

Research progress on combined therapy of traditional Chinese medicine with laser photocoagulation for treatment of diabetic retinopathy

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中药联合激光光凝治疗糖尿病视网膜病变

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摘要

糖尿病视网膜病变 (diabetic retinopathy, DR) 是糖尿病眼病不可逆盲的最严重的并发症, 严重影响患者的生存质

量。目前, 我国在 DR 手术治疗方面已进行了广泛的开展, 对于增殖前期 DR, 增殖期糖尿病视网膜病变 (proliferative DR, PDR) 采取全视网膜光凝术, 破坏缺血区视网膜, 减少需氧量, 以防止新生血管形成, 阻止病情恶化。中医药对治疗 DR 有着非常丰富及个性化的治疗方案, 本文就中药联合激光光凝治疗 DR 的研究进行综述。

关键词: 糖尿病视网膜病变; 中药联合激光光凝; 研究进展

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Abstract

• Diabetic retinopathy (DR) is the most severe complication of diabetic eye disease, which can eventually lead to irreversible blindness, thus seriously impacting on patients' quality of life. At present, surgical operation has been widely carried out on the treatment of DR in China. For the pre proliferative DR (PDR) and PDR, panretinal photocoagulation has often been adopted. By damaging the retina in ischemic area so as to reduce oxygen demand, the neovascularization can be prevented and the patient's condition can be stopped from getting worse. Traditional Chinese medicine (TCM) has an abundant and personalized therapeutic regimen for the treatment of DR. This paper reviews the research progress on combined therapy of TCM with laser photocoagulation for treatment of DR.

• **KEYWORDS:** diabetic retinopathy; combined therapy of traditional Chinese medicine with laser photocoagulation; research progress

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INTRODUCTION

Diabetic retinopathy (DR) is the most severe complication of diabetic eye disease, which can eventually lead to

permanent loss of vision. DR is the result of hyperglycemia-induced microvascular retinal changes. The capillary pericyte necrosis and thinning of the endothelial cells lead to incompetence of the inner barriers. These damages make the retinal blood vessels become more permeable, allowing effusion of fluid into the surrounding tissue, causing retinal pathological changes and dysfunction. With the rising number of diabetic patients and prolonging of human's life span, DR, which rates are also on the rise, has become the most common cause of blindness in the elderly. Therefore, the prevention of the occurrence and development of DR is particularly important. The advantage of the combined therapy of traditional Chinese medicine (TCM) with laser photocoagulation in the treatment of DR is ceaselessly highlighted, which has become an important part in the prevention and treatment of DR. Here follows the research results of the recent 5y.

THEORETICAL RESEARCH

The Mechanism of Laser on Diabetic Retinopathy The mechanism of panretinal photocoagulation on DR; it is now widely accepted that^[1] the mechanism of panretinal photocoagulation is laser destroyed part of the photoreceptor pigment epithelial complex whose oxygen consumption is high, which reduces oxygen demand. At the same time it increased oxygen supply of the inner retina from choroidal capillary and reduce the synthesis of angiogenesis growth factor because of ischemia. Thus, laser prevents the formation of new blood vessels and promotes the extinction of angiogenesis that has been formed. Finally, Laser delays the progress of proliferative DR (PDR). Binz *et al*^[2] think that laser treatment can inhibit the neovascularization and has long-term effect. It is because laser treatment changes genes expression in retinal which is closely related to angiogenesis. After retinal pigment epithelium (RPE) absorbing laser energy, the temperature of local tissue rises and the protein comes to be degenerative, thus can effectively reduce the metabolism and the oxygen consumption of retinal, as well as reduce the factor of promoting neovascularization^[3]. At the same time, those lead to the thinning of retinal and the reduction of the barrier function between choroid and retinal^[4]. Mechanism of local/grid laser treatment for diabetic macular edema (DME): the mechanism of laser treatment inducing DME mainly relates to laser damaged the oxygen consumption of retina photoreceptor^[5]. Stefánsson^[6], Wolbarsht and Landers^[7] find that the oxygen partial pressure of preretinal increases and retinal capillaries decrease in laser photocoagulation area. Oxygen content in treated retinal region is higher than untreated. It prompts that laser treatment makes the leakage area of abnormal vascular and the exudates from intravascular liquid to the inter organizational greatly reduced. Then macular edema (ME) eliminated. It is peripheral retinal scarring that reduces the oxygen consumption and conducive to the improvement of hypoxia in the macular area^[8]. Proliferation of pigment epithelium cells recover with light solidification zone and release anti vascular growth factor after

photocoagulation, which eventually improved DME. Combined treatment of intravitreal injection of low dose triamcinolone acetonide (TA) with grid photocoagulation can effectively reduce the diffuse DME and improve the visual function of patients, which is a short-term, safe and effective therapeutic method for the control of ME and improvement of eyesight^[9].

