Annals of Clinical and Analytical Medicine
Original Research

The effects of intravitreally injected dexamethasone implant and anti-VEGF on macular edema due to retinal vein occlusion

Endothelial growth factors on macular edema and dexamethasone implant and anti-vascular endothelial growth factors

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Abstract

Aim: In this study, we aimed to investigate the efficacy of intravitreal treatment modalities for macular edema secondary to central retinal vein occlusion (CRVO) and branchial retinal vein occlusion (BRVO).

Material and Methods: A total 58 patients with macular edema secondary to CRVO and BRVO were included in this retrospective study. The patients followed up between 2012 and 2018 were subjected to either intravitreal dexamethasone (DEX) implant injection (Group 1), or intravitreal anti-vascular endothelial growth factor (anti-VEGF) containing ranibizumab injection (Group 2). Additionally, the patients who received the combination of intravitreal DEX and anti-VEGF treatment (Group 3) were also assessed in this study. The degree of central macular thickness (CMT) using optical coherence tomography, and best -corrected visual acuity (BCVA) levels were evaluated in all groups before and after treatment.

Results: CRVO and BRVO were present in 12 and 46 patients, respectively, and the mean follow- up time was 38 months. The mean CMT values measured in pretreatment vs. posttreatment period in Group 1, Group 2 and Group 3 were 448±41.3μm vs.217.7±15.9μm ($p<0.05$), 492±38.5μm vs.249.3±13.8μm ($p<0.05$), and 562.5±85.7μm vs.330.3±55.9μm ($p<0.05$), respectively. Regarding the comparison of BCVA levels measured in the pretreatment vs. postreatment period, there was a statistically significant increase in all groups as follows: 0.8±0.08 logMAR vs. 0.4±0.08 logMAR ($p<0.05$) in Group 1, 0.9±0.1 logMAR vs. 0.3±0.05 logMAR ($p<0.05$) in Group 2, and 1.6±0.3 logMAR vs. 0.5±0.1 logMAR($p<0.05$) in Group 3.

Discussion: The intravitreal injection treatments with either dexamethasone implant or anti-VEGFs can have a potential effects on the resolution of macular edema secondary to BRVO. Moreover, their combination can be beneficial for the persistent macular edema arising from CRVO.

Keywords

Retinal vein occlusion; Intravitreal injections; Dexamethasone implant; Aflibercept; Ranibizumab

DOI: 10.4328/ACAM.20378 Received: 2020-10-23 Accepted: 2020-11-23 Published Online: 2020-12-01 Printed: 2021-06-01 Ann Clin Anal Med 2021;12(6):663-666
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Introduction

Retinal vein occlusion, leading to a varying degree of painless visual loss is one of the most commonly encountered retinal vascular diseases in ophthalmic practice. The clinical severity of this disorder usually depends on the degree of retinal venous insufficiency, namely, the visual prognosis is often poor in case of central retinal vein occlusion (CRVO), whereas it may be good if the retinal vein is partially occluded that is branchial retinal vein occlusion (BRVO). Moreover, the ischemic type of CRVO can cause profound painful visual loss owing to neovascular glaucoma. This condition is frequently seen in the retinal artery-vein crossing areas, where they share the same adventitial sheath [1, 2].

There are many systemic and visual causes for the obstruction etiology. Systemic causes include hypertension, diabetes mellitus, and atherosclerosis, while eye-related causes include glaucoma and hyperopia [3, 4].

The increased pressure in the retinal capillaries leads to changes in the serum part of the blood. The fluid enters the retinal layers in the macula and forms a pathology called macular edema. The tight connections between endothelial cells in the inner wall of retinal capillaries are disrupted, and vascular endothelial growth factor (VEGF) secreted from these endothelial cells increases macular edema by increasing permeability of these vessels. Macular edema is the most common cause of decreased vision in retinal vein occlusion [5].

The most commonly used treatment methods are laser photocoagulation, intravitreal steroid injection, and intravitreal anti-VEGF injection [6]. The intravitreal depot form as a dexamethasone (DEX) implant has been developed for more effective treatment in retinal vein occlusions [7]. It has not been determined exactly which treatment is more effective.

In this study, it was aimed to evaluate the effectiveness of the treatment modalities and response to these treatments in patients with CRVO and BRVO, both on visual acuity and macular thickness.

Material and Methods

This study was conducted on patients admitted to Canakkale Onsekiz Mart University Ophthalmology Clinic between the years 2012 and 2018. The study was approved by the local ethics committee.

The study was carried out retrospectively with the review of the medical records of the patients with retinal vein occlusion. Inclusion criteria were: central retinal vein occlusion, branch retinal vein occlusion, and macular edema. Patients with prior ocular surgery, retinal arterial occlusion, dense cataracts obscuring retinal images, central corneal opacity, age-related macular degeneration, central serous chorioretinopathy, and posterior uveitis were excluded.

