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Original Research Article

Efficacy of the combination of intravitreal aflibercept and triamcinolone injections in treatment of diabetic macular edema

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Abstract

Purpose: *To investigate the clinical efficacy of intravitreal aflibercept combined with intravitreal triamcinolone injection in the treatment of diabetic macular edema (DME).*
Methods: *86 patients with diabetic macular edema (DME) were randomly assigned to either a combination therapy group (n = 43) or a control group (n = 43). Both groups received intravitreal aflibercept injection (2 mg, 5 injections per month) while combination therapy group received aflibercept treatment in addition. Central macular thickness (CMT), intraocular pressure (IOP), best-corrected visual acuity (BCVA), serum inflammatory factors (IL-6 and IL-8), VEGF and quality of life were determined before and after treatment at multiple time-points.*
Results: *Combination therapy group achieved a significantly higher total effective rate compared to control group ($p < 0.05$). When compared to the baseline, CMT and BCVA in both groups gradually decreased over 3 months after injection, with combination therapy group showing a greater reduction ($p < 0.05$). The IOP and SQOL-DVI scores in both groups increased over time in both groups, with a greater increase observed in combination therapy group compared to the baseline ($p < 0.05$). Serum inflammatory factors decreased in both groups, with combination therapy group having significantly lower levels ($p < 0.05$).*
Conclusion: *The combination of intravitreal aflibercept and triamcinolone injection has better efficacy than intravitreal aflibercept injection alone in the treatment of diabetic macular edema, improving visual function and enhancing the quality of life of the patients. More elaborate studies are required to elucidate the mechanism of this synagistic therapeutic combination.*

Keywords: *Aflibercept, Triamcinolone, Diabetic macular edema*

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INTRODUCTION

Diabetic macular edema (DME) refers to the thickening of the retina within two-disc diameters of the fovea in the macular region. It is a microvascular complication of type 2 diabetes mellitus (T2DM) characterized by the loss of pericytes, endothelial cell damage, thickening of the basement membrane and vascular occlusion, and leads to diabetic retinopathy (DR) [1,2]. In

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addition, it is a common sign of fundus diseases and a non-specific pathological response to chronic inflammation and disruption of the blood-retinal barrier [3]. The specific pathogenesis of DME is not yet fully understood and effective treatments are lacking in clinical practice. Common treatment methods include pan-retinal photocoagulation and intravitreal drug injections [4]. Aflibercept, widely used for treating DME in adults, is an anti-vascular endothelial growth factor (anti-VEGF) drug mainly used to treat eye diseases related to retinal diseases. Its mechanism of action involves inhibiting VEGF, preventing abnormal blood vessel growth, reducing leakage and inflammation, and helping to improve symptoms and protect vision. It is usually given by injection into the eye and inhibits the binding and activation of VEGF receptors with vascular endothelial growth factor-A and placental growth factor, thereby hindering the formation of pathological neovascularization, thus increasing vascular permeability [3].

On the other hand, triamcinolone is a moderately potent corticosteroid that possesses anti-inflammatory, anti-pruritic and vasoconstrictive properties. It is an anti-inflammatory and immunosuppressive drug often used in combination with aflibercept to treat eye conditions. Its role is to reduce ocular inflammation and immune response, thereby enhancing the efficacy of aflibercept. This combined strategy helps treat eye disease more effectively, improves symptoms and protects vision. This study investigates the efficacy and safety of aflibercept combined with intravitreal triamcinolone injection in the treatment of DME.

METHODS

General information

A total of 86 patients, were diagnosed with diabetic macular edema (DME) and treated in the Department of Ophthalmology, Affiliated Hospital of Hebei University, Baoding, China from January 2020 to December 2021, were selected for this study. They were randomly divided into a combination therapy group (43 cases) and a control group (43 cases). In the combination therapy group, the male/female ratio was 23/20, with an age range of 45 - 72 years (mean age: 60.01 ± 5.18 years) and a duration of type 2 diabetes mellitus (T2DM) ranging from 4 - 15 years (mean duration: 7.51 ± 1.28 years). Nineteen cases had DME in the left eye, while 24 cases had DME in the right eye. In control group, the male/female ratio was 26/17, with an age range of 44 - 71 years (mean age: 60.26 ± 4.95 years) and a duration of T2DM ranging from 4 - 14 years (mean duration: 7.48 ± 1.61 years). Twenty cases had DME in the left eye and 23 cases had DME in the right eye. There were no statistically significant differences in the general information between the two groups ($p > 0.05$), indicating comparability. This study was approved by the Ethics Committee of the Hospital of Hebei University, China (approval no. DAH-2023-114) and followed the guidelines of the Declaration of Helsinki [5]. The patients and their families gave their informed consent for the study.