Understanding of Diabetic Retinopathy in Traditional Chinese Medicine The name DR wasn't recorded in ancient literature of TCM, but the symptoms associating with DR had been well documented. For example, *Hejian liushu* points out that diabetes can lead to night blindness or cataract. *Zhengzhi yaojue* records that if diabetes sustains for a long time, essence and blood would get deficient. Therefore eyes are invisible and limbs disabled like disease caused by the wind but not wind. *Rumen shiqing · liuwansu sanxiaolun*, written by Zihe Zhang, records that diabetes can develop into deafness, blindness, sore ulcer or acne etc. In a sense, DR shares the same scope with "hyphema and vitreous hemorrhage", "blurred vision", and "sudden blind", etc. in TCM.

The Etiology and Pathogenesis of Diabetic Retinopathy

There is a multiplicity of views on the etiology and pathogenesis of diabetes. Modern experts agree that the syndrome-complex of DR is deficiency in origin and excess in superficiality or intermingled deficiency and excess. The changes of pathogenesis is from deficiency of yin to deficiency of both qi and yin, and then to the deficiency of yin and yang. After enduring illness, blood stasis and phlegm arise, which exacerbate the disease. In short, blood stasis runs through the whole course of DR. Li *et al*^[10] believe that the pathogenesis of this disease is dryness-heat due to deficiency of yin, deficiency of liver-yin and kidney-yin, pathogen usually intruding into collateral in protracted disease or stagnation of phlegm and blood stasis. Zhang^[11] thinks the pathogenesis is deficiency of both qi and yin. Tang, master of TCM, considers that the main pathogenesis of DR is deficiency of both qi and yin with blood stasis^[12]. After long time suffering from the chronic diabetes, the body gets weakened and the vital essence of kidney is waning. By the decreasing of qi and blood, blood stasis emerges. With the disease progress, the retinal neovascularization forms.

CLINICAL RESEARCH

The Clinical Status of Laser Treatment for Diabetic Retinopathy PDR and DME are the two main causes of visual impairment for patients with DR. The risk of visual impairment^[13] can be reduced greatly after a correct and timely laser treatment. Two famous US groups for prospective clinical randomized controlled study conducted a comprehensive evaluation in the laser treatment for DR after more than 20y research. It is confirmed by DR study (DRS) that by the treatment of pan retinal photocoagulation, 50% risk of visual loss has been reduced for high-risk PDR patients. Early treatment DRS (ETDRS) confirms that by the timely local photocoagulation, 50% risk of moderate visual

damage caused by clinically significant ME (CSME)^[14-16] has been reduced. Of course, any laser treatment should combine with optimal control of the systemic risk factors, especially blood glucose, blood pressure, blood lipid^[17]. It is manifested by many clinical studies that the optimal control of systemic factors on patients with diabetes can significantly reduce the occurrence and development of DR, with the best control index: (glycosylated hemoglobin < 7%, systolic pressure < 130mmHg (1kPa = 7.5mmHg), low density lipoprotein (LDL)-cholesterol < 2.5mmol/L and triglycerides < 2.0mmol/L). Xu *et al*^[18] contrasted the curative effect of the traditional grid pattern laser with 577nm yellow micro pulse laser photocoagulation and found that 577nm yellow micro pulse laser treatment is more safe and effective than MLG in the treatment of ME. The 577nm yellow micro pulse laser can alleviate ME, improve visual acuity and protect visual function.

