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Clinical Observation on the Treatment of Macular Edema Secondary to Retinal Vein Occlusion by Liuzi Yangmu Wan Combined with Conbercept Ophthalmic Injection

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Abstract: ***To observe the effects of Liuzi Yangmu Wan combined with Conbercept Ophthalmic Injection in the treatment of retinal vein occlusion secondary to macular edema on the visual acuity and macular thickness of the patients, and to further clarify its clinical efficacy. Eighty patients diagnosed with retinal vein occlusion at Xi'an Fourth Hospital from July 2021 to July 2023, meeting the inclusion criteria, were randomly divided into two groups using a random number table method: the combination group (40 patients, 40 eyes, treated with Liuzi Yangmu Wan combined with intravitreal injection of Conbercept Ophthalmic Injection), and the control group (40 patients, 40 eyes, treated solely with intravitreal injection of Conbercept Ophthalmic Injection). Both groups followed a "1+PRN" treatment regime based on the patient's condition. Best corrected visual acuity (BCVA) and central macular thickness (CMT) were recorded before treatment and 3, 6 months after treatment, as well as the recurrence rate and number of anti-VEGF injections administered. Before treatment, there was no statistically significant difference between the two groups in BCVA and CMT (P>0.05). Three months after treatment, compared to before treatment, the BCVA in the combination group improved from 0.81±0.51 to 0.49±0.28 (P<0.05), and in the control group it improved from 0.79±0.41 to 0.51±0.34 (P<0.05). The CMT in the combination treatment group decreased from 603.92±249.51μm to 434.90±157.81μm (P<0.05), and in the control group, it decreased from 595.20±185.93μm to 464.25±122.69μm (P<0.05), with a significant difference between the two groups (P<0.05). During the follow-up period, no adverse reactions were observed in any of the patients. The number of injections during the observation period was lower in the combination group (2.15±0.58) compared to the control group (2.63±0.66). Liu Zi Yang Mu Wan is safe and effective in treating retinal vein occlusion, capable of improving patients' vision, accelerating the resolution of macular edema, and promoting the absorption of hemorrhages. From this, it can be concluded that the combination of Liuzi Yangmu Wan and Conbercept is more effective than the sole use of Conbercept, and it can reduce the number of intravitreal injections needed.***

Keywords: Liuzi Yangmu Wan, Conbercept Ophthalmic Injection, Retinal Vein Occlusion, Macular Edema, Clinical Observation.

1. Introduction

Retinal Vein Occlusion (RVO) is the second most common retinal vascular disease in ophthalmology [1]. This disease, caused by the narrowing of retinal arteriovenous lumens and limited dilatory function, results in obstructed blood flow or vascular thromboembolism, leading to a disorder in retinal blood circulation. Depending on the location of ischemia, it can be classified into two main types: Branch Retinal Vein Occlusion (BRVO) and Central Retinal Vein Occlusion (CRVO) [2]. The macular edema (ME) that follows is the primary cause of vision impairment in patients with RVO [3]. Persistent macular edema can lead to permanent damage to the retinal structure, resulting in a progressive decline in central vision, and ultimately leading to blindness. Existing research has found that the upregulation of various factors, including vascular endothelial growth factor (VEGF), is a key factor leading to macular edema in cases of Retinal Vein Occlusion (RVO-ME) [4]. In pathological conditions, the destruction of the vascular endothelium and the outer blood-retinal barrier, coupled with the disruption of the balance between the production and drainage of intra- and extracellular fluids in the macular area, leads to fluid accumulation, resulting in macular edema (ME) [5]. In clinical practice, macular edema caused by retinal vein occlusion is generally treated with medications, laser therapy, and vitrectomy surgery [6][7][8]. In recent years, with the increasing variety of anti-VEGF drugs, the treatment of RVO-ME through intravitreal injection of anti-VEGF drugs such as Conbercept Ophthalmic Injection has gained widespread recognition and has become the preferred treatment option for retinal vein occlusion [9]. However, the use of anti-VEGF drugs in RVO patients still presents issues with unstable duration of effectiveness and a tendency for recurrent ME. Patients often require frequent intraocular injections, which increases the risk of intraocular infections. Additionally, the high cost of anti-VEGF drugs imposes significant financial and psychological burdens on patients. While anti-VEGF drugs are effective in treating ME and retinal neovascularization (RNV), they do not improve the overall systemic condition of the patient.

