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Original Article

Analysis of the efficacy and safety of Danshen Dripping pills on the eyes of diabetic retinopathy patients with Qi stagnation and blood stasis

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Abstract: Objective: To analyze the efficacy and safety of compound Danshen dripping pills (CDDPs) in the treatment of patients with diabetic retinopathy (DR) with the syndrome of Qi stagnation and blood stasis. Methods: The clinical data of 81 patients with DR admitted to our hospital were analyzed retrospectively, and the patients were divided into an observation group (n=40) and a control group (n=41) in accordance with a random number table. The observation group was treated with CDDPs, while the control group was treated with Captopril. The response rates, change of severity degrees of retinopathy, improvement of vision, incidence of macular edema and symptom scores were compared between the two groups. Results: (1) The ratio of decreasing degree of severity of retinopathy in the observation group was greater than that in the control group, while the ratio of increasing degree of severity of retinopathy in the observation group was lower than that in the control group ($P < 0.05$). There was no significant difference in the constant ratio of degree of severity of retinopathy between the two groups ($P > 0.05$). (2) After treatment, the scores for dim vision, somber facial complexion, dry eyes, encrusted skin and numbness of the limbs in the observation group were lower than those in the control group ($P < 0.05$). (3) The overall response rates (ORRs) were 87.50% and 63.41% in the observation group and the control group, respectively ($P < 0.05$). (4) After treatment, the vision in the left and right eye in the observation group was higher than those in the control group ($P < 0.05$). (5) The incidence rates of macular edema were 12.50% and 31.71% in the observation group and the control group, respectively ($P < 0.05$). Conclusion: CDDPs can effectively elevate the response rate, reduce the degree of severity of retinopathy, mitigate the incidence of macular edema, and improve the vision of DR patients with the syndrome of Qi stagnation and blood stasis, exhibiting a satisfactory safety profile. Therefore, it has a good application value.

Keywords: Syndrome of Qi stagnation and blood stasis, diabetes, retinopathy, compound Danshen dripping pills, treatment

Introduction

Diabetes mellitus (DM) is a chronic life-long metabolic disease with a very high clinical incidence. So far, no effective treatment option has been identified clinically. DM patients must control blood sugar levels with medication [1]. With the progression of disease and the prolongation of the course of disease, DM patients may be accompanied by multiple complications. Among the complications, diabetic retinopathy (DR) has the highest degree of severity [2]. DM patients with DR have retinal detachment, microaneurysm, hemorrhage, exudate, neovascularization, venous beading, all leading to a higher risk of blindness [3].

A study has indicated that blood stasis caused by a blood circulation disorder in a high-sugar environment is the main pathogenesis of DR [4]. Blood stasis leads to a change from dynamic to static blood circulation, blood circulation disorder, damage incurred in the involved tissues, and multiple pathological changes (e.g., inflammation, necrosis, edema, hyperplasia, exudation, hardening and degeneration of tissues and cells) [5]. Clinically, there is no specific drug to treat DR. In Western medicine, surgery or retinal photocoagulation are primarily implemented to treat such patients. However, the efficacy is not exact, the risk of postoperative complications is high, and patients have to bear heavy medical expenses [6]. In traditional

Chinese medicine (TCM), DR is classified into the category of xiaoke eye disease, and it is believed that the obstruction of vessels and networks, blood failing to stay in the channels and an overflow pulse occur as a result of syndrome of Qi stagnating and phlegm congealing, hyperactivity of Yang due to Yin vacuity, Qi stagnation and blood stasis, and Qi vacuity with blood stasis [7]. Stasis is an important cause of DR. Therefore, eliminating the obstructing stasis and anomalous stasis is taken as the treatment principle, hemostasis is performed to treat the tip, and transforming stasis is conducted to treat the root. Drugs for promoting blood flow and removing stasis should be selected for treatment [8].

In this study, a total of 81 patients with DR and syndrome of Qi stagnation and blood stasis were selected as the subjects. The application value of compound Danshen dripping pills (CDDPs) was analyzed, so as to seek more effective methods for the treatment of such patients.