Multi wavelength krypton laser is a model type of laser that can emit three different wavelengths of light^[19]. So there are three laser wavelength can be chosen from: krypton of red light, with the wavelength of 689nm, has strong penetrating force. The light is mainly absorbed by RPE and choroidal melanin, and it will not damage the nerve fiber layer of retina or injury retinal vessels. It is suitable for the cases of early treatment of massive fresh superficial hemorrhages. Krypton of green light, with the wavelength of 532nm, can be absorbed by melanin and hemoglobin. The light can rarely damage foveal retinal nerve fiber layer or lead to formation of fibril. It is suitable for the cases of retinal hemorrhage that has been absorbed and terminal of DR for closing non perfusion and neovascularization. Due to rich lutein in macular retinal inner layer, it has high absorptivity for the yellow light, while low for green light. So the options of laser treatment in macular disease are krypton yellow light with wavelength 586nm which could be absorbed less by lutein^[20] in order to achieve the goal of reducing the damage of nerve fiber layer by laser thermal effect. Chen *et al*^[21] believe that yellow laser have better absorption and conversion effect in the RPE layer, high absorption rate oxygenated hemoglobin and melanin, little absorption on macular lutein and light scattering, which makes it the best wavelength of macular retinal laser photocoagulation.

Although laser treatment may stabilize or delay the progress of DR, every treatment may induce dramatically impairment of vision. Serious complications, irreversible deterioration or even visual loss appears on some patients after laser therapy. A large number of epidemiological studies show that the severity of DR closely relates with duration of diabetes, age of onset, age at diagnosis, type of diabetes, family history, systemic disease, diet, medication history, and individual differences^[22-26]. Are these also the important factors influencing the prognosis of DR laser treatment?

Williams *et al*^[27] speculate kind of low risk patients may exist, and interventions of laser treatment may be effective for them. Kind of high risk patients also exist, but any

intervention can't control the progress of the disease. Whether such differences exist in DR patients, laser treatment combined with control of systemic multi-factor is beneficial.

Research on the Therapy of Traditional Chinese Medicine

By searching and analyzing literature related to treatment of DR by Chinese herbs published in China on National Knowledge Infrastructure (CNKI) from 2000 to 2010, Wang *et al*^[28] find that the most frequently adopted Chinese Medicine are the type of tonic (34.62%), the type of promoting blood circulation and removing blood stasis (26.92%) and the type of clearing heat (23.08%) in turn. It is thus obvious that deficiency, blood stasis and heat run through the course of DR. Wang's^[29] research shows that the significantly syndrome characteristics of DR are combination of plurality syndrome and intermingled deficiency and excess. The fundamental pathogenesis of DR is deficiency in origin. Yin deficiency is dominating the early course of the disease, qi deficiency is subsequent and yang deficiency is finally. Excess in superficiality is along with the progress of the disease. Dryness-heat comes first, then blood stasis, and finally is phlegmatic hygro-sis. Gu^[30] divides DR into 3 stages: 1) the early stage of DR: the symptom is hemorrhage, which color is bright red. The hemorrhage may be a small patch or a large area. Pink tongue, thin and whitish coated tongue, thready rapid pulse can be seen. The therapies are cooling blood and hemostasis, excreting dampness and removing blood stasis. The representative prescriptions are qingying decoction and cattail pollen decoction. 2) The middle stage of DR: the accompanying symptoms may include polydipsia and polyuria, weight loss or irritability. Dark tongue, thin and slightly greasy coated tongue, small and wiry pulse can be seen. The therapies are soothing the liver, regulating qi-flowing for eliminating phlegm, eliminating dampness and improving eyesight. The representative prescriptions are xiaoyao powder and quyu decoction. 3) The late stage of DR: The symptoms are tired, no strength, more sweating, polydipsia, polyuria and losing weight. Pale tongue, greasy oated tongue, feeble and rapid pulse can be seen. The therapies are tonifying qi and yin, promoting blood circulation for removing blood stasis, eliminating phlegm and stagnation, improving eyesight. The representative prescriptions are xuefu zhuyu decoction and zhujing pill.

Treatments According to Syndrome Differentiation of Traditional Chinese Medicine

For the treatment of DR, most of the physicians adopt specific TCM therapy by combining the differentiation of signs and disease. For differentiation of signs, the first thing for consideration is the relationship among deficiency, blood stasis and heat, while for differentiation of disease, the first thing for differentiating is the hemorrhage, fresh hemorrhage or stale hemorrhage. Fresh hemorrhage mostly caused by blood heat. The recommended therapy is to remove heat to cool blood and hemostasis. Stale hemorrhage mostly caused by blood stasis, the recommended therapy for which is to invigorate the circulation of blood in order to remove blood stasis. When

promoting blood circulation, one should be especially careful not to cause bleeding again.

