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A Long-Term Study of Efficacy of Patients with Macular Edema Secondary to BRVO Treated with Ranibizumab Combined with Compound Salvia

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Abstract

Purpose: To study the long-term efficacy of intravitreal ranibizumab injection combined with intravenous compound salvia injection drip in the treatment of patients with macular edema secondary to branch retinal vein occlusion(BRVO). Methods: Sixty-five patients of branch retinal vein occlusion with macular edema were analyzed retrospectively. Thirty-seven patients in the treatment group were treated with ranibizumab injection combined with intravenous compound salvia injection drip, twenty-eight patients in the control group were treated with ranibizumab injection only. All patients were recorded and analyzed changes of clinical efficacy after 3 months, 6 months after a course of treatment of 6 months. Results: During 3 months after 6 months' treatment, there were 5 patients having recurrence in the treatment group, while there were 9 in control group, the rate of recurrence between the two groups had significant difference ($P < 0.05$); during 3 - 6 months after a course of treatment, there were 2 patients having recurrence in the treatment group, while there were 4 in control group, the rate of recurrence between the two groups had significant difference ($P < 0.05$); however, the treatment group's BCVA was better than control group, and the difference between the two groups had significance ($P < 0.05$). Conclusion: Ranibizumab injection combined with intravenous compound salvia injection drip could effectively reduce the impossibility of recurrence, improve the visual activity and bring better therapeutic efficacy in patients with macular edema secondary to branch retinal vein occlusion. The treatment showed great potential in the clinical use.

Keywords

Branch Retinal Vein Occlusion, Macular Edema, Long-Term Follow-Up, Ranibizumab,

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Compound Salvia

1. Introduction

Branch retinal vein occlusion is the second most common cause of retinal vascular blindness after diabetic retinopathy [1]. As the researches [2]-[4] show BRVO could cause the obstruction of venous reflux, whicn leads to an increase in venous blood pressure, retina ischemia, inflammatory cytokine release, dysregulation of endothelial tight junction proteins and finally an increase of the vascular endothelium growth factor (VEGF) production which could cause the leak of vascular and macular edema. Macular edema is the major reason of the vision loss [5]. The treatment options for patients with macular edema secondary to BRVO include drugs, grid laser, operation and intravitreal anti-VEGF injections and so on [6]. For a long time, the guiding principle for the management of BRVO is central grid laser [7], nowadays, anti-VEGF agents, including ranibizumab and bevacizumab, have been the most promising treatment of macular edema. However, these methods can't effectively reduce the edema or are easy to cause recurrence and hard to improve the vision significantly. In the previous research [8], we found intravitreal ranibizumab injection combined with intravenous compound salvia injection drip can significantly reduce the edema and improve the BCVA with less intravitreal injections than simple intravitreal injection. And in this study, we would compare the long-term efficacy between these two treatments.

2. Patients and Methods

2.1. Patients

This retrospective analysis was conducted at Ophthalmology department of Shanghai First People's Hospital from 2013-05 to 2014-05, 65 patients included were confirmed on funduscope and OCT, with central macular thickness (CMT) of ≥300 um and baseline visual acuity of 0.1 or worse. The exclusion criteria were severe cataract, vitreous hemorrhage affecting funduscope, other retinal or optic nerve diseases, previous treatment of grid laser or eyeground operation, and a history of severe systemic diseases. BCVA measurement with standard logarithmic visual acuity chart and CMT measuring with OCT (Zeiss, Germany) were performed at the initial examination and during the follow-up. Patients received initially an intravitreal injection of 0.5 mg ranibizumab (Lucentis; Genentech) and patients in treatment group were thereafter treated with intravenous compound salvia injection (Chinese medicine number Z20027937) 16 mg diluted with saline solution 250 ml drip for 10 days a month. Ophthalmological examinations including BCVA and OCT were taken monthly after the initial intravitreal injection. Another intravitreal injection would be taken if macular edema existed continuously or increased, and repeat the treatment before. The mean duration of total therapy was 6 months. After the treatment, a six-month follow-up would be taken; patients having recurrence with the standard of BRVO would get the extra treatment within the follow-up.