Materials and methods

Data

The clinical data of 81 patients with DR admitted to our hospital were analyzed retrospectively, and the patients were divided into an observation group (n=40; age: 50-73 years old; height: 153-175 cm; body weight: 51-76 kg; course of retinopathy: 1-5 years; course of DM: 4-16 years) and a control group (n=41; age: 51-74 years old; height: 155-178 cm; body weight: 52-77 kg; course of retinopathy: 1-6 years; course of DM: 5-16 years) in accordance with a random number table. (1) Inclusion criteria: defined history of type 2 DM; compliance with the diagnostic criteria for DR [9]; syndrome of Qi stagnation and blood stasis in *Standards of Traditional Chinese Medicine Syndrome Differentiation* [10]; those without cognitive impairment, with clear consciousness; voluntary signing of the informed consent form and approval from the Ethics Committee of Shengli Oilfield Central Hospital. (2) Exclusion criteria: patients without complete clinical medical records; syndromes other than syndrome of Qi stagnation and blood stasis in accordance with TCM syndrome differentiation; persistent hyperglycemia patients with glycosylated hemoglobin > 8.0%; patients in the proliferative phase of retinopathy; retinopathy induced by type 1 DM.

Methods

The control group was treated with Captopril (specification: 25 mg*100 s, SFDA approval number: H19993357, manufacturer: Shanxi Jinhua Huixing Pharmaceutical Co., Ltd.) twice a day, 12.50 mg each time. After 3 months of continuous treatment, the dosage was adjusted to 3 times a day at a dose of 12.50 mg each time. The treatment lasted for 6 months.

The observation group was treated with CDDPs (specification: 25 mg*100 pills, SFDA approval number: Z10950111, manufacturer: Tasly Pharmaceutical Group Co., Ltd.) 3 times a day, 20 pills each time. The treatment lasted for 6 months.

Observational indices

Grading of severity degrees of retinopathy [11]: No obvious lesions: no abnormality was found under the ophthalmoscope after mydriasis. Mild non-proliferative diabetic retinopathy (NPDR): After mydriasis, only microangiomas could be seen under the ophthalmoscope. Moderate NPDR: After mydriasis, microaneurysm and others were seen under the ophthalmoscope, but the degree was lower than that of severe NPDR. Severe NPDR: After mydriasis, any one of the following three items was seen under the ophthalmoscope, but there was no sign of proliferative diabetic retinopathy: there were more than 20 quadrants with retinal internal bleeding points in 4 quadrants; there were more than 2 quadrants with changes in definite venous beading; there were more than one quadrant with definite intraretinal microvascular abnormality (IRMA). Proliferative diabetic retinopathy (PDR): One or more item(s) of preretinal hemorrhage, vitreous hemorrhage and neovascularization. The assessments were performed before treatment and at 6 months after treatment. After treatment, one or more grade(s) lower than that before treatment was regarded as a decrease in severity, no change in grade was regarded as no change in severity, and one or more grade(s) higher than that before treatment was regarded as an increase in severity.

Table 1. Comparison of general data between the two groups ($\bar{x}$±s)/[n (%)]

Data		Observation group (n=40)	Control group (n=41)	t/X^2	*P*
Gender	M	18 (45.00)	19 (46.34)	0.015	0.904
	F	22 (55.00)	22 (53.66)		
Age (year)		62.45 ± 10.13	63.28 ± 10.42	0.363	0.717
Height (cm)		163.45 ± 8.19	165.38 ± 8.21	1.059	0.293
Weight (kg)		62.68 ± 8.34	63.53 ± 8.49	0.454	0.651
Course of retinopathy (years)		3.26 ± 1.85	3.32 ± 1.91	0.144	0.886
Course of DM (years)		11.46 ± 3.38	11.84 ± 3.51	0.496	0.621

Symptom scores: The symptoms include dim vision, somber facial complexion, dry eyes, encrusted skin and numbness of the limbs. Among them, the first three symptoms were scored 0, 2, 4 and 6 points from lower degree of severity to higher degree of severity, and the last one was scored 0, 1, 2 and 3 points from lower degree of severity to higher degree of severity. Symptom scores were assessed before treatment and at 6 months after treatment.