Yuan^[31] divides DR into 3 types: 1) Type of deficiency of both qi and yin, collaterals siltation and stagnant; The representative prescriptions are shengmai powder and qiju dihuang pill. 2) Type of deficiency of liver and kidney, eye collaterals dystrophy; The representative prescription is liuwei dihuang pill. 3) Type of deficiency of yin and yang, blood stasis and phlegm stagnation; For deficiency of yin, the representative prescription is zuogui pill. For deficiency of yang, the representative prescription is yougui pill. According to the syndrome of six meridians, Ye's^[32] research show that syndrome of six meridians have a positive linear correlation with clinical stage. With the development of DR, from stage I to V or from type of simple to the proliferation, syndrome of six meridians have the change order of syndrome of yangming → syndrome of shaoyang → syndrome of taiyin → syndrome of jueyin → syndrome of shaoyin. The rule of six meridians in the progress of DR has relationship with its pathological processes and types. With the increasing of DR staging, the proportion of syndrome shaoyin is also increasing, accounting for the absolute proportion in stage of IV and V. It is suggested that if comes to stage of IV or V in clinic, DR can be treated as syndrome of shaoyin. Wang^[33] divides DR into 6 types: 1) type of dryness-heat in lung and stomach; the therapies are clearing heat - fire, cooling blood and hemostasis. The representative prescription is baihu decoction. 2) Type of splenasthenic fluid-retention; The therapies are regulating the function of the spleen, eliminating dampness, eliminating phlegm and freeing channels. The representative prescription is wendan decoction. 3) Type of yin asthenia generating intrinsic heat; The therapies are nourishing yin to reduce pathogenic fire, moistening dryness and removing blood stasis. The representative prescription is Yunv decoction. 4) Type of deficiency of both qi and yin; The therapies are tonifying qi and yin. The representative prescriptions are shengmai powder and qiju dihuang decoction. 5) Type of asthenia of both the spleen and kidney; The therapies are nourishing the kidney and warming yang, regulating the function of the spleen and removing blood stasis. The representative prescriptions are sijunzi decoction and shenqi pill. 6) Type of blood stasis; The therapies are dispersing blood stasis and dredge collateral. The representative prescriptions are buyang huanwu decoction and taohong siwu decoction. Professor Liao, who has treated DR for decades, divides DR into 4 types according to the patient's symptoms and signs: 1) Deficiency of both qi and yin, main and collateral channels blocked; Select qiming granule or shengmai powder combined with qiju dihuang pill; 2) Deficiency of both qi and yin, blockage of the vein; In the period of non-proliferation of DR, qiming granule together with xuesaitong capsule (Yunnan Weihe pharmaceutical company limited, the STATE MEDICAL PERMIT NO. Z53021143) or shengmai powder and liuwei dihuang pills can be used. In the period of proliferation, raw typha pollen

decoction (Ophthalmology liujing fayao) can be used in condition of hemorrhage, while taohong siwu decoction can be used in stationary phase. 3) Yin deficiency affecting yang, blood stasis and phlegm stagnation; Selecte buyang huanwu decoction and shenqi pill; 4) Deficiency of yin and yang, intermin - gled phlegm and blood stasis; Based on the prescription of yougui yin, Radix pseudostellariae, poria cocos, dodder, epimedium, pseudo-ginseng and concha arcae can be selected to add^[34].

The Special Prescriptions Compound xueshuantong; according to Wang *et al*'s^[35] research, the group of compound xueshuantong (Salvia miltiorrhiza, pseudo - ginseng, radix scrophulariae, astragalus mongholicus) together with calcium dobesilate capsule have a better performance in improving the patient's vision, fundus oculi, syndrome of TCM and blood rheology compared with the group of pure calcium dobesilate. Xu *et al*^[36] randomly divide 46 cases with simple type of DR into 3 treatment groups, namely tongmai tangyanming treatment group (pharmaceutical ingredients: Astragalus membranaceus, radix rehmanniae recens, lycium chinensis, fructus ligustri lucidi, pseudo - ginseng, semen celosiae), doxium control group and blank control group. It is manifested from the compositive evaluation on the therapeutic effects of the 3 groups that the total effective rate of tongmai tangyanming treatment group and doxium control group are higher than the blank control group ($P < 0.01$). There is no significant difference in the total effective rate between tongmai tangyanming treatment group and doxium group, which illustrates that tongmai tangyanming capsule helps improve the visual function of the patients with DR in an effective way. Sheng^[37] brings in 90 cases of patients with DR, 42 cases (52 eyes) of whom are classified into control group and 48 cases (60 eyes) into treatment group. In research, conventional western medicine is adopted for treatment of control group while decoction of zhuxue mingmu yin (pharmaceutical ingredients: Ginseng should be decocted separately for 3g. Asarum, the rhizome of chuanxiong, radix sileris and schisandra chinensis, each with 5g. Radix paeoniae rubra, radix achyranthis bidentatae, angelica sinensis, rhizoma anemarrhenae, yam and tribulus terrestris, each with 10g. Radix rehmanniae recens and the shell of abalone, each with 15g) is applied for the treatment group. The results show that the total effective rate of treatment group is significantly higher than the control group, which suggests that the prescription for treatment group can improve visual acuity and have a better therapeutic effect.

