Efficacy Analysis of Anti-VEGF Combined Compound Anisodine for Macular Edema Caused by Retinal Vein Occlusion

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Abstract: Objective: To evaluate the efficacy of compound anisodine injection combined with anti VEGF in the treatment of macular edema due to branch retinal vein occlusion, and to explore the advantages of the combination. Methods: 72 patients with retinal vein occlusion were randomly divided into combined group and control group, 36 cases in each group. The control group was treated with routine anti VEGF injection once, while the combined group was treated with compound anisodine injection at the same time. One injection was given every day for 14 days, rest for 2 days, and then injection for 14 days. The therapeutic effects of the two groups were compared. Results: compared with the control group and the combined group, the difference of corrected vision was statistically significant at different time points before and after injection, and the improvement of corrected vision at the 30th and 90th day after combined treatment was significantly different from that of the control group ($P < 0.05$). Conclusion: Compound anisodine combined with anti VEGF drugs can improve the therapeutic effect on macular edema patients with retinal vein occlusion.

1. Introduction

Retinal vein occlusion is one of the common causes of blindness, and is the only incidence rate of retinal vascular disease secondary to diabetic retinopathy. Macular edema and vitreous hemorrhage secondary to RVO are the main causes of vision decline. The clinical manifestations of RVO are as follows: dark shadow in front of eyes, blurred vision, sudden visual acuity decline, tortuosity and dilation of retinal vein at the fundus. There are flame like hemorrhage, edema and exudation along the involved vein. When there is more hemorrhage, preretinal hemorrhage can be seen, and even break through the inner boundary membrane into the vitreous body, forming vitreous hemorrhage. According to statistics, the prevalence of RVO in the global general population aged 30 and over is about 0.5%, affecting more than 16 million people. The incidence rate of RVO in Beijing area is 10 years (1.9 + 0.1)%, which is similar to other studies on white race. Risk factors of RVO include systemic diseases, such as hypertension, diabetes and coronary artery disease. Some hematological factors, such as hyperhomocysteinemia, are also associated with RVO. If the treatment is not timely, it may lead to proliferative lesions or even retinal detachment. Some patients may develop iris neovascularization, even neovascularized glaucoma.

It has been reported that intravitreal drug injection (including anti VEGF treatment, glucocorticoid), retinal laser photocoagulation, surgical vitrectomy or macular area internal limiting membrane stripping, arteriovenous sphingotomy, thrombolysis and other methods are used to treat RVO. Among them, anti VEGF treatment has become the main effective and safe treatment method for RVO secondary macular edema. In 2010, rapunzumab was approved by the US FDA as a drug for RVO secondary macular edema, but its clinical application is limited due to its single target, short time and high price. Compound anisodine is widely used in the treatment of fundus diseases such as ischemic optic neuropathy, retinal and choroidal vascular diseases. Compound anisodine is composed of anisodine hydrobromide and procaine hydrochloride. Pharmacological research shows that it can accelerate the recovery of the normal level of vasoactive substances in the ischemic area of the eye,

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relieve vasospasm, maintain the normal tension and contraction function of choroidal blood vessels, increase blood flow, improve blood supply, and promote the rapid recovery of ischemic tissue; it also has the effects of anti free radicals, inhibition of inflammation and fibroproliferation, so as to reduce the local damage caused by inflammation and accelerate the recovery heal. In clinic, systemic application of vasodilators may aggravate local ischemia by reducing retinal vascular perfusion while dilating occluded vessels, while local application will not have such disadvantages, and also reduce the complications of systemic application.

2. Objects and Methods

2.1 Objects

There were 72 patients in this group, 36 males and 36 females. Some patients have been treated with drugs in the hospital or outpatient department, excluding the cases with cataract, glaucoma, high myopia, obvious turbidity of refractive stroma and poor fixation function that affect vision and OCT examination; all patients in the group were examined by vision, macular optical coherence tomography (OCT), fluorescein fundus angiography (FFA), etc. The standard logarithmic visual acuity chart was used. The inclusion criteria included: (1) diagnosis of branch retinal vein occlusion with macular edema and visual impairment; (2) course of disease no more than 3Mo; (3) baseline visual acuity at the time of selection greater than 0.15; (4) age 18-70 years; (5) patients can receive more than two courses of treatment of compound anisodine injection. The study was approved by the ethics committee. All patients were informed of the treatment purpose and potential complications before treatment, and signed the informed consent. In this study, patients were randomly divided into control group and combined group, 30 eyes in each group. In the control group, 15 eyes were treated with anti VEGF, 15 eyes were male and 15 eyes were female, the average age was 45-60 (52.2 ± 4.75) years old, and the average corrected visual acuity was 0.47 ± 0.14. There was no significant difference in age, gender and corrected vision between the two groups ($P > 0.05$).