Efficacy criteria [12]: Marked response: there were differences of over 20% in the decrease in the degree of retinal microvascular lesion before and after treatment; Moderate response: there were differences of 10%-20% in the decrease in the degree of retinal microvascular lesion before and after treatment; No response: proliferative changes (e.g., neovascularization) occur in retina, or there were differences of more than 10% in the increase in the degree of retinal microvascular lesion before and after treatment. ORR = Marked response rate + Moderate response rate.

Vision levels: The vision levels in the two groups were measured before treatment and at 6 months after treatment.

Macular edema: The incidence rates of macular edema were compared between the two groups during treatment and after treatment. Diagnostic criteria [13]: Retinal thickening occurred within 500 um of macular fovea; Hard exudate occurred within 500 um of macular fovea, and the peripheral retina thickened. The retinal thickening occurred at more than one site(s) with an area of ≥1 optic disc(s), and the distance between the lesion at any sites and the macular fovea was less than 1 optic disc diameter. Macular edema is believed to occur if there is one of the above three items.

Statistical analysis

SPSS 22.0 was adopted for statistical analysis. The measurement data were expressed as mean ± standard deviation (mean ± SD), and the results between groups and within groups were compared by independent sample *t* test. The enumeration data were expressed as [n (%)], and the results between groups and within groups were compared by X^2 test. $P < 0.05$ indicated a statistically significant difference.

Results

Comparison of general data between the two groups

There was no significant difference in the ratios of male and female patients, mean age, mean height, mean weight and mean courses of retinopathy and DM between the two groups ($P > 0.05$) (**Table 1** and **Figure 1**).

Comparison of graded degree changes of severity of retinopathy between the two groups

After treatment, there were 10 cases (25.00%) with a reduced degree of severity of retinopathy, 29 cases (72.50%) with no change in the severity degree of retinopathy, and 1 case (2.50%) with an increased degree of severity of retinopathy in the observation group; and there were 3 cases (7.32%) with a reduced degree of severity of retinopathy, 28 cases (68.29%) with no change in the degree of severity of retinopathy, and 10 cases (24.39%) with an increased degree of severity of retinopathy in the control group. The ratio of patients with a reduced degree of severity of retinopathy in the observation group was significantly higher than that in the control group ($P < 0.05$), while the ratio of patients with an increased degree of severity of retinopathy in the obser-

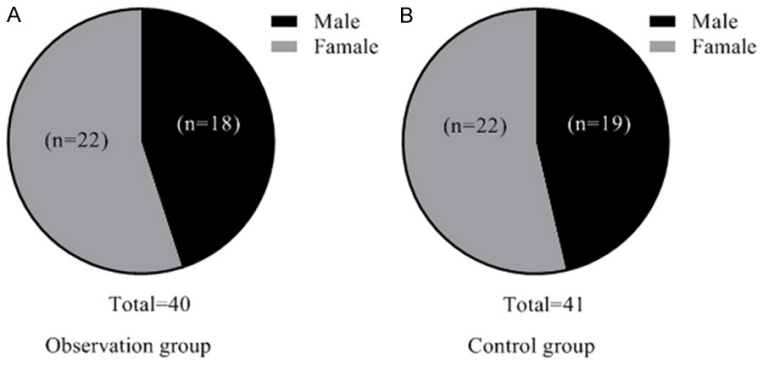

Figure 1. Comparison of the ratios of male and female patients between the two groups. There was no marked difference in the ratios of male and female patients between observation group and control group ($P > 0.05$).

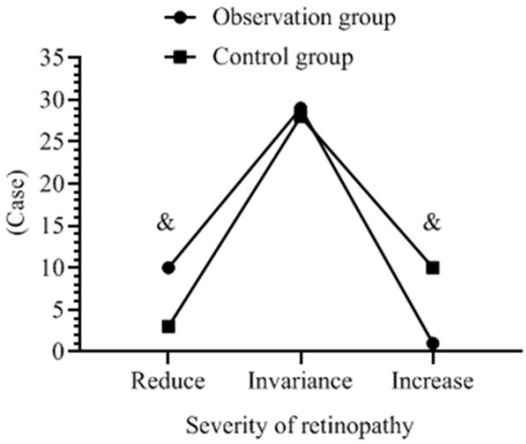

Figure 2. Comparison of degree of graded severity changes of retinopathy between the two groups. The ratio of patients with reduced grades of severity degree of retinopathy in the control group was significantly higher than that in the observation group ($P < 0.05$); there was no considerable difference in the ratio of patients with no change in the severity degree of retinopathy between the two groups ($P > 0.05$); the ratio of patients with an increased grade of severity of retinopathy in the control group was markedly lower than that in the observation group ($P < 0.05$). &indicates comparison between the two groups ($P < 0.05$).