Liu Zi Yang Mu Wan was independently developed by the Xi'an Fourth Hospital, formulated by Chief Physician XiaoQin Lei, who combined traditional Chinese holistic medical thinking and years of clinical experience. It is based on the principles of classic Chinese medicine formulas: Bu Yang Huan Wu Tang and Sheng Mai Yin, and consists of ingredients such as Astragalus, Radix Adenophorae (North Radix), Ophiopogon Japonicus, Salvia Miltiorrhiza, Ligusticum Chuanxiong, Angelica Sinensis, Paper Mulberry (Chu Shi Zi), Plantago Seed (Che Qian Zi), Cuscuta Seed (Tu Si Zi), Goji Berry, Leonurus (Chong Wei Zi), Earthworm (Di Long), and Borneol. This formulation is intended to nourish

the liver and kidney, supplement qi and nourish the blood, and clear the channels to improve vision. After years of clinical trials, it has become a distinctive in-house preparation. To further explore the efficacy of Liu Zi Yang Mu Wan, this study observed the recovery of vision and the regression of macular edema in 80 patients with retinal vein occlusion, providing a reference for clinical treatment.

2. Subjects and Methods

2.1 General Information

A total of 80 patients (80 eyes) diagnosed with RVO-ME from July 2021 to July 2023 at the Xi'an Fourth Hospital were selected. Through random number table method, the patients were divided into two groups: the combination group (40 patients, 40 eyes, treated with Liu Zi Yang Mu Wan in combination with intravitreal injection of Conbercept), and the control group (40 patients, 40 eyes, treated solely with intravitreal injection of Conbercept). In the observation group: 19 males and 21 females, aged between 32 and 79 years, with an average age of 58.38±13.19. In the control group: 20 males and 20 females, aged between 33 and 78 years, with an average age of 57.73±11.96. There was no statistically significant difference in age, duration of disease, and other general information between the two groups ($P>0.05$). All patients met the inclusion criteria.

2.2 Inclusion/Exclusion Criteria

Inclusion Criteria:

(1) Conforming to the diagnostic criteria for retinal vein occlusion as outlined in "Diagnosis and Treatment of Fundus Diseases (2nd edition)" [10].
(2) Presenting with clinical symptoms such as blurred vision, visual distortion, floaters, and photopsia at the time of enrollment.
(3) OCT showing macular edema.
(4) Best-corrected visual acuity ranging from 0.01 to 0.5.
(5) No history of intraocular surgery or other eye diseases.
(6) Complete previous medical history.
(7) No history of blood diseases, immune system diseases, severe cardiovascular and cerebrovascular diseases, or major infectious diseases.
(8) All patients provided informed consent before the procedure.

Exclusion Criteria:

(1) Allergy to the medications used in this study.
(2) Concurrent glaucoma or other fundus diseases.
(3) Concurrent corneal diseases, moderate to severe cataracts, and vitreous hemorrhage.
(4) Need for other treatments during the study period.
(5) Retinal vein occlusion in patients with systemic diseases.

2.3 Treatment

2.3.1 Control group

Under local anesthesia, patients underwent intravitreal injection of Conbercept.

Preoperative Care: For 3 consecutive days before the procedure, patients used Tobramycin Eye Drops (s. a. ALCON-COUVREUR n. v., Approval No. H20091082) and Levofloxacin Eye Drops (Santen Pharmaceutical Co., Ltd., Noto Factory, Approval No. J20150106), 4 times per day, 1 drop per time.

Intraoperative Care: The operative eye was routinely disinfected, surface anesthesia was administered with 5% Proparacaine Eye Drops (s. a. ALCON-COUVREUR n. v., Approval No. H20090082), and the conjunctival sac was rinsed with Povidone-Iodine Solution. A 1ml syringe was used to draw 0.05ml/0.5mg of Conbercept, which was injected 4mm below the corneal limbus into the vitreous cavity. After the needle was withdrawn, the injection site was pressed with a cotton swab for 30 seconds, and Tobramycin and Dexamethasone Eye Ointment was applied. The eye was bandaged and unbandaged the next day. Postoperatively, patients continued using Tobramycin Eye Drops and Levofloxacin Eye Drops for one week, four times per day.

Follow-up: Monthly follow-ups were conducted to check visual acuity, intraocular pressure, slit-lamp examination, and OCT. Repeat injections were considered if there was an increase of 100um in central macular thickness or a two-line decrease in best-corrected visual acuity. Patients were educated preoperatively about eye care methods and common adverse reactions. They were instructed to follow up regularly and seek immediate consultation if they experienced any discomfort.

