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Original Article

HBOT combined with STS improves hemodynamics and hemorheology in RVO patients

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Abstract: Objective: This study was designed to analyze the effects of hyperbaric oxygen therapy (HBOT) combined with sodium tanshinone IIa sulfonate (STS) in RVO (retinal vein occlusion) patients. Methods: 85 RVO patients admitted to our hospital from December 2017 to October 2018 were included, retrospectively analyzed, and randomly divided into the control group (CG, n=42) for HBOT and the observation group (OG, n=43) for HBOT combined with STS. The two groups were compared in terms of hemodynamics and hemorheology. Results: (1) At the end of, 1, 3, and 6 months after the treatment, the OG reported higher BCVA and lower CRT compared with the CG (P<0.05); (2) No significant differences were observed in the 2 groups in terms of intraocular pressure (IOP) before, at the end of, and at 1 week and 1 month after the treatment (P>0.05); (3) After the treatment, the whole blood viscosity (high/low shear rate), plasma specific viscosity, and fibrinogen levels were lower, and the RI, Vmax and Vmin were better in the OG compared with the CG (P<0.05); (4) After the treatment, the total effective rate was 90.70% in the OG and 73.81% in the CG (P<0.05). Conclusion: The combination of HBOT and STS improves the hemodynamics and hemorheology indices in RVO patients and is worthy of an extensive application in the future.

Keywords: RVO, HBOT, STS, hemodynamics, hemorheology

Introduction

Retinal vein occlusion (RVO) is a common retinal vascular disease in ophthalmology. It may compromise patients' visual acuity significantly due to macular edema, the most important factor, and other factors such as neovascularization and macular ischemia [1].

According to statistical data, about 30% of RVO patients end up with low vision and 20% with ablepsia [2]. Through no consensus has been reached in the clinical study on the pathogenic mechanism of RVO, most of scholars support the conclusion that during the development and progression of RVO, high blood viscosity, arteriosclerosis, hypertension, diabetes, and abnormal hemodynamics may exert impacts to varying degrees [3]. The unclear explanation of the pathogenic mechanism also results in the absence of specific standards, effective methods, or drugs in the clinic. Therefore, drug injection to the vitreous chamber and endolaser photocoagulation are mostly used regardless of their unsatisfactory efficacy [4].

In the studies by Gaynon et al. [5] and Călugăru et al. [6], it was found that in CRVO patients, the macular edema is significantly alleviated by HBOT, inhibited by tanshinone in formation, and promoted in absorption, so as to reduce the impact on vision and improve vision. This study included 85 RVO patients to specifically explore the effectiveness of HBOT and STS in the treatment, in order to provide a reference for the clinical treatment of RVO.

Materials and methods

Materials

85 RVO patients admitted to our hospital from December 2017 to October 2018 were included, retrospectively analyzed, and found to suffer from cerebral infarction, diabetes, and hypertension. The patients were randomly divided into the CG (n=42) and the OG (n=43). The patients in the CG ranged in age between 43 and 69 with a disease course between 1 week and 4 months; the patients in the OG ranged in age between 41 and 68 with a dis-

ease course between 2 weeks and 4 months. (1) Inclusion criteria: patients diagnosed with RVO in one eye for less than 6 months using optical coherence tomography (OCT), color fundus photography (CFP), fundus fluorescein angiography (FFA) and slit-lamp examinations were also included; patients who agreed to undergo continuous follow-ups for observation; we received written informed consents from them, and the study was approved by the Ethics Committee of Nanfang Hospital. (2) Exclusion criteria: some patients were excluded as they had other severe ophthalmological diseases, cataracts, macular holes, keratopathy which affects vision, they were allergic to the drug studied, they had contradictions to HBOT, they had undergone ophthalmological surgical treatment before, or they were unable to complete a follow-up schedule lasting more than 3 months.

Methods

A laser photocoagulation was performed on all patients by the same medical team. After the operation, the patients in the CG were treated with HBOT once a day. An HBOT cycle consisted of compressed oxygen uptake lasting 20 min, stabilized oxygen uptake lasting 1 h, a break lasting 5 min before another round of compressed oxygen uptake lasting 15 min. A course of treatment lasted for 10 days, after which, the patients had to rest for 5 days before starting the second course.

The patients in the OG were treated with HBOT following the same method, time and course, and STS (Nuoxinkang, specification: 2 ml ampoules, 6 pieces per box, approval document No. GYZZ H31022558, manufacturer: SPH No. 1 Biochemical & Pharmaceutical Co., Ltd.) by dissolving 80 mg in 250 ml of 5% glucose injection for an intravenous drip. They were treated once a day for 2 courses of 10 days each.