vation group was remarkably lower than that in the control group ($P < 0.05$). There was no significant difference in the ratio of patients with no change in the severity degree of retinopathy ($P > 0.05$) (**Figure 2**).

Comparison of symptom scores between the two groups

Before treatment, the symptom scores for dim vision, somber facial complexion, dry eyes, encrusted skin, and numbness of the limbs were (4.23 ± 1.16) points and (4.35 ± 1.21) points, (4.51 ± 1.09) points and (4.41 ± 1.23) points, (4.22 ± 1.10) points and (4.17 ± 1.05) points, (4.31 ± 1.21) points and (4.38 ± 1.26) points, and (2.02 ± 0.34) points and (2.10 ± 0.36) points in the observation group and the control group, respectively. After treatment, the symptom scores for dim vision, somber facial complexion, dry eyes, encrusted skin, and numbness of the limbs were (1.62 ± 0.38 points and (2.57 ± 0.56) points, (1.34 ± 0.42) points and (2.61 ± 0.59) points, (1.63 ± 0.37) points and (2.96 ± 0.54) points, (1.50 ± 0.49) points and (2.61 ± 0.57) points, and (0.54 ± 0.19) points and (0.92 ± 0.24) points in the observation group and the control group, respectively. There was no statistical difference in symptom scores between the two groups before treatment ($P > 0.05$). After treatment, the symptom scores in the two groups were lower than those before treatment ($P < 0.05$), and the symptom scores in the observation group were significantly lower than those in the control group ($P < 0.05$) (**Figures 3**, **4**).

Comparison of response rates between the two groups

In the observation group treated with CDDPs, there were 12 patients with marked response, 23 patients with moderate response, and 5 patients with no response, with an ORR of 87.50%. In the control group treated with western medicine, there were 8 patients with marked response, 18 patients with moderate response, and 15 patients with no response, with an ORR of 63.41%. There were statistically significant differences in the ORRs between the two groups ($P < 0.05$) (**Table 2**).

Comparison of changes of vision between the two groups

Before treatment, the vision level in the left eye were (4.55 ± 0.37) and (4.59 ± 0.36) in the observation group and the control group, respectively, and the vision level in the right eye were (4.44 ± 0.32) and (4.43 ± 0.35) in the

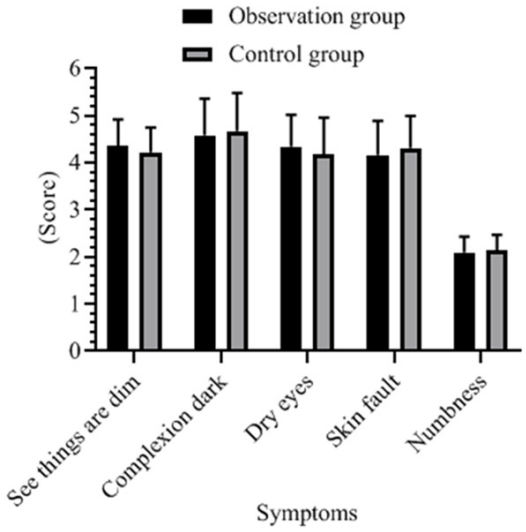

Figure 3. Comparison of symptom scores between the two groups before treatment. Before treatment, there was no significant difference in the symptom scores for dim vision, somber facial complexion, dry eyes, encrusted skin, and numbness of the limbs between the two groups ($P > 0.05$).