2.3.2 Joint group

In the control group, patients started taking Liu Zi Yang Mu Wan orally for 3 consecutive days before the procedure, three times a day, one bag each time after meals, continuing the medication for three months.

2.4 Observation Indicators

BCVA and CMT Measurements

Timing: Measurements were taken before treatment, at 3 months post-treatment, and at 6 months post-treatment.

Best-corrected visual acuity (BCVA) was measured using an international standard vision chart and converted using the LogMAR scale. BCVA was recorded before treatment, at 3 months, and at 6 months post-treatment.

Central macular thickness (CMT) was measured using Optical Coherence Tomography (OCT) from Heidelberg Engineering, Germany. Measurements were taken before treatment, at 3 months, and at 6 months post-treatment. The distance from the retinal pigment epithelium to the inner boundary membrane of the macular fovea was measured three times, and the average value was recorded.

Number of Intravitreal Conbercept Injections

The number of intravitreal injections of Conbercept administered to each patient was recorded.

2.5 Statistical Analyses

Statistical analyses were performed using SPSS statistical software version 26. 0.Quantitative data were analyzed using the t-test, and are expressed as (mean standard deviation). Repeated measures data were analyzed using repeated measures ANOVA. A p-value of less than 0.05 was considered statistically significant.

3. Result

Comparison of BCVA Before and After Surgery in Patients: The pre-treatment BCVA comparison between the two groups showed no statistically significant difference (P>0.05). At 3 months and 6 months post-treatment, the combined treatment group showed lower BCVA compared to the control group (P<0.05), and these differences were statistically significant. BCVA at different time points post-treatment improved significantly compared to before treatment in both groups (P<0.05). At 3 months post-treatment, BCVA in the combined treatment group improved from 0.81±0.51 to 0.49±0.28, and in the control group from 0.79±0.41 to 0.51±0.34. At 6 months post-treatment, BCVA was 0.46±0.25 in the combined group, lower than 0.48±0.31 in the control group, but the comparison between 3 and 6 months post-treatment showed no statistically significant difference (P>0.05), indicating that the condition of patients in both groups had stabilized by 6 months post-treatment, as shown in Table 1.

Table 1: Comparison of Best Corrected Visual Acuity Before and After Treatment in Patients ($\bar{x} \pm s$)

Group	n	BCVA		
		After treatment	At 3 months post-treatment	At 3 months post-treatment
Control	40	0.79±0.41	0.51±0.34	0.48±0.31
Joint	40	0.81±0.51	0.49±0.28	0.46±0.25

Comparison of CMT Before and After Treatment in Patients: The comparison of central macular thickness (CMT) before and after treatment in both groups showed statistically significant differences (P<0.05). At 3 months and 6 months post-treatment, the reduction in CMT was more significant in the combined treatment group, indicating better resolution of macular edema compared to the control group.

At 3 months post-treatment, CMT in the combined treatment group significantly decreased from 603.92±249.51μm before treatment to 434.90±157.81μm, while in the control group, CMT reduced from 595.20±185.91μm to 464.72±124.70μm.

At 6 months post-treatment, CMT in the combined treatment group was 423.53±126.31μm, which was lower than in the control group (447.25±122.96μm), and this difference was statistically significant (P<0.05). This indicates that the resolution and stability of macular edema in the control group were less effective compared to the combined group, as illustrated in Table 2.

Table 2: Comparison of CMT Before and After Treatment in Patients($\bar{x} \pm$ s,μm)

Group	n	CMT(μm)		
		After treatment	At 3 months post-treatment	At 3 months post-treatment
Control	40	595.20±185.93	464.72±124.70	447.25±122.69
Joint	40	603.92±249.51	434.90±157.81	423.53±126.31

Number of Injections and Adverse Reactions in Patients: The average number of intravitreal injections of Conbercept in the combination group was 2.15±0.58. In the control group, the average number of intravitreal injections of Conbercept was 2.63±0.66. The difference in the number of injections between the two groups was statistically significant. During the follow-up period, no patients experienced retinal detachment, choroidal detachment, vitreous hemorrhage, endophthalmitis, or other ocular complications, nor were there any systemic adverse reactions. In the combination group, 3 patients had recurrent macular edema, while in the control group, 6 patients had recurrent macular edema.

