Visual and Anatomic Outcomes of Cases That Have Received Dexamethasone Implant Treatment for Venous Occlusion

Retina Ven Tıkanıklığı Nedeniyle İntravitreal Dexamethasone İmplant Uygulanan Vakaların Görsel ve Anatomik Sonuçları

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ABSTRACT

Purpose: To investigate the anatomical and visual results of intravitreal dexamethasone implant treatment for macular edema secondary to retinal vein occlusion.

Materials and Methods: The study included a total of 25 patients undergoing dexamethasone implant for macular edema secondary to retinal vein occlusion. Retrospective evaluation included best corrected visual acuity (BCVA) measured with ETDRS charts and macular thickness using optical coherence tomography (OCT) at each visit. The contrast sensitivity levels of patients were evaluated with Pelli-Robson chart

Results: The mean age of the patients was 59.5±13.3 years (range, 34-84years). The mean follow-up time was14.6 ± 5.5 months (range, 6-27 months) and the mean number of implants was 2.6±1.5 (range,1-6). The increase in the visual acuity according to time was statistically significant ($p<0.005$). The decrease in macular edema was statistically significant ($p<0.005$). The initial mean contrast sensitivity before implant was 0.72±0.50 log, and the final mean contrast sensitivity was 1.08±0.46 log ($p<0.005$). No systemic adverse events were observed in any of the cases. When the ocular adverse effects were assessed, cataract progression was seen in 54.5% and cataract operations were performed on 4 patients (18.1%). The increase in intraocular pressure was statistically significant ($p<0.005$) and only one patient needed medical treatment.

Conclusion: Dexamethasone implant had a positive effect on anatomic and visual results in retinal vein occlusion-associated macular edema but the ideal repeat interval for intravitreal dexamethasone treatment should be shorter than 6 months .

Key Words: Dexamethasone implant, Macular edema, Retinal vein occlusion.

ÖZ

Amaç: Retina ven tıkanıklığına sekonder makula ödemi tedavisinde intravitreal deksametazon implantın anatomik ve görsel sonuçlarını değerlendirmek

Gereç ve Yöntem: Çalışmaya retinal ven tıkanıklığına ikincil makula ödemi nedeniyle deksametazon implant uygulanmış 25 hasta dahil edildi. Her vizit optik koherens tomografi (OKT) ile ölçülen makula kalınlıkları ve ETDRS eşeli ile ölçülmüş en iyi düzeltilmiş görme keskinliği retrospektif olarak incelendi. Hastaların kontrast sensitivite düzeyleri Pelli-Robson eşeli ile değerlendirilmiş.

Sonuçlar: Hastaların ortalama yaşı 59.5±13.3 yıl (34-84) idi. Ortalama takip süresi14.6 ± 5.5 ay (6-27 ay) ve ortalama implant sayısı 2.6±1.5 (1-6) idi. Zamana gore görme düzeyindeki artış istatistiksel olarak anlamlı idi ($p< 0.005$). Zamana gore makula ödemindeki azalma istatistiksel olarak anlamlı idi ($p< 0.005$). İmplant öncesi başlangıç ortalama kontrast sensitivite 0.72±0.50 log, final ortalama kontrast sensitivite 1.08±0.46 log idi ($p=0.001$). Hiçbir hastada sistemik yan etki görülmedi. Okuler yan etkiler değerlendirildiğinde ise %54 hastada katarakt progresyonu görüldü ve 4 hastaya (%18.1) katarakt ameliyatı yapıldı. Göz içi basıncı artışı istatistiksel olarak anlamlı bulundu ($p<0.005$) ve sadece bir hastada medikal tedaviye ihtiyaç duyuldu.

Tartışma: Deksametazon implant retina ven tıkanıklığı ile ilişkili makula ödeminde anatomik ve görsel sonuçlar üzerine pozitif etkilidir ancak deksametazon implant tedavisinin ideal tekrar aralığı 6 aydan kısa olmalıdır.

Anahtar Kelimeler: Deksametazon implant, Makula ödemi, Retina ven tıkanıklığı.