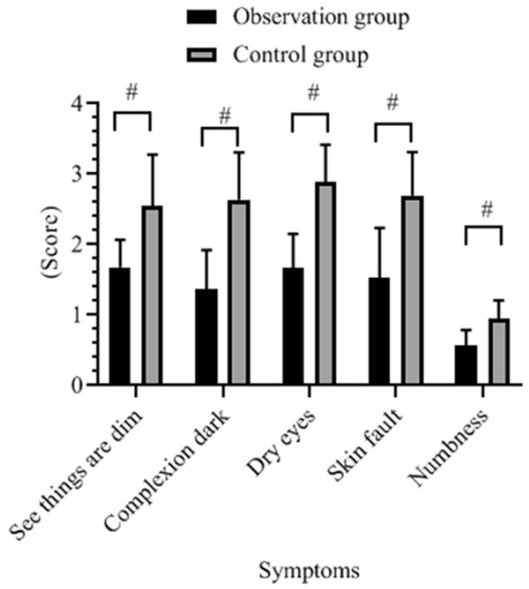

Figure 4. Comparison of symptom scores between the two groups after treatment. After treatment, the symptom scores for dim vision, somber facial complexion, dry eyes, encrusted skin, and numbness of the limbs in the observation group were remarkably lower than those in the control group ($P < 0.05$). #indicates comparison between the two groups ($P < 0.05$).

observation group and the control group, respectively. After treatment, the vision level in the left eye were (4.86 ± 0.29) and (4.52 ± 0.21) in the observation group and the control group, respectively, and the vision level in the right eye were (4.89 ± 0.31) and (4.49 ± 0.25) in the observation group and the control group, respectively. Before treatment, there was no significant difference in the vision level of the left and right eyes between the two groups ($P > 0.05$). After treatment, the vision level in the left and right eyes in the observation group was markedly higher than those in the control group ($P < 0.05$) (**Figure 5**).

Comparison of incidence rates of macular edema between the two groups

During treatment and after treatment, there were 5 patients with macular edema (incidence rate: 12.50%) in the observation group and 13 patients with macular edema (incidence rate: 31.71%) in the control group, respectively. The comparison of the incidence rates of macular edema between the two groups was statistically significant ($P < 0.05$) (**Table 3**).

Discussion

Recently, the rising incidence of DM has led to the increasing incidence rate of DR. To date, the pathogenesis of DR has not been fully defined clinically. Therefore, there is no unified standard for the treatment of DR, and there are multiple treatment options [14, 15]. Based on the specific degree of severity of the patients' conditions, drug therapy, laser therapy and vitrectomy can be selected. After treatment, the clinical symptoms can be improved to a certain extent, but the treatment has certain risks, which may lead to many complications [16, 17]. Over these years, the in-depth studies on TCM have been extensively conducted. As a result, there are new options for the treatment of DR.

TCM believes that the eyes are a closed organ. If there is internal bleeding, the blood cannot flow out and be absorbed, eventually forming blood stasis [18]. TCM believes that the causes of blood stasis include Qi deficiency, Yin deficiency, phlegm dampness, and blood heat, and that blood stasis occurs throughout the entire process of retinopathy. Therefore, special attention should be paid to accelerate the blood flow and remove stasis during treatment [19]. The study by Fang et al. [20] proved that drugs for quickening blood flow and removing stasis effectively improved hemorhe-

Table 2. Comparison of response rates between the two groups [n (%)]

Group	Marked response	Moderate response	No response	ORR
Observation group (n=40)	12 (30.00)	23 (57.50)	5 (12.50)	35 (87.50)
Control group (n=41)	8 (19.51)	18 (43.90)	15 (36.59)	26 (63.41)
X^2				6.317
P				0.012