Inclusion criteria

The criteria for including participants in this study are as follows: Patients diagnosed with type 2 diabetes mellitus according to the diagnostic criteria of "Guidelines for the Prevention and Treatment of Type 2 Diabetes in China" [6]; patients confirmed with diagnosis of DME through fundus examination and fluorescein fundus angiography (FFA); patients with central macular thickness (CMT) ≥ 300 μm as determined by optical coherence tomography (OCT) and those with unilateral involvement.

Exclusion criteria

Participants were excluded from this study based on the following criteria: Patients with a history of previous relevant surgical treatments, history of intravitreal or posterior subtenon steroid injections within the past one and a half months; patients with coexistence of other fundus diseases such as glaucoma or optic neuritis; patients with significant organ dysfunctions involving the cardiovascular, cerebrovascular, or hematopoietic systems, and those with inability to cooperate with the study due to other physical conditions.

Treatments

Both groups of patients received levofloxacin eye drops (0.5 % (w/v)) in each eye, at a frequency of 4 - 6 times per day for 3 - 5 days. Application of eye drop was stopped three days before injection. After injecting the site was pressed for about half a minute to prevent drug reflux, and antibiotic eye drops were applied for 1 - 2 weeks. Within one week after injection, daily monitoring of intraocular pressure and slit lamp examination were performed.

Control group

The affected eye was dilated using cyclotropine (1 % or 2 % v/v) and locally anesthetized through the use of eye drops or an injection [4]. The skin

was disinfected with povidone-iodine solution and the conjunctival sac was rinsed with 5 % povidone-iodine. Using a 30-gauge needle, the sclera was punctured 3.5 - 4.0 mm from the limbus and advanced 5 - 6 mm deep. Carefully, 0.05 mL of aflibercept solution (Vetter Pharma-Fertigung GmbH & Co.KG, Germany, approval number: S20180010) was injected into the posterior vitreous [6].

Combination therapy group

In addition to the procedures in control group, intravitreal injection of triamcinolone was included. After routine disinfection, the ocular surface was anesthetized three times with proparacaine. Then, the conjunctival sac was rinsed with 5 % povidone-iodine. A 1 mL syringe was positioned 3.5 - 4.0 mm behind the temporal corneal limbus and directed vertically towards the scleral surface, and 0.05 mL of a 40 mg/mL triamcinolone solution was slowly injected. Afterward, the eye was covered with a sterile dressing containing tobramycin-dexamethasone ointment. On the following day, the dressing was removed and levofloxacin eye drops were applied four times daily.

Evaluation of parameters/indices

Central macular thickness

Central Macular Thickness (CMT) was measured using an optical coherence tomography (OCT) device (Nidek Medical Instruments Co., Ltd.) before treatment at a frequency of 1 day, 1 week, 1 month, 3 months and 6 months after injection. Three consecutive measurements were taken and the average value was recorded [7].

Intraocular pressure

Intraocular pressure (IOP) was determined using a non-contact tonometer (manufacturer: Canon Medical Systems Corporation, Japan) before treatment, 1 day, 1 week, 1 month, 3 months, and 6 months after injection. Three consecutive measurements were taken, and the average value was recorded [7].

Best-Corrected Visual Acuity (BCVA)

The visual acuity of the patients was evaluated using the national standard logarithmic visual acuity chart before treatment, 1 day, 1 week, 1 month, 3 months and 6 months after injection [7]. The test results were subsequently converted to the logarithm of the minimum angle of resolution (LogMAR) values.

Levels of inflammatory cytokines

The levels of VEGF, IL-6 and IL-8 in the patients' serum were determined using an enzyme-linked immunosorbent assay (ELISA) before treatment, 1 day, 1 week, 1 month, 3 months and 6 months after injection [8].

