DR. Almost all the diabetic patients with a longer course of disease will develop different degrees of retinopathy [9,10]. According to traditional Chinese medicine, DR belongs to the category of "dispersion-thirst eye disease ", a disease that is “asthenia in origin and asthenia in superficiality”, which means that diabetes is the origin of DR and are formed on the basis of deficiency of liver and kidney and of both Qi and Yin [11]. DR is a result of dryness-heat due to deficiency of yin. The patients experience stagnation of blood, syndrome of yin deficiency and depletion of fluid, which will subsequently lead to the deficiency of both Qi and Yin, yin-deficiency will cause fire-hyperactivity, bringing damages to eye collaterals, eventually leading to the failure of blood to circulate in the vessels and blockage of eye collaterals. Therefore, the treatment should be decided according to the principles such as nourishing liver and kidney, moistening and reducing dryness and heat of liver, promoting blood flow and removing blood stasis [12,13]. In this study, the use of Chinese medicine as an adjuvant therapy can significantly improve the clinical effectiveness of DR treatment, alleviate the inflammatory response of patients, improve vascular endothelial function, and inhibit the formation of new blood vessels.

This study showed that after treatment, the total effectiveness rate of the observation group was significantly higher than that of the control group ($P<0.05$), and the patients' vision and symptoms of microangioma were significantly improved. The astragalus contained in the traditional Chinese medicine prescription has the functions of regulating blood circulation, nourishing Qi and promoting blood. Pueraria lobata and wolfberry have the functions of nourishing liver and kidney and regulating blood circulation. Cassia seeds and leech can also nourish the liver and kidney, promote blood circulation and remove blood stasis. The effects of nourishing the liver and kidney, promoting blood circulation and removing blood stasis significantly improve the clinical effectiveness of the treatment. Chronic inflammatory factors play a very important role in DR, because damaged retinal function of DR patients will lead to the continuous activation and proliferation of inflammatory cells, resulting in long-term inflammatory state of retinal cells. In addition, this study showed that after treatment, the serum levels of inflammatory factors IL-6, hs-CRP, and TNF-α in the observation group were sharply lower than those in the control group ($P<0.05$), indicating that the inflammatory response of the patients was effectively alleviated. Studies have demonstrated that [14] the active components of astragalus and wolfberry fruit, Astragalus Polysaccharide and Lycium Barbarum Polysaccharide, could inhibit inflammatory response, thereby alleviating the micro-inflammatory state and reducing the content of inflammatory factors in the patient's serum.

Retinal vascular endothelial dysfunction, specifically, vascular endothelial function ET-1, FMD and vascular growth factors VEGF and Ang-2, play key roles in the occurrence and development of DR patients. ET-1, VEGF, Ang-2 decrease, the permeability of capillary vessel and angiogenesis capacity decrease accordingly, and retinal microcirculation is improved. A higher FMD indicates a better vascular endothelial function of the patients [15]. This study showed that after treatment, the levels of ET-1, VEGF, and Ang-2 in the observation group were significantly lower than those in the control group ($P<0.05$), and FMD was noticeably higher than the control group ($P<0.05$), indicating that retinal microcirculation and vascular endothelial function in DR patients were improved, and capillary accumulation caused by excessive vascular permeability and rapid blood vessel proliferation was relieved. Such an improvement could be explained by the functions of wolfberry, cassia seed, leeches, etc., which can moisten and reduce dryness and fire, promote blood circulation and remove blood stasis. Carotene contained in wolfberry can be converted into retinol in the human body to improve vision, at the same time, it also protects the

body's blood vessels, improves the hematopoietic microenvironment and other functions, thereby enhancing the patient's vascular endothelial function and inhibiting the formation of new blood vessels.

In summary, the adjuvant therapy with traditional Chinese medicine can significantly improve the clinical treatment effectiveness of patients with DR, relieve patients' inflammatory response, improve vascular endothelial function, and inhibit the formation of new blood vessels.

Declaration of conflict-of-interest

The authors declare no conflict-of-interest.

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