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INTRODUCTION

Retinal vein occlusion(RVO) is the second most common retinal vascular disease after diabetic retinopathy and is a common cause of visual morbidity and blindness in the elderly.[1] Branch retinal venous occlusion (BRVO) is seen more frequently than central retinal venous occlusion (CRVO).[2] The leading cause of visual loss in retinal venous occlusions is macular edema. Laser photocoagulation, anti-VEGF (vascular endothelial growth factor) bevacizumab, ranibizumab, aflibercept, and the corticosteroids, triamcinolone acetonide and dexamethasone implant are used for the treatment of macular edema secondary to RVO.[3-7] Corticosteroids exert anti-inflammatory effects by inhibiting the arachidonic acid pathway that ensures formation of prostaglandin and in the cellular membrane leukotrienes. Furthermore, they reduce production of TNF-alpha and VEGF, also known as the vascular permeability factor by decreasing leukocyte migration.[8] Recently, the slow-releasing dexamethasone implant (OZURDEX; Allergan, Irvine, CA, USA) has come into use in the treatment of cases with macular edema secondary to BRVO and CRVO. Dexamethasone is a potent and water-soluble corticosteroid with anti-inflammatory effects 6-fold greater than triamcinolone and 30-fold greater than cortisol. This drug complex is placed intraocularly through the pars plana with the help of a special applicator (22 gauge) and releases the total dosage gradually into the vitreous cavity over a period of months.[9] The effects of dexamethasone implant 0.7 mg on macular edema secondary to RVO has been shown for up to 6 months in phase 2 and phase 3 studies. However, recent studies have shown that the effect on the macular thickness and visual acuity, which is greatest at 1 or 2 months following the treatment, is reduced later, and the optimum re-treatment interval is shorter than 6 months.[10-11]

The objective of this study was to assess the anatomical and visual results of intravitreal dexamethasone implant treatment in macular edema secondary to retinal vein occlusion.

MATERIALS AND METHODS

Approval for this study was granted by the local ethics committee. The study included a total of 25 patients diagnosed with macular edema secondary to RVO in our clinic, who were treated with intravitreal dexamethasone implants between December 2011 and October 2014. The diagnosis of macular edema related to RVO was made based on the findings of fundus examination supported by OCT and FFA findings. The patients included in the study were those with records of visual acuity findings at the baseline and at each visit after injection with ETDRS chart and follow up with OCT (Zeiss Stratus and HeidelbergSpectralis). Criteria for inclusion in the study were determined as the presence of retinal vein occlusion and macular edema in ophthalmoscopy, minimum ≥250 μm central macular thickness in the stratus OCT analysis, and absence of neovascularization at the baseline FFA. Criteria for exclusion from the study included active neovascularization, glaucoma, uncontrolled diabetes and hypertension in the history and previous treatment for macular edema.

Patients were informed about macular edema related to RVO and the possible course of their disease. Patients were also informed about the way of administering the intravitreal injections, the effects expected from implantation and potential complications, and informed consent forms were obtained from all participants for the performance of the procedure. Ophthalmological examinations were carried out before each implantation and at months 1, 2,3 and 6 after implantation.Patients who were administered with more injections and had longer follow up were also examined at months 9, 12, 15 and the final visit. The measurements taken at these visits were recorded and analyzed. Follow-up ophthalmic examination, including BCVA with ETDRS, detailed fundus biomicroscopy examination, tonometry and OCT was performed at all of the visits. Goldmann applanation tonometer was used to measure the intraocular pressure. The contrast sensitivity levels of patients were evaluated with Pelli-Robson charts at the baseline and final examination. Foveal thicknesses were measured with TD-OCT at each visit. Detailed foveal evaluations were carried out using SD-OCT at the baseline and at the final examination. Foveal ischemia was evaluated with FFA before injection and in the final examination. Re-treatment criteria at follow-up visits included persistent or increased intraretinal or subretinal fluid on OCT and a decrease of visual acuity more than ≥5 letters on the EDRS scale. Intravitreal implantations were performed in the operating theatre under sterile conditions

The statistical analysis of data was done using SPSS version 21 (IBM). Categorical data were summarized as percentages, and digital data were summarized as mean ±standard deviation or minimum-maximum values. Comparison of two groups for a digital variable in case of the lack of verification of a parametric assumption was evaluated with the Mann-Whitney U test. The Chi-square test was used in the comparison of categorical data. Results were evaluated at a confidence level of 95%, and $p \leq 0.05$ was accepted as the level of statistical significance. Generalized Estimating Equation (GEE), which takes the intra-subject variations into consideration, was used for data measured repeatedly. In the evaluation, $p=0.05$ was accepted as statistically significant.

