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Original Article

The clinical therapeutic effect of ranibizumab intravitreous injection combined with phacoemulsification on diabetic macular edema

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Abstract: Objective: To compare the effect of ranibizumab (anti-vascular endothelial growth factor) intravitreous injection combined with phacoemulsification and conventional laser surgery on the degree of macular edema in patients with diabetic macular edema (DME). Methods: Ninety patients with DME were divided into a control group (45 cases, grid-like photocoagulation) and an observation group (45 cases, ranibizumab vitreous injection combined with phacoemulsification). The clinical efficacy, best corrected visual acuity (BCVA), degree of macular edema, degree of retinopathy, and complications in the two groups of patients were compared. Results: The clinical efficacy of the observation group was significantly higher than the clinical efficacy of the control group ($P<0.05$). The BCVA, macular edema, and retinopathy were improved, and the incidence of complications was decreased in the observation group compared to the control group ($P<0.05$). Conclusion: An intravitreous injection of ranibizumab combined with phacoemulsification can effectively reduce the degree of macular edema and retinopathy and reduce the incidence of complications in DME patients.

Keywords: Vitreous injection, ranibizumab, phacoemulsification, diabetes, macular edema

Introduction

In recent years, with the increasing seriousness of medical problems resulting from the aging population, the incidence of diabetic retinopathy in China has increased significantly [1]. Diabetic macular edema (DME) can occur at any stage of diabetes, and it is currently a clinically recognized cause of visual impairment in diabetic patients. The visual acuity will generally decrease two levels within 2 years of onset [2]. Macular edema is a typical clinical feature of patients with DME. The long-term symptoms of macular edema can easily lead to various complications or sequelae, such as mechanized membrane formation, full-thickness lamellar, macular layer, retinal folds, etc., thereby impacting the patient's vision, or even causing blindness [3].

The traditional clinical treatment of DME is based on laser therapy. However, laser therapy may cause trauma to the surrounding normal tissues if the laser parameters are not well controlled and, in general, its treatment effect is limited. Phacoemulsification is another common option for the treatment of DME, and it can temporarily relieve the disease, but there are more postoperative complications, and the treatment effect doesn't meet the needs of current patients [4]. Ranibizumab is a monoclonal antibody fragment that is an angiogenesis inhibitor currently approved for use in the treatment of "wet", age-related, macular degeneration. Raymondizumab completely penetrates the whole layer of the retina. Recently, studies have suggested that if combined with phacoemulsification, it can quickly eliminate macular edema and protect central vision [5, 6].

In this randomized controlled trial, we compared the efficacy of conventional laser surgery with ranibizumab intravitreous injection combined with phacoemulsification in the treatment of diabetic macular edema, and hope to

provide a theoretical basis for improving the efficacy of DME.

Materials and methods

Baseline data

Ninety patients with DME who were admitted to The Third People's Hospital of Zhangjiagang from January 2017 to January 2019 were recruited and divided into the observation group (45 cases) and the control group (45 cases) using the random number table method. All patients and their families signed an informed consent form. This study was approved by the ethics committee of our hospital.

Inclusion criteria: All the patients were diagnosed with diabetic retinopathy II-IV using optical coherence tomography (OCT) or other ophthalmology, in line with the diagnostic criteria of DME in the 2014 edition of Guidelines for Clinical Diagnosis and Treatment of Diabetic Retinopathy in China.

Exclusion criteria: (1) Lactating, pregnant women; (2) Patients with severe cognitive, communication, or hearing impairment; (3) Patients with malignant tumors; (4) Patients with heart failure or respiratory failure; (5) Patients with surgical contraindications; (6) Patients with other eye diseases; (7) Patients with major infections; (8) Patients with a recent history of ophthalmic trauma and surgery; (9) Patients with serious complications such as vitreous prolapse.

Methods

In the control group (grid pattern photocoagulation): A multi-wavelength laser therapy device (Beijing Longhuiyi Medical Technology Development Co., Ltd.) was adopted with a spot size of 100-200 um, an exposure time of 0.2 s, and an energy level of 100-200 mw. The spot distance is in a spot size, and the average photocoagulation is 138 points. The intensity is preferably a pale white light spot on the lesion.