4. Discussion

Retinal vein occlusion is a common clinical retinal vascular disease with complex etiology and multiple proposed pathogenesis mechanisms. The causes often include systemic factors such as hypertension, diabetes, hyperlipidemia, and atherosclerosis, as well as local factors like high intraocular pressure, glaucoma, arteriovenous crossing compression, and the unique physiological structure of the lamina cribrosa. The pathogenesis theories include thrombosis formation, which involves changes in the vessel wall, hemorheology, and hemodynamics; cytokine theories; and other pathogenic factors [11]. Macular edema is a common complication of RVO that causes vision impairment. Its pathogenesis involves retinal circulatory disorders, disruption of the retinal vascular barrier, and functional damage to retinal pigment epithelial cells, leading to fluid leakage and accumulation in the macular area, resulting in macular edema. Additionally, retinal ischemia and hypoxia can promote the release of VEGF, inducing the formation of new blood vessels, increasing vascular permeability, further exacerbating macular edema, and severely impairing vision [12]. Many traditional Chinese medicine practitioners believe that retinal vein occlusion can be categorized under terms such as "Shi Zhan Hun Miao" (dim vision), "Bao Mang" (sudden blindness), and "Luo Sun Bao Mang" (sudden blindness due to vessel damage) in Chinese medicine. References to "seeing straight lines as curved" in "*Meng Xi Bi Tan*" and "seeing upright as slanted" in "*Mu Jing Da Cheng*" resemble the clinical manifestations of macular edema described in modern medicine. "*The Spiritual Pivot (Lingshu) - The Great Confusion Treatise*" [13] states: "The essence and qi of the five viscera and six bowels all ascend to the eyes and form the essence of vision. The essence of the organs forms the eyes, the essence of the bones forms the pupils, the essence of the tendons forms the blackness, and the essence of the blood forms the vessels." In the "*Treatise on Internal and External Obstacles·Shenshi Yaohan*" [14], it is stated: "The eyes are the essence of the five viscera and six bowels, ascending to the eyes to form vision, much like a house having a skylight. It all originates from the liver and gallbladder, with internal vessels and apertures connecting to the eyes, resulting in vision. Just as underground springs flow through veins, if there is any blockage, the water will not flow."

"*The Treatise on Blood Syndromes*" [15] records: "When blood stagnation persists for a long time, water will eventually form," and "Water disease affects the blood, causing the blood to transform into water." "*The Standard of Diagnosis*

and Treatment" [16] states: "There are no other symptoms inside or outside the eyes, only dim and unclear vision… This may be due to mental fatigue, blood deficiency, weakened vital energy, or depleted essence causing dim vision… It is also related to damage to the qi, blood, essence, and vessels within the eyes." If the blood does not flow smoothly, it turns into water. When emotions are not relieved, liver qi stagnates, obstructing the flow of qi. Stagnant qi can transform into fire, consuming the yin fluids and affecting the circulation of qi, blood, and body fluids. This leads to the deprivation of nourishment in the blood vessels and stagnation of the divine water. Alternatively, prolonged stagnation can result in liver and kidney deficiency, leading to insufficient nourishment of the eyes and depletion of the source of spiritual light [17]. The macula belongs to the spleen, the pupil to the kidney, and the liver opens into the eyes. Retinal vein occlusion and subsequent macular edema are closely related to the liver, spleen, and kidney. Weng Wenqing [18] and others divide RVO-ME into three stages: In the early stage, the onset is acute with blood obstructing the vessels. It is necessary to improve blood circulation to promote the absorption of retinal hemorrhage and macular edema, thus using treatments to invigorate blood and remove stasis. In the middle stage, patients experience a decline in vision, affecting their emotions, which can lead to liver qi stagnation impacting the spleen. Spleen deficiency generates phlegm, further aggravating macular edema. Treatment should focus on regulating qi, soothing the liver, invigorating blood, and unblocking the collaterals. In the late stage, prolonged illness leads to liver and kidney deficiency, and spleen deficiency causes water retention. Treatment should aim to tonify the liver and kidneys, boost qi, and invigorate blood. The principle of treating RVO-ME should combine tonification with unblocking the collaterals, supplemented with promoting urination and removing dampness.