All patients underwent a detailed ophthalmological examination. Systemic diseases were questioned. The diagnosis of vein occlusion was established both by fundoscopic examination and by fluorescein angiography imaging. Optical coherence tomography OCT (Zeiss Cirrus, Zeiss Meditec. Inc, Germany) was performed to detect macular edema in all patients. The first and last visual examinations were recorded as the best-corrected visual acuity according to the Early Treatment Diabetic Retinopathy Study (ETDRS) chart.

These patients have been followed up between the years 2012 and 2018 and were subjected to either intravitreal anti-vascular endothelial growth factor (anti-VEGF) containing ranibizumab injection (Group 1) or intravitreal dexamethasone (DEX) implant injection (Group 2). Additionaly, the patients who received the combination of intravitreal DEX and anti-VEGF treatment (Group 3) were also assessed in this study. All patients had unilateral involvement.

All intravitreal injections were performed in the operating room under aseptic conditions with an order of topical anesthetic, 10 % povidone iodine instillation, sterile draping, injection of dexamethasone implant or anti-VEGF with a 30G needle from the superonasal or superotemporal pars plana, topical antibiotic instillation, and eye patching.

The preference for an intravitreally injected agent was primarily made according to the presence of subretinal fluid, intraretinal cystic changes, and hyperreflective dots in the retinal layers. Phacoemulsification surgery was performed in patients who developed cataracts. Trabeculectomy was performed in case of no response to medical therapy for glaucoma.

Statistical Analysis

The Wilcoxon test, available in the SPSS 20.0 software, was performed for comparison of CMT before and after treatment of the same patients. The p-value of less than 0.05 was considered significant (Table 1).

Results

The right eye was affected in 27 patients and the left eye in 31 patients. The patients were followed up for an average of 38.1 months (min: 14, max: 89). CRVO and BRVO were detected in 12 (20.7%) and 46 (79.3%) patients, respectively. The mean follow-up time was 38 months.

The mean age of the patients was 66.9 ± 10.5 (min: 46, max: 88) years. The study included 28 women (48.3%) and 30 men (51.7%). The most commonly seen systemic disease was hypertension in 27 patients (46.5%), while no systemic disease was detected in eighteen patients (31%). Other systemic diseases are shown in Table 2.

Ranibizumab was intravitreally injected to 22 patients with a varying number of injections. Central macular edema was decreased in 19 patients. The average central macular thickness (CMT) before treatment was 448±41.3μm and after treatment it decreased to 217.7±15.9μm ($p < 0.05$). While the mean pre-injection visual acuity was 0.8±0.08 logMAR, it was found to be 0.4±0.08 logMAR after treatment ($p < 0.05$). Intravitreal DEX-implant was done in 24 patients with varying numbers of injections. The mean CMT before treatment was 492±38.5μm and after treatment it decreased to 249.3±13.8μm ($p < 0.05$). The mean visual acuity was 0.9±0.1 logMAR before treatment and 0.3±0.05 logMAR after treatment ($p < 0.05$). Twelve patients received ranibizumab injections and DEX-implants at different times as change therapy. In this group, the mean CMT before the injections was 562.5±85.7μm and the vision was 1.6±0.3 logMAR, while the macular thickness after treatment was 330.3±55.9μm and the vision was 0.5±0.1 logMAR. The changes in both visual acuity and macular thickness were statistically significant ($p < 0.05$).

In CRVO patients, the injections were the form of a DEX-implant in three (25%), anti-VEGF in three (25%), and a combination in the remaining six (50%) patients. Among BRVO patients, 21 (45.7%) were treated with DEX-implant, 18 (39.1%) were treated with anti-VEGF, and seven (15.2%) were treated with mixed treatments.

The average number of injections was 2.6, 1.3, and 7.2 in Group 1, Group 2, and Group 3, respectively. Out of 58 patients, an increase in visual acuity was detected in 53 (91.4%). In two patients, visual acuity decreased compared to their first visit. In three patients, visual acuity did not change. Only in one eye, the visual acuity fell to the level of hand motion, and in the other eye, visual acuity remained at the level of hand motion. There was no loss of light perception in any eye.

Two patients had glaucoma at the time of the diagnosis. During follow-up, four patients developed glaucoma: two patients in Group 1 and two patients in Group 2. Two patients who developed glaucoma following DEX-implant and did not respond to medical treatment underwent trabeculectomy. Glaucoma was kept under control without medication after trabeculectomy in both patients. Cataract surgery was performed in nine patients. While eight of these patients were in Group 2, only one case was in Group 1.