RESULTS

The demographic data of patients with retinal vein occlusion are given in Table 1. The mean follow-up time of patients was 14.6±5.5 (6-27) months, and the mean number of implants was 2.6±1.5 (1-6).The mean interval between the 1st implant and the 2nd implant in 20 patients where implants were

Table 1. *Demographic data of patients with retinal vein occlusion.*	
Number of patients	Male= 15 (60%) Female= 10 (40%) Total= 25
Mean age of patients (years)	59.5±13.3 (34-84)
Comorbidities	Hypertension= 13 (52%) Coronary artery disease= 5 (20%) Hyperlipidemia=4 (16%) Diabetes mellitus= 2 (8%) Essential thrombocytosis= 1(4%) Senile macular degeneration= 1 (4%)
Number of CRVO	12 (48%)
Number of BRVO - Small branches of the macular vein	13 (52%) 3 (12%)

administered twice (1st implant interval) was 5.3±1.6 months (3-9); the mean interval between the 2nd implant and the 3rd implant in 11 patients where implants were administered 3 times (2nd implant interval) was 4.1±0.6 months (3-5);the mean interval between the 3rd implant and 4th implant in 6 patients where implants were administered 4 times (3rd implant interval) was 4.8 ± 1.1(4-7) months; the 5th implant was administered to 4 patients with an-implant interval of 5± 1.4(3-6) months. The sixth implant was administered to only 2 patients, and the mean implant interval was 4±1.4 (3-5) months. The mean implant interval was 5.1 (3-9) months in CRVO and 4.3 (3-8) months in BRVO. For the CRVO cases, mean 2.6 ± 1.7 (1-6) implants were administered within a mean follow-up period of 14.7±6.3 (6-27) months, and mean 2.6 ± 1.3 (1-6) implants were administered to BRVO cases within a mean follow-up period of 14.6±4.9 (6-23) months.

With regard to visual outcomes, the mean BCVA based on months is shown in Figure 1. Based on these results, the increase in the visual acuity over time was statistically significant (p<0.005). When the increases in BCVA were compared to the baseline BCVA individually, statistically significant increases were found in all the months (p<0.005, p<0.005, p<0.005, p<0.005, p<0.005, p=0.047 and p<0.005 respectively) (Figure 1). The mean BCVA are shown in Figure 2 separately for CRVO and BRVO.

An increase in visual acuity of ≥15 letters compared to the baseline was seen in 34.8% of patients at month 1, in 69.6% of patients at month 2, in 47.8% of patients at month 3, in 68% of patients at month 6, in 65.2% of patients at month 9, in 61.1% of patients at month 12, in 45.5% of patients at month 15 and in 56% of patients at the final visit. In the subgroups, an increase of ≥15 letters was seen in the CRVO group in 50% of patients at month 1, in 90% at month 2, 70% in month 3, 75% in month 6, 70% in month 9, 62.5% in month 12, 42.9% in month 15, and in 58.3% at the final visit. The increase of ≥15 letters was seen in the BRVO group in 23.1% patients in month 1, in 53.8% in month 2, 30% in month 3, 61.5% in month 6, 61.5% in month 9, 60% in month 12, 50% in month 15 and in 53.8% at the final visit.

A statistically significant decrease was observed in the contrast sensitivity. The initial mean contrast sensitivity was 0.72±0.50 log, and the final mean contrast sensitivity was 1.08±0.46 log (p<0.005).