Incidence of complications

The occurrence of complications such as vitreous hemorrhage, neovascular glaucoma, pupillary membrane exudation and aggravated lens opacity during the treatment period was observed and recorded [8].

Clinical efficacy

Six months after treatment, clinical efficacy was assessed and classified into three levels based on the fluorescence leakage in the macular area, as previously reported as follows: *Remarkably effective* (RE) – when there is no obvious fluorescence leakage in the macular area; *Effective* (E)– when there is a reduction in the fluorescence leakage; and *Ineffective* (I) – when there is no significant change in the fluorescence leakage in the macular area, with an absorption of less than half of the leakage [8]. The total effective rate (TE) was calculated using Eq 1.

TE (%) = RE (%) + ER (%) …….. (1)

Quality of life

The quality of life of the patients was assessed using Visual Functioning Impairment-Related Quality of Life Scale (SQOL-DVI) before treatment and 6 months after injection [9]. The scale included clinical symptoms and four dimensions (visual function – 8 items, physical function – 4 items, social activities – 4 items, and mental and psychological aspects – 4 items). Each item had a maximum score of 10, and the total score on the scale was 200. A higher score indicated a better quality of life.

Statistical analysis

Statistical analysis was performed using Statistic Package for Social Science (SPSS) 20.0 software (IBM, Armonk, NY, USA). For comparisons between the groups without time factors (CMT, BCVA, intraocular pressure, levels of inflammatory cytokines), t-test was used, and results were presented as mean ± standard deviation (SD). For comparisons between groups with time factors (clinical efficacy and incidence of complications), the chi-square test was used, and results were presented as percentages (%).

A *p-value* less than 0.05 was considered statistically significant.

RESULTS

Clinical efficacy of the treatments

Table 1 highlights the overall clinical efficacy of the two groups six months after completion of treatment. There was a statistically significant difference between the clinical efficacy observed in the combination therapy group compared to control group.

CMT, IOP and BCVA

There was no significant difference in CMT between the two groups before treatment, 1 day and 1 week after injection ($p > 0.05$). However, at 1 month, 3 months and 6 months after injection, a significant difference in CMT between the combined treatment group and control group was observed ($p < 0.05$). In addition, no significant difference was seen in the IOP and BCVA between the two groups before treatment and 1 day after injection ($p > 0.05$). However, at 1 week, 1 month, 3 months and 6 months after injection, the IOP and BCVA of the combined treatment group were significantly different from those of control group ($p < 0.05$; Figure 1).

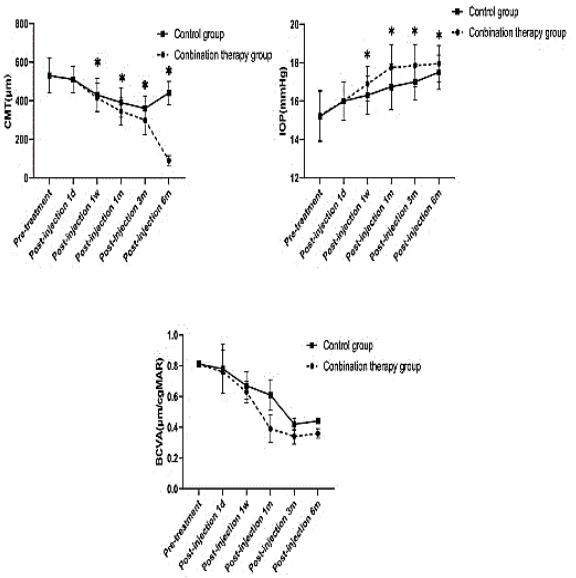

Figure 1: Comparison of CMT, IOP and BCVA levels before and after treatment in the two groups. *$P < 0.05$ *vs.* control group

Serum inflammatory factor levels

The results of the comparison of the serum inflammatory factors between both groups are displayed in Figure 2. There was no significant difference in the serum VSGF between the groups before treatment and 1 day after injection ($p > 0.05$). The serum VSGF was significantly higher in the combined treatment group than in control group at 1 week, 1 month, 3 months and 6 months post-treatment ($p < 0.05$).