Observation indices

(1) Best Corrected Visual Acuity (BCVA): BCVA was measured by the international standard visual chart before, and at the end of, 1 month, 3 months, and 6 months after the treatment.

(2) Macular central retinal thickness (CRT): CRT was measured using OCT before, and at the end of, 1 month, 3 months, and 6 months after the treatment.

(3) IOP: IOP was measured with a non-contact tonometer before, and at the end of, 1 week and 1 month after treatment.

(4) Hemorheology: 4 ml blood was drawn from the veins of all the patients (who fasted before the blood draw) in the morning both before and after the treatment (2 courses), and collected into a anticoagulation tube containing heparin, fully shaken and measured for whole blood viscosity (high/low shear rate), plasma specific viscosity, fibrinogen level in 4 h.

(5) Hemodynamics: Before and after the 2 courses of treatment, all the patients were measured for their resistance index (RI), minimum and maximum diastolic blood flow velocity (Vmin and Vmax) in the systole of central retinal arteryocclusion (CRA) using the following methods: a color Doppler ultrasound diagnostic instrument was adopted with the controlled probe set to a frequency between 5 and 12 MHz. Patients lied in a dorsal position with both eyes closed. The probe was placed gently without pressure on the surface of the eyelids for the measurements.

(6) Efficacy criteria: The efficacy criteria were formulated according to the *Guiding Principles for Clinical Research of New Traditional Chinese Medicines* [7], in which, “cured” is defined as the vision recovers to 1.0 or above, the fundus hemorrhage is completely absorbed, and the FFA returns to normal in the re-examination; “upturn” is defined as vision improved by more than 3 lines but still under 1.0, more than 35% of the fundus hemorrhage is absorbed, and obvious improvements in the FFA are observed in the re-examination; “invalid” is defined as instead of improvement, the patient’s vision and FAA further worsen after the treatment, and the fundus hemorrhage increases rather than being absorbed. Total effective rate = cured rate + upturn rate.

Statistical analysis

The statistical analysis was performed with SPSS 22.0. In the case of numerical data expressed as the mean ± standard deviation, the intergroup comparisons were carried out using independent-samples *t* tests; in the case of nominal data expressed as [n (%)], the intergroup comparisons were carried out using X^2 tests. ANOVOA and F inspection were adopted

Table 1. Comparison between the OG and the CG in the general data ($\bar{x}$ ± s)/[n (%)]

Data		OG (n=43)	CG (n=42)	t/X^2	*P*
Gender	Male	20 (46.51)	19 (45.24)	0.014	0.906
	Female	23 (53.49)	23 (54.76)		
Age (y)		53.46±8.19	52.19±8.21	0.714	0.477
BMI (kg)		61.28±10.13	62.75±10.18	0.667	0.507
Course of disease (month)		2.75±1.13	2.78±1.15	0.121	0.904
Complicated disease	Cerebral infarction	5 (11.63)	4 (9.52)	0.099	0.753
	Diabetes	7 (16.28)	8 (19.05)	0.112	0.738
	Hypertension	10 (23.26)	8 (19.05)	0.225	0.635

for the comparison between multiple points in a group. For all the statistical comparisons, significance was defined as P<0.05.

Results

A comparison of the two groups' clinicopathological data

No significant differences were observed in the two groups in the proportions of males and females, the average age, the average disease course, the average BMI, or the weights of the various complicated diseases (P>0.05, **Table 1**).

Comparison of the two groups in terms of their BCVA

Before the treatment, the BCVA was (0.171±0.04) in the OG and (0.172±0.06) in the CG (P>0.05); but at the end of 1 month, 3 months, and 6 months after the treatment, the BCVA gradually rose to (0.336±0.09), (0.453±0.10), (0.516±0.12) and (0.568±0.15) in the OG and (0.231±0.08), (0.312±0.09), (0.412±0.11) and (0.504±0.13) in the CG. The BCVA in the OG was higher after the treatment and at 1, 3, and 6 months after the treatment than it was before the treatment (P<0.05), and the BCVA in the CG was higher after the treatment and at 1, 3 and 6 months after the treatment than it was before the treatment (P<0.05). The BCVA in the OG was significantly higher than it was in the CG at the end of the treatment and at 1, 3, and 6 months after the treatment (P<0.05) (**Figure 1**).