2.2 Methods

All patients were given one intravitreal injection, which was completed by the same doctor in the operating room. The needle was injected into the flat part of the ciliary body, and the intravitreal injection of 10mg / ml was 0.05ml. The combined group was treated with compound anisodine injection at the same time of intravitreal injection: 2ml / time, subcutaneous injection at the superficial temporal artery of the affected side, once a day, for 14 days, after stopping for 2 days, the treatment continued for 14 days. OUTCOME MEASURES: follow up was carried out on the 15th, 30th and 90th day after treatment. During the follow-up period, the same equipment and methods before treatment were used. The changes of vision and CRT in the two groups before and after treatment were analyzed. Before the examination, the pupil was fully dilated to $\geq$ 6mm × 6mm with compound tropicamide eye drops, the examinee was instructed to sit, the mandible was placed in the mandible, the forehead was pressed against the forehead baffle plate, the eye position was adjusted, the examinee looked directly into the scanning lens to inject the viewpoint, and the scanning area was divided into the center according to the built-in automatic zoning method The diameter of the fovea is 1mm, the diameter of the inner ring is 3mm, and the diameter of the outer ring is 6mm. The inner ring and the outer ring are divided into four areas: the temporal side, the upper part, the nasal side and the lower part. The retinal topographic map of the macula is divided into nine areas. Each candidate was scanned by the same experienced ophthalmologist. Statistical software spss21.0 was used to analyze the measurement data. The mean ± standard deviation was used to express the measurement data. $\chi 2$ test was used to compare the gender and eye distribution between the two groups. Independent sample t test was used to compare the age, macular area retinal thickness and visual field ms between the two groups. Pearson correlation analysis was used to analyze the correlation between visual field MD and the upper half of the central inner ring and the upper half of the central outer ring. Inspection level: $\alpha = 0.05$.

3. Results

In the control group, 30 eyes (83.3%) had improved vision, and 6 eyes (16.7%) had stable vision. In the combined group, 33 eyes (91.7%) had improved vision, and 3 eyes (8.33%) had stable vision. The difference of corrected visual acuity before and after injection was statistically significant (f time = 185.05, P time < 0.01; F group = 3.34, P group = 0.025). After combined treatment, the improvement of corrected visual acuity on the 30th and 90th day was significantly higher than that in the control group (P = 0.028, 0.007).

The CRT of the patients in the control group and the combined group were 368.8 ± 61.66 μ m and 376.67 ± 50.17 μ m respectively before and after treatment. The difference was statistically significant (f time = 286.2, P time < 0.01; F group = 12.46, P group < 0.01). On the 30th day after treatment, the CRT of the patients in the control group and the combination group decreased compared with the 15th day after treatment; on the 90th day after treatment, the CRT of the patients in the control group and the combination group increased compared with the 30th day after treatment. On the 30th and 90th day after the combined treatment, the CRT of the patients was 137.97 ± 41.04 and 101.92 ± 56.28 μ m lower than that of the control group, respectively (P < 0.01), but there was no significant difference on the 15th day (P > 0.05).

In 8 eyes of RVO, 7 eyes were treated with retinal laser photocoagulation, 5 eyes with CRVO and 2 eyes with BRVO. During the treatment and follow-up, there was no case of non blood deficiency and then to blood deficiency. During the follow-up period, 1 eye had a flash in the anterior chamber, and the signs disappeared and did not recur after 4 days of glucocorticoid eye drops; 2 eyes had subconjunctival hemorrhage, which improved after 10 days of symptomatic treatment such as hot compress; no local and systemic serious complications such as high intraocular pressure, endophthalmitis, cataract progress, retinal hemorrhage, retinal detachment, etc.