In the observation group (intravitreous injection of ranibizumab combined with phacoemulsification): (1) Phacoemulsification: the patients were given the compound tropicamide (Shentian Pharmaceutical Co., Ltd.) for mydriasis, and after topical anesthesia, an incision of about 3.0-3.2 mm was made on the limbus on the upper temporal side. The anterior chamber was injected with sodium hyaluronate gel (Hangzhou Xiehe Medical Supplies Co., Ltd.). A side incision was made in the limbus, continuous circular capsulorhexis and water separation were performed, and the intraocular lens (Beijing Yuanhao Technology Co., Ltd.) was implanted into the capsular bag. (2) Intravitreous injection of ranibizumab: 0.05 ml/0.5 mg of ranibizumab (Novartis Pharma Schweiz AG.) was injected into the vitreous cavity with a 27-gauge needle (1 mL syringe), and the needle was pulled out and the cavity was pressed for 1 minute. In the anterior chamber, the viscoelastic agent was infused, the incision was closed by water tightness.

Observation indicators and evaluation criteria

The clinical efficacy, the best corrected visual acuity (BCVA) before and after treatment, the degree of macular edema, the degree of retinopathy, and the complications were recorded and compared between the two groups.

(1) Clinical efficacy: The clinical efficacy was evaluated at four weeks after the surgery. The specific criteria for the clinical efficacy were as follows: markedly effective, non-fluorescence leakage of the macular area appeared; below 50% fluorescence leakage was effective; more than 51% fluorescence leakage was invalid. The total effective rate was defined as the sum of markedly effective and effective cases divided by the total number of cases (the condition was judged as invalid when one eye was valid and the other eye was invalid).

(2) BCVA: An ophthalmic ultrasound diagnostic instrument (Master VuPad, Shanghai Yimu Medical Devices Co., Ltd.) was used to evaluate the BCVA before treatment and at 2 weeks after treatment.

(3) Retinopathy: The degree of retinopathy was determined at four weeks after the surgery: Grade 0, retinal structure and vitreum is clear; Grade 1, the structure of the retina can be discerned and the vitreum is mildly turbid; Grade 2, the branches of the retinal vessels are unclear and the vitreum is turbid; Grade 3, the retina and vitreum are heavily turbid.

(4) Complications: The incidence of complications including (retinal detachment, lens damage, and endophthalmitis) within 4 weeks after surgery was recorded.

Table 1. Comparison of the baseline data

Groups	Gender		Age (year)	Duration of disease (year)	Degree of retinopathy (n)		
	Male	Female			Grade II	Grade III	Grade IV
Observation (n=45)	25	20	70.0±4.0	10.2±1.0	16	18	11
Control (n=45)	24	21	69.86±4.18	10.33±1.02	17	16	12
X^2/U	0.045		0.115	0.374	0.191		
P	0.832		0.908	0.710	0.909		

Table 2. Comparison of the clinical efficacy (n, %)

Groups	Markedly effective	Effective	Invalid	Total efficiency
Observation (n=45)	16 (35.56)	27 (60.00)	2 (4.44)	43 (95.56)
Control (n=45)	12 (26.67)	21 (46.67)	12 (26.67)	33 (73.33)
X^2				8.459
P				0.004

Table 3. Comparison of BCVA ($\overline{x}$ ± sd)

Groups	Before treatment (logMAR)	After treatment (logMAR)	t	P
Observation (n=45)	0.92±0.13	0.41±0.02	28.800	<0.001
Control (n=45)	0.93±0.14	0.69±0.04	13.080	0.001
t	0.351	42.000		
P	0.726	<0.001		

Note: logMAR indicates that the visual acuity is off-standard. BCVA: best corrected visual acuity.

Statistical analysis

In this study, the collected data was statistically analyzed using the SPSS 25.0 software package. The measurement data were expressed as the means ± standard deviations; a two-sample independent t-test was used for the comparisons between groups, and a paired t-test was used for comparisons within a group. The count data were expressed as n/(%) and analyzed using a chi-squared test. A Mann-Whitney U test was used to compare the degree of retinopathy between the two groups. P<0.05 indicates that there is a significant statistical difference.

Results

Baseline data

There were no significant differences in terms of gender, age, duration of disease, or degree of disease between the two groups, as shown in **Table 1**.

The combination treatment had better clinical efficacy

The total clinical effective rate of the observation group (95.56%) was significantly higher than the rate of the control group (73.33%, P<0.05), as shown in **Table 2**.

The combination treatment showed a better BCVA

There was no significant difference in the BCVA between the two groups before treatment (P>0.05); the BCVA of the observation group was significantly lower than it was in the control group after the treatment (P<0.05). The BCVA after the treatment was significantly lower than it was before the treatment in both groups (P<0.05). See **Table 3**.