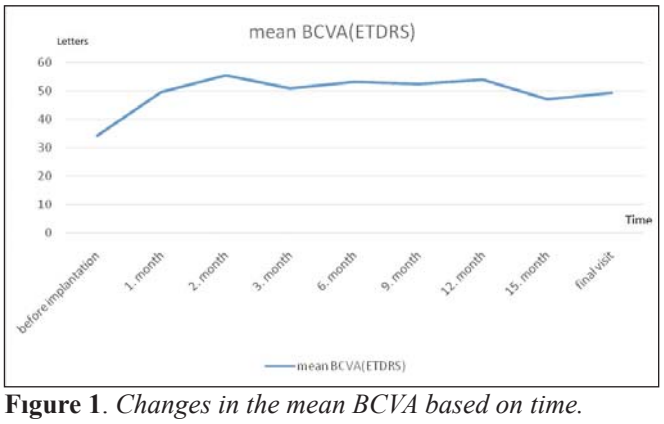

Figure 1. *Changes in the mean BCVA based on time.*

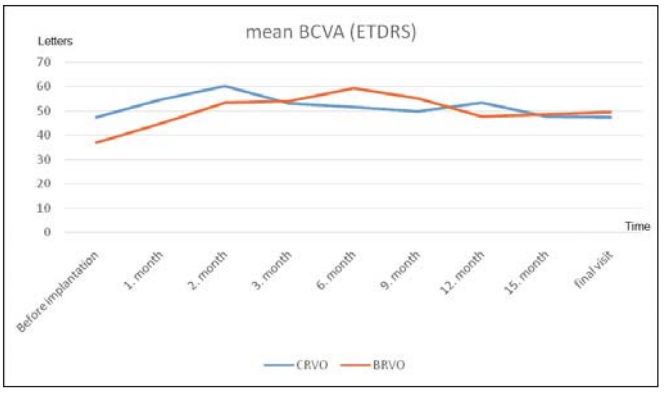

Figure 2. *Changes in the mean BCVA based on time in the BRVO and CRVO groups.*

When the FFA findings were reviewed, 10 of 24 patients evaluated (41.5%) were non-ischemic, and 14 patients (58.5%) were ischemic. Transformation from non-ischemic venous occlusion to ischemic venous occlusion was seen in 1 patient out of 10 (10%), while transformation from ischemic to non-ischemic venous occlusion was seen in 2 patients out of 14 (14.3%). FFA was not possible in 1 patient because of fluorescein allergy and that patient was not included in the evaluation.

The mean central foveal thickness (CFT) values are shown in Figure 3. The decreases in macular thickness were determined to be statistically significant both throughout the follow-up, and at the individual months ($p<0.005$) ($p<0.005$, $p<0.005$, $p<0.005$, $p<0.005$, $p<0.005$, $p<0.005$, $p=0.024$, and $p<0.005$, respectively). The mean CFT values are given separately for CRVO and BRVO in Figure 4.

In periods when the drug was considered effective, the macular thickness that increased more during the treatment compared to the macular thickness before the injection was accepted as a rebound effect, and this was seen in 5 patients (20%).

In 24 patients with initial and final controls performed on Spectralis OCT, at the baseline, IS-OS bands were impaired in 66.7% and at the final visit, impairment was present in 54.2%.