Comparison of the two groups in terms of their CRT

Before the treatment, the CRT was (448.52±102.13) μm in the OG and (450.16±95.72) μm in the CG (P>0.05), but at the end of 1 month, 3 months, and 6 months after the treatment, the CRT gradually decreased to (372.16±82.16) μm, (246.32±35.19) μm, (242.52±40.33) μm and (239.31±38.46) μm in the OG and (421.31±86.47) μm, (298.64±62.34) μm, (291.41±53.34) μm, and (288.31±50.13) μm in the CG. The CRT in the OG was lower after treatment and at 1, 3, and 6 months after the treatment than it was before the treatment (P<0.05), and the CRT in the CG was lower after the treatment and at 1, 3, and 6 months after the treatment than it was before the treatment (P<0.05). The CRT in the OG was significantly lower than it was in the CG at the end of the treatment and at 1, 3, and 6 months after the treatment (P<0.05) (**Figure 2**).

Comparison of the two groups in terms of their IOP

No significant difference in IOP was demonstrated in the two groups at the end of the treatment and at 1 week and 1 month after the treatment (P>0.05, **Table 2**).

Comparison of the two groups in their hemorheology

Before Hemorheology treatment, no statistical difference was found between the OG and the CG in whole blood viscosity (high/low shear rate), plasma specific viscosity, or fibrinogen level (P>0.05). At the end of treatment, those indices in the OG were lower than they were before the treatment (P<0.05), and the levels in the CG were lower than they were before the treatment. These indices in the OG were significantly lower than those in the CG at the end of treatment (P<0.05, **Table 3**).

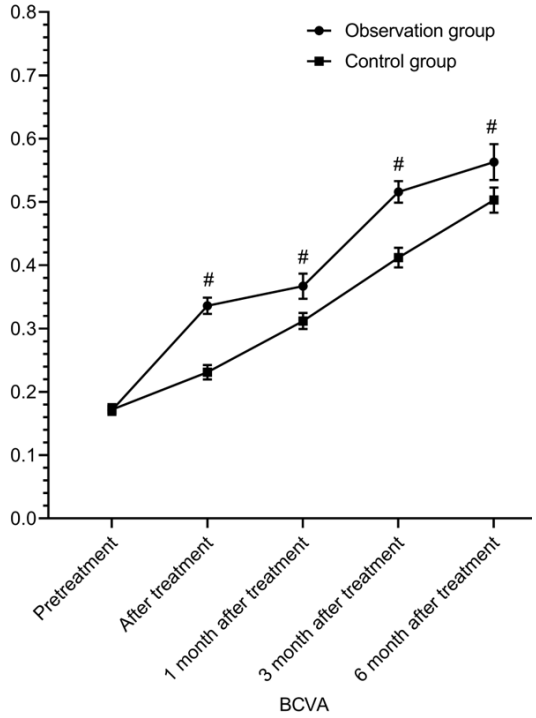

Figure 1. Comparison between the OG and the CG in their BCVA. While no statistical difference was observed before the treatment, the OG demonstrated better BCVA at the end of 1 month, 3 months, and 6 months after the treatment (P<0.05) compared with the CG. #indicates P<0.05 compared between the two groups at the same time point.

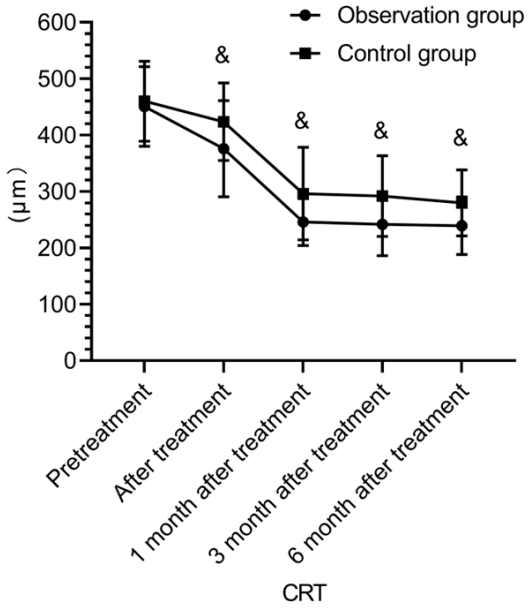

Figure 2. Comparison between the OG and the CG in their CRT. Before the treatment, the CRT was not statistically different compared between the two groups (P>0.05). At the end of 1 month, 3 months, and 6 months after the treatment, it was reduced in the OG more significantly compared with the OG (P<0.05). &indicates P<0.05 as compared between the two groups at the same time point.

Comparison of the two groups in terms of their hemodynamics

Without any statistical difference before the treatment (P>0.05), after the treatment, the RI in the OG was lower than before the treatment, and Vmax and Vmin were higher than they were before the treatment (P<0.05). After the treatment, the RI in the CG was lower than it was before the treatment, and Vmax and Vmin were higher than they were before the treatment (P<0.05). After the treatment, the RI in the OG was significantly lower than it was in the CG, and Vmax and Vmin were significantly higher than they were in the CG (P<0.05, **Table 4** and **Figure 3**).