4. Conclusions

Compound anisodine injection is composed of anisodine hydrobromide and procaine hydrochloride. Anisodine is a cholinergic nerve blocker, which can relieve the spasm of smooth muscle, mydriasis and other anticholinergic effects. Procaine can effectively improve the local microcirculation, improve the blood supply to the fundus of the eye. Meanwhile, compound anisodine can also regulate the choroidal blood vessels to a certain extent, making the choroidal vasoactive substances The quality is stable in the normal range, so as to improve the function of choroidal vascular activity, improve the visual function, at the same time, it can also effectively remove free radicals, reduce oxidation, improve the symptoms of tissue ischemia and hypoxia, so as to improve the prognosis of patients. The relative stability of endothelin is helpful to regulate and maintain the basic tension of blood vessels, improve circulation and alleviate the damage caused by ischemia. Early application of compound anisodine can stabilize and protect the level of endothelin with immune activity in the choroidal vessels of retina, thus inhibiting the abnormal expression and release of endothelin. Kang et al. Showed that compound anisodine could change the expression levels of CyclinD1 and HIF-1 α, VEGF and p-ERK. Therefore, compound anisodine can alleviate ischemia to a certain extent, thus indirectly reduce the release of VEGF, and play a role in strengthening the efficacy of anti VEGF drugs. In addition, the results of this study confirmed that the best corrected visual acuity and central retinal thickness in the treatment group were better than those in the control group at 90 days, suggesting that the combination of compound anisodine may reduce the number of anti VEGF treatment.

RVO is a common vascular disease of retina. Because of anatomical characteristics, blood vessel oxygen supply and other factors, BRVO often occurs in the supratemporal branch. At the intersection of retinal artery and vein, the factors such as the pressure of thickened artery wall on vein, hemorheology, hemodynamics, etc. lead to the formation of retinal vein thrombosis, the decrease of blood perfusion, the occlusion of retinal vein blood vessels for a long time, the increase of pressure in the lumen, making the fluid more easily pass through the vascular wall under the effect of pressure gradient, and leak into the adjacent retinal tissue. In addition, there may be abnormalities of retinal

microvascular system, release of inflammatory factors, destruction of blood retinal barrier, increase of vascular permeability and macular edema caused by the damage of venous endothelial cells. OCT can directly and clearly observe the abnormal changes of macular retinal structure. In this study, it was observed that the retina in the macular area with macular edema in the patients with temporal RVO can show a variety of morphological manifestations, such as sponge like diffuse retinal thickening, macular cystic edema, serous retinal detachment and mixed changes. The edema can be located in multiple layers of the retina, and even there is subretinal hemorrhage, similar to the results observed by Xue Kang. On this basis, this study quantitatively analyzed the retinal thickness of macular regions in patients with temporal BRVO and macular edema. Although BRVO occurs in the superior temporal branch, the change of retinal thickness is not only limited to the fovea and the superior temporal retina, but also involves all parts of the macular area, showing the characteristics of diffuse change. Previous research results of Tao Xiangyi et al showed that the amplitude density and latency of N1 wave and P1 wave in the temporal RVO multifocal electroretinogram did not change in the temporal and inferior nasal quadrants. It is speculated that OCT may be more sensitive to the assessment of retinal changes, and can detect morphological subtle abnormal changes before the changes of retinal functions, so as to assess the changes of retinal functions Transformation provides structural foundation. Under physiological condition, the oxygen consumption of retina in macular area is significantly higher than that in peripheral area, and the metabolism is the most vigorous. When RVO occurs, the oxygen supply of retina decreases, while the lipid, protein, fibrinogen, red blood cells and other tangible components in the plasma deposit in the fovea of macula, resulting in the significant increase of CMT. The reason of retinal thickening around the fovea of macular region is speculated to be related to the structural change of retinal pigment epithelium. The normal biological activity of RPE cells is involved in many cell metabolism, especially the phagocytosis of photoreceptors. When RVO occurs, the phagocytosis of RPE weakens, which slows down the metabolism of the membrane disc of rod cells and accumulates. Rod cells are mainly distributed outside the fovea of macula, so that the retina around the fovea of macula area thickens.

Although the follow-up time of this study is short, and the number of cases is too small to carry out the statistics and analysis of the time point of repeated treatment and the proportion of BRVO patients who cannot repeat the treatment, our research results can still show that 90 days after the treatment, compared with before the treatment, the improvement of vision and the reduction of macular edema in the anti VEGF combined with compound anisodine group are significantly better than that in the anti VEGF group alone. Combined therapy can improve the visual function of patients with branch retinal vein occlusion, which is a safe and effective treatment strategy.

The high price of anti VEGF drugs and the need for multiple intraocular injections will reduce the compliance of patients, intravitreal injection will bring a certain risk of infection, as well as the drug into the systemic blood circulation and cause some adverse consequences, such as cerebral infarction, angina, myocardial infarction and other cardiovascular and cerebrovascular accidents. The use of steroid in vitreous may cause secondary side effects of glaucoma and cataract. Therefore, the exploration of new treatment methods has been a research hotspot in this field. Compound therapy has its own unique features in the treatment of this disease. It has obvious advantages in promoting macular edema reduction, visual function recovery, general condition improvement and so on. Treatment can shorten the course of the disease. I hope that we can make a breakthrough in the study of this disease in the near future.

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