2.2. Statistical Analysis

Statistical analysis was performed with a commercial software (SPSS17.0). Descriptive statistics were used to summarize patient demographics and baseline ocular characteristics. Independent t test was used for comparison of means and ×2 was used for comparison of proportions between groups. $P < 0.05$ was considered as statistically significant.

3. Results

Patient demographic and baseline characteristics are presented in **Table 1**. Sixty-five eyes of 65 patients were assigned to receive combined treatment (n = 37) or simple injection (n = 28). Demographic and baseline characteristics were well matched between the 2 groups and are listed in **Table 1**, and there was no significant difference in it. The average age of patients was 51.7 years (range from 45 - 65), and 53.8% (45 of 65) were male. The mean time from diagnosis of BRVO to the baseline examination was 12.3 weeks. The mean study eye BCVA at baseline was 0.089. The average CMT at baseline as measured by OCT was 680 um.

Table 1. Baseline demographic data in two different groups.

Parameter	Baseline		
	combined treatment (n = 37)	simple injection (n = 28)	All (n = 65)
Age (y ± SD)	51.7 ± 13.6	53.3 ± 12.8	52.1 ± 12.7
Sex, n (%)			
Male	21 (56.8)	14 (50.09)	45 (53.8)
Female	16 (43.2)	14 (50.0)	34 (46.2)
Study eye characteristics			
Time(wk) from diagnosis to inclusion (Mean ± SD)	10.6 ± 6.4	14.2 ± 5.1	12.3 ± 6.3
BCVA	0.088 ± 0.079	0.090 ± 0.067	0.089 ± 0.071
CMT before treated (μm ± SD)	645 ± 228	655 ± 180	649 ± 199
CMT after a course of treatment (μm ± SD)	278 ± 118	439 ± 188	369 ± 147

3.1. Change from Baseline Bese-Corrected Visual Acuity

After a course of 6 months' treatment, patients in both groups had a mean BCVA improvement before treated ($P < 0.05$), and this gain maintained at the following 6 months. BCVA of patients in treatment group improved significantly more than in control group since 1 week after the initial treatment to the end of the follow-up ($P < 0.05$) (**Figure 1** summarizes the changes of BCVA of the two groups).

3.2. Change of CMT

The mean CMT of BRVO patients in treatment group at baseline was 645 ± 228 μm and 278 ± 118 μm at 6 month, 265 ± 130 μm at 9 month, and further decreased to 257 ± 123 μm at 12 month. In control group, mean CMT decreased from 655 ± 180 μm at baseline to 439 ± 188 μm at 6 month, 389 ± 143 μm at 9 month, and 402 ± 126 μm at 12 month, the changes in CMT of the two groups from baseline were statistically significant ($P < 0.05$). In the intergroup comparison, CMT decreased more in treatment group than in control group, the decrease was statistically significant ($P < 0.05$) (**Table 2** summarized the changes of CMT of the two groups).

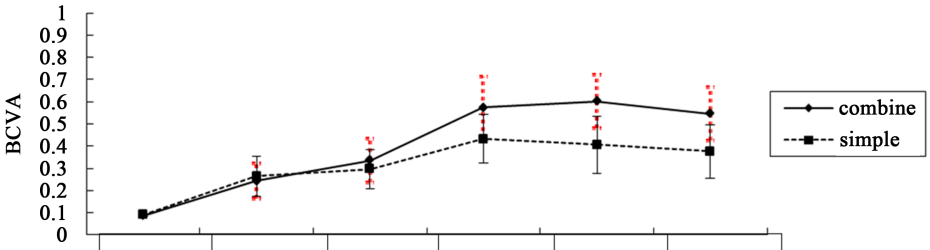
3.3. Rate of Recurrence during 6 Months after a Course of Treatment

During three months in the follow-up after treatment, the rate of recurrence was 13.5% in treatment group and 32.1% in control group, the difference between the two groups was statistically significant ($P < 0.05$). During three to six month in the follow-up, the rate of recurrence decreased from 13.5% to 5.4% than the before three months, however, the rate of recurrence in treatment group were significantly less than the rate of 14.3% in control group ($P < 0.05$) (**Table 3** summarized the rate of recurrence of the two groups).