The combination treatment improved macular edema better

The degree of macular edema in the two groups was not significantly different before the treatment (P>0.05), but it was significantly lower in the observation group than it was in the control group after the treatment (P<0.05). The degree of macular edema after the treatment was significantly lower than it was before the treatment in both groups (P<0.05). See **Table 4**.

The combination treatment avoided retinopathy better

Four weeks after the surgery, the degree of retinopathy was significantly lower in the observation group than it was in the control group (P<0.05). See **Table 5**.

Table 4. Comparison of the degree of macular edema ($\bar{x}$ ± sd)

Groups	Before treatment (um)	After treatment (um)	t	P
Observation (n=45)	458.26±15.11	242.25±3.14	93.893	<0.001
Control (n=45)	459.31±15.35	358.24±10.01	36.998	0.001
t	0.327	74.167		
P	0.744	<0.001		

Table 5. Comparison of the degree of retinopathy at 4 weeks after surgery (n, %)

Groups	Grade 0	Grade I	Grade II	Grade III
Observation (n=45)	10 (2.22)	15 (33.33)	20 (44.44)	0 (0.00)
Control (n=45)	3 (6.67)	12 (26.67)	28 (62.22)	2 (4.44)
U		9.340		
P		0.002		

Table 6. Comparison of the incidence of complications (n, %)

Groups	Endophthalmitis	Lens injury	Retinal detachment	Total incidence of complications
Observation (n=45)	1 (2.22)	1 (2.22)	0 (0.00)	2 (4.44)
Control (n=45)	5 (11.11)	3 (6.67)	2 (4.44)	10 (22.22)
χ^2				6.154
P				0.013

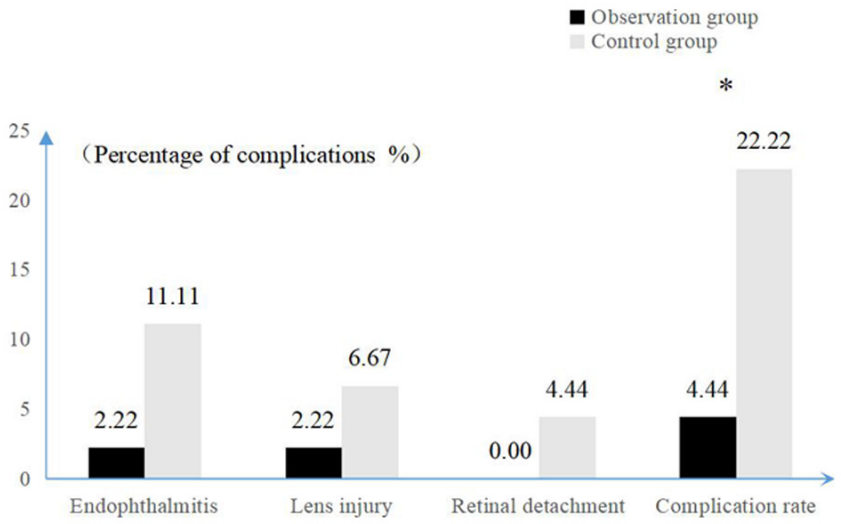

Figure 1. Comparison of the incidence of complications. Compared with the control group, *P<0.05.

The combination treatment had a lower incidence of complications

The incidence of complications in the observation group (4.44%) was significantly lower than it was in the control group (22.22%, P<0.05). See **Table 6**; **Figure 1**.

Discussion

In recent years, with the constant changes in the lifestyles and diets, the incidence of diabetes has increased significantly, and the population of diabetics tends to be young [7]. DME is extremely common in ophthalmology and is characterized by a hard exudation or thickening of the retina caused by the accumulation of extracellular fluid within the focal diameter of the fovea. The severity of DME is closely related to the degree of retinopathy, which often causes irreversible damage to the retina [8, 9]. According to one survey, nearly one-third of diabetics have DME [10]. If the treatment is not timely or the treatment method is not correct, the macula will develop cystic lesions and can even develop into irreversible blindness [11, 12]. Diabetic macular edema is divided into diffuse edema and focal edema. At present, the pathogenesis of the former is not clear, and it is generally believed to be caused by blood-retinal dysfunction; the pathogenesis of the latter is considered to be closely related to microaneurysm leakage and capillary segmental expansion [13, 14].