Professor Xiaoqin Lei, a renowned traditional Chinese medicine (TCM) practitioner from Shaanxi Province, formulated the Liuzi Yangmu Wan based on clinical experience. This prescription is an adaptation of the Buyang Huanwu Tang and Shengmai Yin, and it is a special in-hospital preparation of the Xi'an Fourth Hospital. The basic ingredients of Liuzi Yangmu Wan are: Astragalus, Rehmannia glutinosa, Glehnia, Ophiopogon japonicus, Schisandra, Salvia miltiorrhiza, Ligusticum chuanxiong, Angelica sinensis, Broussonetia papyrifera, Plantago asiatica, Pueraria, Cuscuta chinensis, Leonurus japonicus, Lycium barbarum, Pheretima, and Borneol. Its effects include tonifying qi and nourishing blood, benefiting the liver and kidneys, invigorating blood and removing stasis, unblocking the collaterals, and improving vision. Among these, Astragalus tonifies qi and strengthens the body's surface, expels toxins, and promotes pus discharge, thereby enhancing immune regulation. It has made significant progress in anti-aging, anti-tumor, and diabetes treatments [19],[20]; Rehmannia glutinosa nourishes yin and supplements blood, benefits essence, and replenishes marrow. When used together with other herbs, it tonifies the liver and kidneys, benefits qi and blood, and can promote the proliferation of stem cells [21]; Glehnia and Ophiopogon japonicus nourish yin and moisten dryness, tonify qi, and generate fluids, thus promoting the healthy functioning of middle qi;Salvia miltiorrhiza can invigorate blood, remove stasis, and promote blood circulation in the vessels. Previous studies have shown that Salvia miltiorrhiza has effects such as anti-lipid peroxidation and free radical scavenging. It can dilate blood vessels and accelerate blood flow, thereby improving microcirculation in the fundus of the eye [22]; Ligusticum (chuanxiong) is a commonly used herb for invigorating blood and removing stasis. Its nature ascends to the head and eyes, promoting angiogenesis, anti-inflammation, and antioxidant effects, as well as protecting nerves. It is widely used in ophthalmology [23]; Angelica sinensis has the effect of invigorating blood and removing stasis. It is an essential herb for tonifying and invigorating blood. It has antioxidant properties and can increase blood flow [24]; Mulberry fruit, plantain seed, dodder seed, goji berry, and motherwort seed all can tonify the liver and kidneys and improve vision [25]. There is also a wealth of research findings on their anti-tumor, antioxidant, and anti-aging effects; Schisandra has functions of astringing and securing essence, benefiting Qi, generating fluids, tonifying the kidneys, and calming the heart. Earthworm and borneol can clear heat, extinguish wind, unblock the meridians, and open orifices. The Liuzi Yangmu Wan targets the pathogenesis of RVO-ME by nourishing the liver and kidneys, benefiting Qi, enriching the blood, unblocking the meridians, and improving vision. A large amount of clinical data from earlier studies shows that the Liuzi Yangmu Wan can control or improve the vision of RVO patients, improving fundus signs (such as hemorrhages, exudates, and vascular leakage), subjective symptoms (such as blurry vision and dry eyes), and reducing the frequency of intraocular injections. However, the mechanism by which the Six Seeds to Nourish Eyes Pill treats RVO remains unclear and requires further research.

Conbercept is a new generation anti-VEGF fusion protein, and it has good efficacy and safety in treating RVO-ME [26], [27]. However, follow-up studies have found that some patients experience a recurrence of macular edema due to the limited duration of the drug's effect and relatively high treatment costs. This study showed significant differences in BCVA and CMT before and after treatment, with some improvements in patient vision and good resolution of macular edema. Both groups showed significant improvement, but the combination group treating RVO-ME showed a significant reduction in macular edema, which remained stable. A few patients experienced recurrence of macular edema 3 months post-treatment, but the condition of the majority in the control group tended to stabilize. The reason analyzed is that the Liuzi Yangmu Wan can promote microcirculation around the eyes, increase blood flow around the eyes, establish collateral circulation for ischemic tissues at the fundus, increase oxygen supply to the retinal tissues, enhance metabolism, thereby protecting the optic nerve and improving visual function.

In conclusion, the combination of Liuzi Yangmu Wan and intravitreal injection of conbercept can effectively improve vision, promote the absorption of retinal hemorrhage and exudate, and resolve macular edema in the treatment of RVO-ME. Of course, this study has certain limitations, such as a small sample size, necessitating further increase in the number of cases to verify complications and recurrence rates. It is also worth observing the hemodynamics of the eyes and the absorption of fundus hemorrhage in patients. Further

research on the mechanism of the Liuzi Yangmu Wan is needed, which paves the way for future studies.

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