3.4. Average Numbers of Intravitreal Injection

Every patient was measured with the following standard of cure (BCVA improved more than 3 rows, or macular edema decreased to 200 μm by the examination of OCT), effective (BCVA improved more than 1 rows, or macular edema reduced more than 200 μm by the examination of OCT) and non-effective (BCVA had no improvement or even reduced, or macular edema had no reduce or increased).

The mean number of intravitreal injections of the patients with cure and effective efficacy was 1.37 in treatment group while it was 2.62 in control group after a course of 6-month treatment, the difference between the two group was statistically significant ($P < 0.05$). At the end of follow-up, the mean number of intravitreal injections raised to 1.79 in treatment group and 3.84 in control group, the raise was of no statistical significance ($P > 0.05$) and the difference between the two groups was of statistical significance ($P < 0.05$) (**Table 4** summarized the number of intravitreal injections of the two groups).



	0 d	1 w	3 m	6 m	9 m	12 m
Treatment group	0.0873	0.243	0.335*	0.573*	0.601*	0.545*
Control group	0.0912	0.265	0.296	0.433	0.406	0.376

Figure 1. Changes of BCVA in 6 months' treatments and 6 months' follow-up in two different groups. Annotation: "*" means significant difference of the two groups in the same time ($P < 0.05$).

Table 2. Changes of CMT after 6 months' treatments in two different groups.

	Treatment group	Control group
0 d	645 ± 228μm	655 ± 180μm
6 m	278 ± 118μm*	439 ± 188μm
9 m	265 ± 130μm*	389 ± 143μm
12 m	257 ± 123μm*	402 ± 126μm

Annotation: "*" means significant difference of the two groups in the same time ($P < 0.05$).

Table 3. Rate of recurrence between the two groups during 6 months' follow-up.

	Treatment group	Control group
Patients with recurrence during 0 m - 3 m follow-up	5(13.5%)*	9(32.1%)
Patients with recurrence during 3 m - 6 m follow-up	2(5.4%)*	4(14.3%)
Total patients with recurrence	7(18.9%)*	13(46.4%)

Annotation: "*" means significant difference of the two groups in the same time ($P < 0.05$).

Table 4. Number of injections between the two groups during 6 months' follow-up.

	Treatment group	Control group
Number of injections of cure patients during treatment	2.50 ± 0.52*	4.66 ± 0.83
Number of injections of effective patients during treatment	1.41 ± 0.48*	3.35 ± 0.99
Numbers of injections of total effective patients with recurrence during in 6m's follow-up	1.37 ± 0.31*	2.62 ± 0.43
Total number of injections of all patients in 12 months	1.79 ± 0.40*	3.84 ± 0.55

Annotation: "*" means significant difference of the two groups in the same time ($P < 0.05$).

4. Discussion

Intravitreal anti-VEGF injection has been widely used in the treatment of BRVO. Ranibizumab is showed to be effective in the treatment of macular edema due to BRVO [9], rapid and sustained visual improvement was seen in the first 6 months in patients with 0.3 mg and 0.5 mg ranibizumab in Branch Retinal Vein Occlusion (BRAVO) study. As a new kind of anti-VEGF drugs, ranibizumab is a recombinant, monoclonal antibody fragment (Fab) created from the same parent mouse antibody [10]. It acts against all VEGF isoforms of VEGF-A with binding to the receptor-binding site of active forms of VEGF-A and prevents VEGF-A from binding to its receptors (VEGFr-1 and VEGFr-2) on the endothelial cell surface, thus inhibiting endothelial cell proliferation, reducing