The laser is a common method for the clinical treatment of DME. It can promote the diffusion of the choroidal blood supply to the patient's retina, improve the supply of retinal nutrients,

correct the vision in time, and have certain clinical effects on the treatment of DME. However, if the laser parameters are not well controlled, it is easy to cause complications such as lens damage [15]. The current methods for clinically treating DME include vitreoretinal surgery, intravitreous drug injection, and corneal-like photocoagulation [16, 17]. The macular-area grid pattern photocoagulation has no obvious effects on the treatment of diffuse edema and retinal thickening in the macular area, so it cannot be promoted in the clinic. Vitreoretinal surgery and vitreous drug injection are the currently preferred clinical treatment methods for DME [18].

Phacoemulsification is the most commonly used vitreoretinal surgery, and it can effectively improve the internal environment of the patient's eye, destroy the blood-retinal barrier, increase the permeability of the retinal blood vessels in the macular area, and improve the patients' quality of life [19, 20]. Ranibizumab is a novel VEGF inhibitor that penetrates the patient's retina more easily. It has high bioavailability, can effectively inhibit neovascularization, induce and promote vascular endothelial cell proliferation, improve local blood circulation, increase ocular blood flow, form new blood vessels, increase microvascular permeability, and maintain the stability and activity of endothelial cells to some extent, which will contribute to the normal development of retinal blood vessels [21]. The safety and efficacy of VEGF inhibitors have been confirmed by a large number of clinical studies. Combined with phacoemulsification, it can effectively reduce the degree of macular edema in DME patients, improve vision, and greatly improve patients' quality of life. This study showed that the total clinical effective rate of the observation group was significantly higher than it was in the control group. The BCVA, macular edema degree, retinopathy degree, and complication rate were significantly lower in the observation group than in the control group ($P<0.05$), which is consistent with previous research results [22, 23].

Therefore, the use of vitreous injection of ranibizumab combined with phacoemulsification in DME patients can effectively reduce intraocular pressure, maintain and improve the stability of the ocular environment, reduce the incidence of complications, and improve safety.

Disclosure of conflict of interest

None.

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References

[1] Cao D, Yang D, Huang Z, Zeng Y, Wang J, Hu Y and Zhang L. Optical coherence tomography angiography discerns preclinical diabetic retinopathy in eyes of patients with type 2 diabetes without clinical diabetic retinopathy. Acta Diabetol 2018; 55: 469-477.

[2] Lawrenson JG, Graham-Rowe E, Lorencatto F, Rice S, Bunce C, Francis JJ, Burr JM, Aluko P, Vale L, Peto T, Presseau J, Ivers NM and Grimshaw JM. What works to increase attendance for diabetic retinopathy screening? An evidence synthesis and economic analysis. Health Technol Assess 2018; 22: 1-160.

[3] Tomida C, Yamagishi N, Nagano H, Uchida T, Ohno A, Hirasaka K, Nikawa T and Teshima-Kondo S. VEGF pathway-targeting drugs induce evasive adaptation by activation of neuropilin-1/cMet in colon cancer cells. Int J Oncol 2018; 52: 1350-1362.

[4] Nemeth J, Szabo D, Toth G, Sandor G, Lukacs R, Pek A, Szalai I, Papp A, Resnikoff S and Limburg H. Feasibility of the rapid assessment of avoidable blindness with diabetic retinopathy module (RAAB+DR) in industrialised countries: challenges and lessons learned in Hungary. Ophthalmic Epidemiol 2018; 25: 273-279.

[5] Lee SE, Han K, Baek JY, Ko KS, Lee KU and Koh EH. Association between diabetic retinopathy and Parkinson disease: the Korean National Health Insurance service database. J Clin Endocrinol Metab 2018; 103: 3231-3238.

[6] Department of Ophthalmology, Chinese Medical Association, Ophthalmology Group. Guidelines for Clinical Diagnosis and Treatment of Diabetic Retinopathy in China (2014). Chinese Journal of Ophthalmology 2014; 50: 851-865.