Comparison between the two groups for total effective rate

Amongst the 43 patients in the OG, 39 were judged as effective, for a total effective rate of 90.70%, and in the CG of 42 patients, 31 were judged as effective, for a total effective rate of 73.81%, which was a statistically significant difference (X^2=4.170, P=0.041, **Table 5**).

Discussion

RVO is a major factor leading to reduced vision in the middle and senior populations in most cases. However, there is a possibility of RVO occurring among different age groups [8, 9]. RVO patients may suffer from sudden painless visual loss with a diversified expression in the fundus, for instance, scattered small pieces of cotton-wool patches, retinal hemorrhage or deep hemorrhage in the fundus [10, 11]. Forasmuch as the macular function of all RVO patients will be damaged to varying degrees, and the continuous presence of macular edema will lead to a complete loss of central visual acuity, RVO treatment becomes very important [12].

Clinically, HBOT is an important way to treat ischemic hypoxic diseases by improving the partial pressure of oxygen in the blood and tissue fluid, promoting the effective dispersion distance of blood oxygen and the diffusion radius of oxygen in tissues so as to achieve a higher

Table 2. Comparison between the OG and the CG for IOP before and after the treatment ($\bar{x}$ ± s, mmHg)

Group	n	Before treatment	At the end of treatment	1 week after treatment	1 month after treatment
OG	43	15.62±1.19	14.78±1.21	15.16±1.15	15.82±1.33
CG	42	15.58±1.22	15.01±1.26	15.24±1.19	15.89±1.35
t		0.153	0.858	0.315	0.241
P		0.879	0.393	0.753	0.810

Table 3. Comparison between the OG and the CG in terms of hemorheology before and after treatment ($\bar{x}$ ± s)

Group	Time	Whole blood viscosity (high shear rate) (mPa·s)	Whole blood viscosity (low shear rate) (mPa·s)	Plasma specific viscosity (mPa·s)	Fibrinogen (g/L)
OG (n=43)	Before treatment	7.36±0.36	17.29±0.16	3.02±0.17	0.72±0.40
	At the end of treatment	5.99±0.44	15.43±0.22	2.33±0.12	0.53±0.19
CG (n=42)	Before treatment	7.33±0.34	17.26±0.18	3.01±0.15	0.73±0.42
	At the end of treatment	6.61±0.42	16.51±0.20	2.85±0.14	0.64±0.23
t		6.643	23.665	18.400	2.406
P		0.000	0.000	0.0000	0.018

Note: t and p are the comparative statistical values of the two groups at the end of treatment.

Table 4. Comparison between the OG and the CG in terms of hemodynamics before and after treatment ($\bar{x}$ ± s)

Group	Time	RI	Vmax (cm/s)	Vmin (cm/s)
OG (n=43)	Before treatment	0.76±0.05	8.29±3.26	3.18±1.13
	At the end of treatment	0.66±0.03	11.27±3.55	4.26±1.25
CG (n=42)	Before treatment	0.77±0.06	8.31±3.19	3.19±1.15
	At the end of treatment	0.70±0.04	9.71±3.42	3.64±1.21
t		5.224	2.063	2.323
P		0.000	0.042	0.023

Note: t and p are the comparative statistical values of the two groups at the end of treatment.

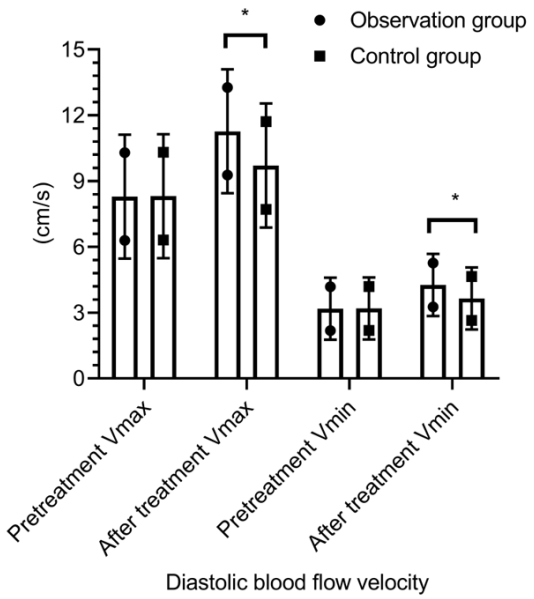

Figure 3. Comparison between the OG and the CG in their diastolic blood flow velocity of central retinal artery. Before the treatment, no significant difference was observed between the two groups in their Vmax and Vmin during diastole (P>0.05); at the end of treatment, both indices rose significantly in the OG (P<0.05). *indicates P<0.05 as compared between the two groups at the same time point.