Table 1. Anatomical and functional values and changes in maculas of Group 1, Group 2 and Group 3

	Group-1 (n=24)	Group-2 (n=22)	Group-3 (n=12)
Pretreatment CMT	448±41.3μm	492±38.5μm	562.5±85.7μm
Posttreatment CMT	217.7±15.9μm	249.3±13.8μm	330.3±55.9μm
Pretreatment BCVA(logMAR)	0.8±0.08	0.9±0.1	1.6±0.3
Posttreatment BCVA(logMAR)	0.4±0.08	0.3±0.05	0.5±0.1
P Value pretreatment & post-treatment CMT comparison	<0.05	<0.05	<0.05
P Value pretreatment & post-treatment BCVA comparison	<0.05	<0.05	<0.05

Intravitreal DEX implant injection; Group-2: Intravitreal anti-VEGF injection; Group-3; combined intravitreal DEX and intravitreal anti-VEGF injection.
CMT: Central macular thickness; BCVA: Best corrected visual acuity
Statistical comparisons were performed by using Wilcoxon signed rank test

Table 2. Associated Systemic Diseases

Systemic Diseases		
	Number	Percent
None	18	31
Hipertension	27	46,5
Diabetes Mellitus	3	5,3
Hipertension + Diabetes mellitus	6	10,4
Coronary Artery Disease	2	3,4
Hipertension + Diabetes mellitus + Renal Insufficiency	1	1,7
Behçet's Disease	1	1,7

Discussion

In the treatment of retinal diseases, intravitreal injections have frequently been used as a first-line treatment. The most commonly used injections are anti-VEGF agents and DEX-implant.

In their study with anti-VEGF, Ayyildiz et al. injected a single dose of anti-VEGF to the patients with BRVO or CRVO who developed macular edema. They observed a decrease in CMT in both groups. The decrease in BRVO was significant, while in CRVO was not [8]. Shiono et al. reported a significant decrease in CMT and an increase in visual acuity after anti-VEGF injection in patients with macular edema due to BRVO [8]. In similar studies, Fukami et al., and Sarikaya et al. also reported significant decrease in CMT [9, 10].

In our study, similar to the literature, a significant reduction in CMT was also observed in 86.4% of the patients with anti-VEGF injection. The average CMT was decreased from 448 microns to 217 microns after the treatment. This decrease was also associated with an increase in visual acuity.

Macular edema related to vein occlusion may persist despite anti-VEGF treatment leading to the search for alternative treatments such as DEX-implant, slow-release and long-acting steroid implant [11,12]. Kanra et al., reported a significant decrease in patients with retinal vein occlusion [13]. In our study, we also found significant decrease in CMT with the DEX-implant. The mean CMT was decreased from 492 microns to 249 microns after the treatment with an associated increase in visual acuity.

The studies related to DEX-implant show the effectiveness of the treatment. Unsal et al., reported a decrease in CMT in the first three months then it maintained following three months [22]. Eter et al. reported improvement in both visual acuity and macular edema in a multi-center study [23]. Donati et al. reported a significant increase in visual acuity with better retinal functions in the early period [14].

Development of cataract and glaucoma has been seen more than other treatments in DEX-implant [15]. In our study, while eight of 34 (23.5%) patients developed cataract impairing visual acuity, and two (5.9%) patients required trabeculectomy after DEX-implant. Rajesh et al. reported the rate of cataract and glaucoma surgery as 32% and 0.5%, respectively [16]. The lower rate of glaucoma surgery than in our study may be attributed to the higher rate of diabetic macular edema in their study instead of vein occlusion. In another study similar to our rates, Hemarata et al. reported that 4.6% of patients required glaucoma surgery [17].

In our study, the average reduction in CMT was 217 microns in the anti-VEGF group, and 242 microns in the DEX-implant, with no statistical significance between the groups (p>0,05). Gu et al. compared the two treatment methods and reported no difference between them. The only difference was the increase in intraocular pressure in the steroid group [18]. Ji et al. also found no difference between the two methods in a meta-analysis study [19].

If there was no response to one of the treatment regimens, another option was used. Manousaridis et al. reported the decrease in CMT after DEX-implant in retinal vein occlusion patients with no response to anti-VEGF treatment [20].

In our study, in one fifth of the patients, changes were done between DEX-implant and anti-VEGF injections. The changes were done from anti-VEGF to dexamethasone implant in ten patients, and reverse in two with a response rate of 91.7% . Balal et al reported that anti-VEGF treatment could be done after DEX-implant in case of persistant macular edema [21].

In conclusion, the intravitreal injection treatments with either dexamethasone implant or anti-VEGFs can have a potential effects on the resolution of macular edema secondary to BRVO. Moreover, their combination can be beneficial for the persistent macular edema arising from CRVO.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

Funding: *None*

Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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How to cite this article:

Aydin Yıldız, Sedat Arıkan. The effects of intravitreally injected dexamethasone implant and anti-VEGF on macular edema due to retinal vein occlusion. Ann Clin Anal Med 2021;12(6):663-666