vascular permeability and formation of new vessels [11]-[13]. An intravitreal injection of ranibizumab every month for 6 months and then another injection when edema is persistent or recurrent are marked significantly in edema and visual acuity internationally [14]. However, a long-time follow-up of 50.2 months found that 50% of BRVO patients could get good visual acuity and need no more intravitreal injection in the following 6 months, the other 50% still needed average 3 injections to reduce edema or maintain visual acuity [15]. Repeated intravitreal injection is always needed in the treatment of BRVO, which increases the risk of endophthalmitis, A long-term follow-up study of Gallego-Pinazo R [16] found that after 12.5 momths of follow-up, patients with macular edema secondary to BRVO ≤ 367. 9 ± 175.2 μm needed 5.0 ± 2.98 (range from 2 to 13) intravitreal injections on average. In China, Bingw Lu [17] found that intravitreal ranibizumab injection combined with intravenous compound salvia injection drip could effectively reduce the edema, improved the vision and visual field. Yalan Feng [7] found that with the treatment of ranibizumab combined with compound salvia, almost 50% patients could cure BRVO with on average 2.5 intravitreal injections, and 84% patients could get a distinct decrease in CMT. Compound salvia is a traditional Chinese medicine emphasized of salvia and lignum Dalbergiae Odoriferae, it has the efficacy of activating blood circulation to dissipate blood stasis, remissing fatigue, and soothing the nerves [18] and has been widely used for cardiovascular disorders for hundred years in China. The active ingredients of tanshinone IIA, sodium sulfate, danshensu can decrease the activity of blood platelet spectrin, reduce TXA2 production, relieve the general arterioles spasms and inhibit platelet aggregation, accelerate the blood-bleeding, inhibit the aggregation of red blood cells, increase the oxygen and blood supply to the tissue, improve microcirculati and enhances absorption of haematocele [19] [20], which have the both efficacy of hemostasis and promoting blood circulation. Salvianolic acid A, which is another effective ingredient of compound salvia, was found to be responsible for the protection of RPE cells [21].

In our research,we combine intravitreal ranibizumab injection with intravenous compound salvia injection drip in the treatment of BRVO. We found cure or effective patients in combined treatment group suffered from on average 2.50 or 1.41 intravitreal injections, which was much less than those in simple injection group with 4.66 or 3.35 intravitreal injections. Though with less intravitreal injections, we observed significantly better visual acuity outcomes and more reduction in CMT comparing simple intravitreal injections with combined treatment. Similar result could be found during 6-month follow-up after a couse of treatment. During the long-term follow-up, in treatment group, the rate of recurrence (18.9%) was much less than that (46.4%) in control group, almost half patients need extra intravitreal injections to solve the edema. However, the number of injections was less than in the course of treatment. At the end of the research, almost 88% patients in treatment group and 73% patients in control group had solved the edema secondary to BRVO, indicating that the effect of combined treatment was considerable superior to the simple injections. Though the treatment of simple intravitreal ranibizumanb injections can reduce macular edema through inhibiting the formation of new vessels, reducing vascular permeability and regulating blood-retinal barrier [22], but due to ranibizumab's short half-life, monthly injections for 6 months and extra injections thereafter are always needed to maintain efficacy; compound salvia has the ascendancy of improving microcirculati of retina, it can effectively increase the oxygen and blood supply to retina, inhibit the increase of VEGF and finally the formation of macular edema.

In conclusion, patients using intravitreal ranibizumab injection combined with intravenous compound salvia injection drip to treat macular edema secondary to branch retinal vein occlusion can significantly reduce the number of intravitreal injections, have less possibility of recurrence, and get better clinical efficacy with less cost, the treatment is valuable in clinical promoting. Thus, although we have made considerable progress in the treatment of patients with BRVO, new randomized, double-blind, large-simple treatment is still needed to confirm the outcome.

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