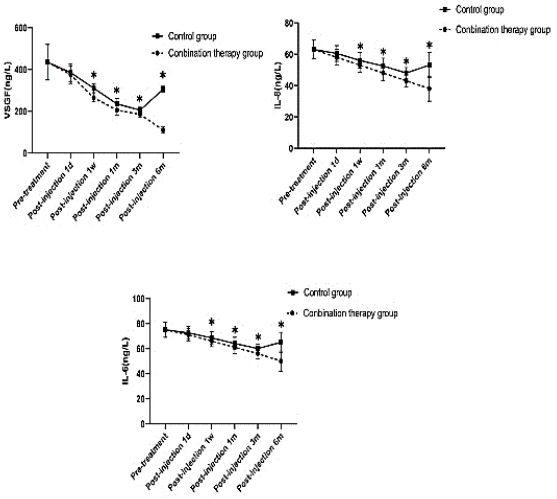

Figure 2: Comparison of serum inflammatory factor levels before and after treatment in the two groups. *$P < 0.05$ *vs.* control group

Complications during treatment

During the treatment, the incidence of vitreous hemorrhage and other complications in the combined treatment group was similar to that in control group, and the difference was not statistically significant ($p > 0.05$; Table 2).

Table 1: Comparison of the curative status between the groups

Group	Remarkable	Effective	Ineffective	Total effectiveness
Combination therapy	29	11	3	40 (93.02)
Control	21	12	10	33 (76.74)
χ^2				4.440
P-value				0.035

Table 2: Comparison of the incidence of complications between the groups (n, %)

Group	VH	NG	PME	ALO	Overall incidence
Combination therapy	1 (2.33)	1 (2.33)	0 (0.00)	1 (2.33)	3 (6.98)
Control	2 (4.65)	0 (0.00)	1 (2.33)	1 (2.33)	4 (9.30)
χ^2					0.156
P-value					0.693

Note: VH: Vitreous hemorrhage, NG: Neovascular glaucoma, PME: Pupillary membrane exudation, ALO: Aggravated lens opacity

Quality of life scores of patients

Before treatment, there was no statistically significant difference in the SQOL-DVI score between the combined treatment group and control group ($p > 0.05$). However, at 6 months after treatment, the SQOL-DVI scores of the two groups were compared, and the difference was statistically significant ($p < 0.05$; Table 3).

DISCUSSION

Type 2 diabetes mellitus (T2DM), also known as non-insulin-dependent diabetes, is characterized by hyperglycemia, relative insulin deficiency, and insulin resistance and leads to complications such as heart disease and stroke [10]. Diabetic macular edema (DME) is one of the complications of T2DM that occurs at any stage of diabetic retinopathy (DR), significantly affecting visual acuity in patients [11]. It is the main cause of visual impairment in patients with DR. In DME patients, leakage of capillaries in the macular area causes retinal thickening within two disc diameters of the macular center (central macular thickness, CMT) [12]. Vascular endothelial growth factor (VEGF) plays a key role in the development of DR and can disrupt the blood-retinal barrier, leading to the accumulation of extracellular fluid in the macular area [13]. Endothelial cell damage activates platelets, causing adhesion and aggregation, resulting in systemic hypercoagulability, accelerated atherosclerosis and plaque formation. Additionally, the narrow diameter of retinal capillaries and their susceptibility to blockage cause retinal ischemia and hypoxia, resulting in vitreous hemorrhage, retinal detachment, or neovascularization, culminating in visual impairment as well as decreased best-corrected visual acuity (BCVA) [13]. Currently, corticosteroids are the main drugs used for the treatment of DME, and though their therapeutic efficacy and safety have been proven, their use may lead to increased intraocular pressure and related complications [14].

The results of this study showed that the total effective rate in combination therapy group was 93.02 %, significantly higher than the 76.74 % in control group. The incidence of complications was comparable between the two groups. When compared to the baseline, CMT and BCVA in both groups gradually decreased over 3 months after injection, with combination therapy group showing a greater reduction. At the 6th-month follow-up, control group experienced a significant rebound in CMT and a pronounced decrease in visual acuity, while combination therapy group showed a sustained decrease in CMT. Both groups experienced a slight rebound in BCVA after 6 months, with control group showing a greater rebound than combination therapy group. This may be because aflibercept only temporarily promotes fluid absorption in the retinal layers without fundamentally reversing the retinal changes caused by hyperglycemia, thus being unable to provide a complete cure for DME. Triamcinolone, on the other hand, is a synthetic hormone that inhibits the proliferation of retinal endothelial cells induced by fibroblast growth factors, thereby obstructing the growth of neovascularization and preventing retinal damage. The combination of aflibercept and triamcinolone in combination therapy group resulted in a stable or improved visual acuity for 6 months, with the best improvement observed at 1 month after treatment and a slight decrease in visual acuity at 3 and 6 months, but still improved compared to the baseline.