reserve of oxygen to improve ischemia and hypoxia in the body [13, 14]. By combining HBOT with RVO in this study, effective improvements to the local ischemia and hypoxia on the retina, the inhibition of anaerobic glycolysis in cells, the amelioration of cellular metabolism and promoted metabolism recovery were observed and shown to be able to prevent the vicious cycle induced by edema, bleeding, and hypoxia, and play an assisting role in the promotion of overall efficacy [15, 16]. STS is mainly

Table 5. Comparison between the OG and CG in terms of the total effective rate

Group	Heal	Upturn	Invalid	Total effective rate
OG (n=43)	18 (41.86)	21 (48.84)	4 (9.30)	39 (90.70)
CG (n=42)	14 (33.33)	17 (40.48)	11 (26.19)	31 (73.81)
X^2				4.170
P				0.041

made of tanshinone II A extracted from the root of red-rooted salvia, whose solubility in water is reinforced by sulfoacid tanshinone IIA, so as to achieve a higher utilization ratio [17]. Modern medical studies have proved that tanshinone IIA can regulate coagulation function in a two-way manner, and its resistance to coagulation and thrombin ensures reduced edema, accelerated absorption of hematomas, and hemostasis [18, 19].

In this study, after 2 courses of treatment by HBOT and STS, the total effective rate was 90.70% in the OG, significantly higher than that of 73.81% in the CG. In addition, at the end of the treatment, and at 1 month, 3 months, and 6 months after the treatment, the BCVA in the OG was significantly higher than it was in the CG; after the treatment, the hemorheological indices in the OG, including whole blood viscosity (high/low shear rate), plasma specific viscosity, and fibrinogen were lower than they were in the CG, and the hemodynamic indices of RI, Vmax, and Vmin in the OG were superior to those in the CG ($P<0.05$), indicating that compared with the cases when HBOT was applied alone, its combination with STS demonstrated a more significant contribution to the improvement of RVO patients' vision, the alleviation of related syndromes, and a more significant improvement of the hemodynamics and hemorheology in patients with RVO. The mechanism of action may be that HBOT can induce the formation of erythrocyte lipids, promote its peroxidation to raise the fragility of red blood cells, and accelerate the dissolution and softening of thrombus and blood clots. Furthermore, HBOT can increase the activities of phagocytic cells and fibrinolytic enzymes, accelerate the absorption of blood clots, and restore the patency of venous channels and blood circulation. The studies of Edwards [20] and Weaver [21] all showed that the application of hyperbaric oxygen can significantly improve the hemodynamic status. Moreover, the element tanshinone II A in STS is capable of effectively resisting platelet aggregation, leading to a significant reduction of the whole blood viscosity. Its resistance to free radicals contributes to the improvement of hemodynamics and hemorheology and of the blood supply to ischemic parts. Park et al. [22] and Yin et al. [23] found that the combination of STS in the treatment can achieve better results. In this study, no significant difference was found in IOP between the two groups before the treatment, at the end of the treatment, or at 1 week and 1 month after the treatment ($P>0.05$), but the CRT was lower in the OG at the end of the treatment and at 1 month, 3 months, and 6 months after the treatment ($P<0.05$), indicating that compared with the treatment with HBOT alone, its combination with STS could yield better effects on the improvement of macular edema without affecting the patients' IOP. The mechanism of action may be because HBOT can inhibit the optic disk and macular edema in patients with RVO, promote edema absorption, control IOP, and promote recovery after treatment. In the combination, HBOT and STS can act on RVO synergistically to obtain a better overall effect. According to the studies by Ishibashi et al. [24], HBOT can effectively resist angiotelectasis to mitigate the bleeding, exudation, and edema symptoms induced by RVO. The study of Zhou et al. [25] also showed that HBOT combined with STS can improve the maculopathy.

In conclusion, the combination of HBOT and STS in the treatment of RVO patients deserves popularization on the basis of its significant improvements to hemodynamics, hemorheology, and clinical efficacy. However, as a retrospective study with a small cohort, the study failed to comprehensively analyze the results, and its conclusions are somehow biased. Future studies will focus on larger sample sizes and more aspects, and will be forward-looking in order to obtain more scientific and representative conclusions for the benefit of RVO patients when they select among the treatment methods available.

Disclosure of conflict of interest

None.

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