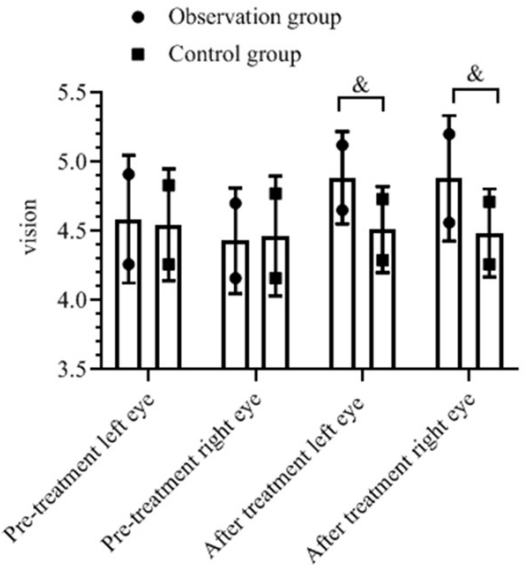

Figure 5. Comparison of changes of vision between the two groups. Before treatment, there was no significant difference in the vision level in the left and right eyes between the two groups ($P > 0.05$). After treatment, the vision level in the left and right eyes in the observation group was remarkably higher than those in the control group ($P < 0.05$). [&]indicates comparison between the two groups ($P < 0.05$).

ology and fundus microcirculation, controlled blood lipid levels and blood sugar levels, significantly reduced blood viscosity, dilated blood vessels, and markedly increased ocular blood flow of DR patients. In addition, the study of Qiu et al. [21] showed that drugs for accelerating blood flow and removing stasis inhibited the formation of platelet aggregation, improved insulin resistance, and delayed the occurrence and progression of retinopathy. In this study, the observation group receiving CDDPs showed more marked improvement in the degree of severity of retinopathy compared with the control group. After treatment, the symptom scores in the observation group were remarkably lower than those in the control group, and the vision level in the left and right eyes in the observation group were higher than those in the control group ($P < 0.05$). This proved that TCM significantly alleviated the degree of severity of retinopathy in patients, effectively improved their symptoms, and elevated their vision level. Chen et al. [22] found that the CDDPs effectively improved vision and fundus conditions of DR patients. In addition, the ORR (87.50%) in the observation group was markedly higher than that (63.41%) in the control group ($P < 0.05$). The incidence rate (12.50%) of macular edema in the observation group was remarkably lower than that (31.71%) in the control group ($P < 0.05$). This indicated that a more satisfactory therapeutic effect could be obtained and the complications could be reduced using TCM.

The CDDPs, mainly composed of Radix Notoginseng, Borneolum Syntheticum and Radix Salviae Miltiorrhizae, can accelerate the blood and remove stasis, and rectify Qi and relieve pain. Modern pharmacological studies have proved that CDDPs can improve blood flow, realize angiectasis, control blood lipid levels, and inhibit platelet aggregation and adhesion [23]. Among them, Salviae Miltiorrhizae has been proved to have a satisfactory inhibitory effect on platelet aggregation, and it has an anticoagulatory effect and can mitigate the risk of thrombosis [24]. Song et al. [25] indicated that CDDPs effectively improved insufficient blood perfusion and reduced blood viscosity of rats with DR, and accelerated the blood and removed stasis. Jun et al. [26] proved that CDDPs remarkably improved the fundus condition and fundus microcirculation, effectively delayed the progression of retinopathy, and significantly improved the vision level. According to the TCM theory and relevant studies on retinopathy, CDDPs can rectify Qi and relieve pain and accelerate the blood and remove stasis through the compatibility of its components, so that a more satisfactory clinical treatment efficacy and an improved prognosis of DR patients can be achieved.

In summary, CDDPs can effectively elevate the response rate, reduce the severity degree of retinopathy, mitigate the incidence of macular

Table 3. Comparison of incidence rates of macular edema between the two groups [n (%)]

Group	Number of cases	Incidence	Without incidence
Observation group	40	5 (12.50)	35 (87.50)
Control group	41	13 (31.71)	28 (68.29)
X^2		4.322	
P		0.038	

edema, and improve the vision of patients with DR who have syndrome of Qi stagnation and blood stasis, exhibiting a satisfactory safety profile. Therefore, it has a good application value. However, this study is a retrospective study. The study subjects cannot be screened beforehand, the number of study subjects is insufficient, the analysis of study results lacks comprehensiveness, and the results are not representative enough. Therefore, future in-depth studies with a larger sample size and a focus on multiple aspects should be performed, so as to obtain more scientific and representative study conclusions, thereby providing more guidance on the treatment of DR patients with syndrome of Qi stagnation and blood stasis.

Disclosure of conflict of interest

None.

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