Combined Therapy of Traditional Chinese Medicine with Laser Photocoagulation The clinical study indicates that the combined treatment of laser with TCM have positive curative effect for DR. Xu *et al*^[38] adopt compound xueshuantong capsule combined with krypton laser to treat 300 cases of DR patients. The total efficiency is 83.1% in the observation group, while that is 62.5% in control group. It is suggested that the effect of combination therapy is remarkable. Wang^[39] uses Chinese medicine combined with retinal

photocoagulation to treat 60 cases of DR patients in stage IV (type of deficiency of liver-yin and kidney-yin and blood stasis). Results: 1) vision: after 3mo treatment, the vision (ametropia with best corrected visual acuity) in treatment group is 0.50 ± 0.50 , while control group is 0.40 ± 0.38 . The comparison between the two groups has statistical significance ($P < 0.05$). The vision improvement of treatment group is superior to the control group. 2) The change of eye-ground hemorrhage, exudation and edema on patients with diabetes by ophthalmoscope: according to the analysis of correlation statistics, the effective rate of treatment group is 92.5%, while the control group is 75%. The comparison between the two groups has statistical significance ($P < 0.05$) and the treatment group has a better performance than the control group. 3) Fundus fluorescein angiography: After 3mo, the leakage area in treatment group is 1.75 ± 1.50 , while control group is 2.00 ± 1.50 . The comparison between the two groups has statistical significance ($P < 0.05$) and the treatment group behaves better than the control group. 4) The comparison of neovascularization degrading: After 3mo, the effective rate of treatment group is 90.0%, while the control group is 72.2%. The comparison between the two groups has statistical significance ($P < 0.05$), while the treatment group is better than the control group. 5) Comparison of the efficacy of macular edema: After 3mo, the effective rate of treatment group is 86.4%, while the control group is 68.4%. The comparison between the two groups has statistical significance ($P < 0.05$) and the treatment group is better than the control group. 6) The overall curative effect: The overall curative effect rate of the treatment group is 75%, while the control group is 52.8%. The comparison between the two groups has statistical significance ($P < 0.05$) and the treatment group is better than the control group. Chen and Bu^[40] use the therapy of syndrome differentiation of TCM to treat 126 cases of DR patients after the treatment of retinal photocoagulation. The efficacy of the treatment group is better than the control group. Wang *et al*^[41] treat 30 cases of DR patients using the method of Chinese medicine combined with laser. Results: the visual acuity and improvement of eye fundus in observation group is better than control group ($P < 0.05$).

CONCLUSION

Although DR is not reversible, it is preventable and controllable. By studying on the literature research in recent years, it is not difficult to find that the combined therapy of TCM with laser has unique advantages in the treatment, prevention, prognosis of DR. In the combined therapy, the pharmacological function of Chinese medicine can produce synergistic effect with that of laser. At the same time, they can make up the deficiency of each other. Compared with the simple laser treatment, combined therapy can more effectively promote the degrading of DR neovascularization, alleviate macular edema, and improve the patients' visual function. But at present there are still some problems for the combined treatment. 1) Most of the clinical curative effect observation is still based on personal clinical experience, lacking the

support of evidence-based medicine theory. 2) The animal experiment research is still not enough. Moreover, it is short of animal model that matching with TCM syndrome types. The mechanism of action of combined therapy calls for further exploration. 3) Criteria for classification of syndrome differentiation and treatment are not unified at present. 4) Many of the prescriptions for treatment of DR are self made and its mechanism is not clear, which brings difficulties for promotion or Manufacture of stable preparation of Chinese patent medicine. So they are not conducive to the clinical and scientific research in the future. But with the development of modern medicine and the gradual objectification of TCM, we should believe that the combined therapy of TCM with laser in the treatment of DR will surely reach a higher stage of development.

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