Intraocular pressure (IOP) represents the pressure exerted by the contents of the eye, including aqueous humor, lens and vitreous humor. A balance between production and outflow of aqueous humor is maintained under normal conditions, but excessive production or impaired outflow can lead to increased IOP, which can gradually progress to primary open-angle glaucoma [15]. Triamcinolone and aflibercept have different pharmacological effects and their combined use results in better efficacy. Therefore, in this study, IOP in both groups gradually increased over time, with a greater increase observed in combination therapy group compared to the baseline. Vascular endothelial growth factor (VEGF) is the most potent pro-angiogenic factor involved in the development of vascular abnormalities in DR. It can accelerate disease progression by regulating low-density lipoprotein receptor-related protein 6 and lipid metabolism [16].

Table 3: SQOL-DVI scores before and after treatment in the combination and control groups

Group	Clinical symptoms and visual function		Social activities		Physical function		Mental and psychological state		Total score	
	Pre-treatment	***Post-treatment***	***Pre-treatment***	***Post-treatment***	***Pre-treatment***	***Post-treatment***	***Pre-treatment***	***Post-treatment***	***Pre-treatment***	***Post-treatment***
Combination therapy	43.57±3.88	56.72±5.09*	17.16±1.34	28.97±1.99*	20.28±2.13	31.25±2.87*	16.15±2.08	29.14±2.32*	97.16±7.58	146.08±11.83*
Control	43.29±3.95	51.42±5.01*	17.22±1.51	24.06±2.02*	20.37±2.12	26.79±2.61*	16.26±2.07	24.95±2.27*	97.14±7.36	127.22±10.34*
T-value	0.332	4.866	0.195	11.355	0.196	7.539	0.246	8.865	0.012	7.871
P-value	0.741	0.000	0.846	0.000	0.845	0.000	0.806	0.000	0.990	0.000

Note: **P* < 0.05 vs. pre-treatment group

Pro-inflammatory cytokines such as IL-6 and IL-8 play a role in the inflammatory response of diabetic macular edema and contribute to vascular leakage. As the disease progresses, their levels increase in the serum [17]. In this study, the levels of inflammatory cytokines in both groups gradually decreased over 3 months after injection, with combination therapy group showing a greater reduction compared to control group. This may be attributed to the stronger anti-inflammatory effect produced by the inclusion of triamcinolone in combination therapy group, which inhibits cell regeneration and disease progression.

At 6 months after injection, both groups showed increased SQOL-DVI scores compared to the baseline, with a greater increase observed in combination therapy group. Previous studies have shown that intravitreal injections of triamcinolone and aflibercept effectively reduce CMT, serum VEGF, IL-6 and IL-8 levels, improve BCVA and SQOL-DVI scores, and circumvent rebound, providing effective treatment for DME [18,19].

The results of this study indicate that both intravitreal aflibercept injection alone and the combination of intravitreal aflibercept and triamcinolone injection potentially alleviate the suffering of patients with DME to a certain extent, with the combination therapy demonstrating a greater improvement in patients' quality of life.

Limitations of this study

The study was conducted in a single center and very few subjects were used. In the future, there would be the need to repeat this study using different centers.

CONCLUSION

Compared to intravitreal aflibercept injection alone, the combination of intravitreal aflibercept and triamcinolone injection shows superior efficacy in the treatment of diabetic macular edema, effectively improving visual function, reducing serum levels of VEGF, IL-6 and IL-8, and enhancing patients' quality of life. However, more elaborate clinical trials are wo required to elucidate the exact mechanism of this synergistic interaction.

DECLARATIONS

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None provided.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

Ethical Approval

This study was approved by the Ethics Committee of the Hospital of Hebei University, China (approval no. DAH-2023-114).

Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

*Use of Artificial Intelligence/*Large Language Models

None provided.

Use of Research Reporting Tools

None provided.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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