[7] Singer MA, Dugel PU, Fine HF, Capone A Jr and Maltman J. Real-world assessment of dexamethasone intravitreal implant in DME: find-

ings of the prospective, multicenter reinforce study. Ophthalmic Surg Lasers Imaging Retina 2018; 49: 425-435.
[8] Muc R, Saracen A and Grabska-Liberek I. Associations of diabetic retinopathy with retinal neurodegeneration on the background of diabetes mellitus. overview of recent medical studies with an assessment of the impact on healthcare systems. Open Med (Wars) 2018; 13: 130-136.
[9] Mikhail M, Stewart S, Seow F, Hogg R and Lois N. Vitreomacular interface abnormalities in patients with diabetic macular oedema and their implications on the response to anti-VEGF therapy. Graefes Arch Clin Exp Ophthalmol 2018; 256: 1411-1418.
[10] Lingam S, Rani PK, Sheeladevi S, Kotapati V and Das T. Knowledge, attitude and practices on diabetes, hypertension and diabetic retinopathy and the factors that motivate screening for diabetes and diabetic retinopathy in a pyramidal model of eye health care. Rural Remote Health 2018; 18: 4304.
[11] Regillo CD, Callanan DG, Do DV, Fine HF, Holekamp NM, Kuppermann BD, Singer MA and Singh RP. Use of corticosteroids in the treatment of patients with diabetic macular edema who have a suboptimal response to anti-vegf: recommendations of an expert panel. Ophthalmic Surg Lasers Imaging Retina 2017; 48: 291-301.
[12] Hussain RM, Hariprasad SM and Ciulla TA. Treatment burden in neovascular AMD: visual acuity outcomes are associated with Anti-VEGF injection frequency. Ophthalmic Surg Lasers Imaging Retina 2017; 48: 780-784.
[13] Yao J, Wang J, Yao Y, Wang K, Zhou Q and Tang Y. miR133b regulates proliferation and apoptosis in high glucose induced human retinal endothelial cells by targeting RAS homolog family member A. Int J Mol Med 2018; 42: 839-850.
[14] Guan RJ, Li L, Zhang R, Ma XY, Sun WD and Ophthalmology DO. Analysis on concentration of VEGF in aqueous humor in patients with wAMD after Ranibizumab treating at high altitude. International Eye Science 2017.
[15] Imai S, Otsuka T, Naito A, Shimazawa M and Hara H. Triamcinolone acetonide suppresses inflammation and facilitates vascular barrier function in human retinal microvascular endothelial cells. Curr Neurovasc Res 2017; 14: 232-241.
[16] Slominski B, Ryba-Stanislawowska M, Skrzypkowska M, Mysliwska J and Mysliwiec M. The KL-VS polymorphism of KLOTHO gene is protective against retinopathy incidence in patients with type 1 diabetes. Biochim Biophys Acta Mol Basis Dis 2018; 1864: 758-763.
[17] Zhao XY, Xia S and Chen YX. Antivascular endothelial growth factor agents pretreatment before vitrectomy for complicated proliferative diabetic retinopathy: a meta-analysis of randomised controlled trials. Br J Ophthalmol 2018; 102: 1077-1085.
[18] Chawla R, Venkatesh P, Tripathy K, Chaudhary S and Sharma SK. Successful management of proliferative diabetic retinopathy and multiple choroidal tubercles in a patient with miliary tuberculosis. J Ophthalmic Vis Res 2018; 13: 210-211.
[19] Nakashima H, Iwama Y, Tanioka K and Emi K. Paracentral acute middle maculopathy following vitrectomy for proliferative diabetic retinopathy: incidence, risk factors, and clinical characteristics. Ophthalmology 2018; 125: 1929-1936.
[20] Alzahrani SH, Bakarman MA, Alqahtani SM, Alqahtani MS, Butt NS, Salawati EM, Alkatheri A, Malik AA and Saad K. Awareness of diabetic retinopathy among people with diabetes in Jeddah, Saudi Arabia. Ther Adv Endocrinol Metab 2018; 9: 103-112.
[21] dell'Omo R, Vogt D, Schumann RG, De Turris S, Virgili G, Staurenghi G, Cereda M, Costagliola C, Priglinger SG and Bottoni F. The relationship between blue-fundus autofluorescence and optical coherence tomography in eyes with lamellar macular holes. Invest Ophthalmol Vis Sci 2018; 59: 3079-3087.
[22] Karbalaei R, Allahyari M, Rezaei-Tavirani M, Asadzadeh-Aghdaei H and Zali MR. Protein-protein interaction analysis of Alzheimer's disease and NAFLD based on systems biology methods unhide common ancestor pathways. Gastroenterol Hepatol Bed Bench 2018; 11: 27-33.
[23] Lee JW, Yang DH, Park S, Han HK, Park JW, Kim BY, Um SH and Moon EY. Trichostatin A resistance is facilitated by HIF-1α acetylation in HeLa human cervical cancer cells under normoxic conditions. Oncotarget 2018; 9: 2035-2049.