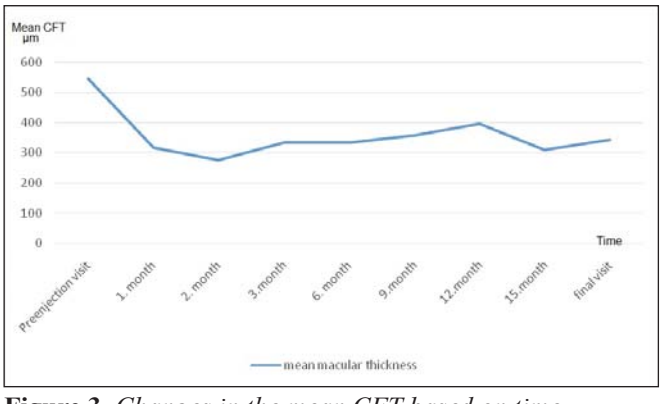

Figure 3. *Changes in the mean CFT based on time.*

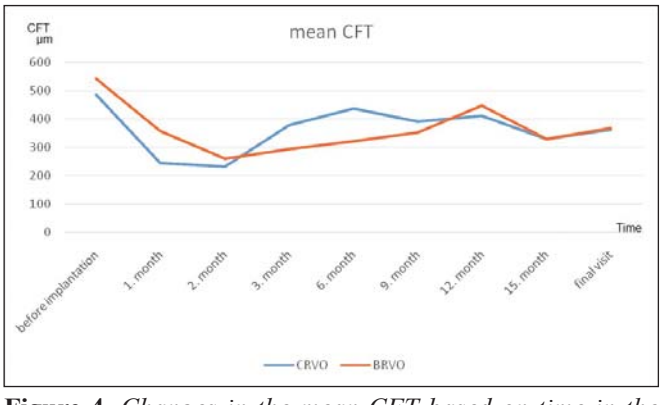

Figure 4. *Changes in the mean CFT based on time in the BRVO and CRVO groups.*

When systemic complications were evaluated, no systemic adverse events were seen in any of the cases. When the ocular adverse effects were evaluated cataract progression was seen in 12 patients (54.5%) and cataract operations were performed on 4 of these patients.

Evaluation of the change in intraocular pressure over time showed that there was a significant increase ($p=0.00$). The mean intraocular pressure was 13.60±2.59 mmHg before the treatment, 15.30±2.05 mmHg at month 1, 18.04±2.72 mmHg at month 2, 16.60±2.51 mmHg at month 3, 16.52±2.71 mmHg at month 6and 15.76±2.91 mmHg at the final visit. In the evaluation based on months, comparison of the intraocular pressures at months 1, 2, 3 and 6 and the final visits with the baseline intraocular pressure, it was seen that the increase was significant at all times except for month 1($p=0.18$ for month 1, $p<0.005$ for months 2, 3 and 6, and $p=0.022$ for the final visit) (Figure 5). The value was ≥25 mmHg (35mmHg) in only 1 patient, dorzolamid+timolol combination drops was started for this patient and medical treatment was stopped after 3 months when IOP fell down to normal levels. No other injections were needed in this patient within the follow-up period.

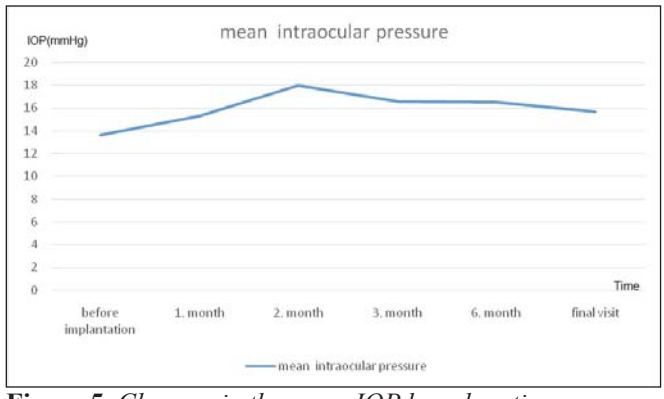

Figure 5. *Changes in the mean IOP based on time.*

The development of the long-term complication of retinal neovascularization was seen in 5 patients [20% (16% in CRVO and 38.5% in BRVO)]. Vitreus hemorrhage was seen in only 1 patient (4%) with SRVO. Rubeosis iridis or neovascular glaucoma was not observed. Endophthalmitis, retinal tears or retinal detachment were not seen in any patient.

CONCLUSION

RVO is a retinal vascular disease that is seen with the second highest frequency after diabetic retinopathy.[12] Population studies have shown that 16 million adults are affected globally each year, and these are mostly older than 60 years of age.[13]

In the current study, an evaluation was made to determine the effectiveness of slow-release dexamethasone implants

administered intravitreally on visual and anatomic outcomes, frequencies and mean numbers of injections. It has been reported that dexamethasone implant administered every 6 months in the early period is effective for a shorter time and should therefore be repeated at shorter intervals.[10,14] VA and OCT findings are the guidance used in the determination of the need for re-implantation.[10]

The benefits of intravitreal dexamethasone implant in macular edema secondary to RVO have been shown in GENEVA study, which was a randomized and controlled study.[7,15] That study showed that the significant effects on visual acuity start on day 30 and the peak increase occurs at day 60, after which, the effectiveness reduces gradually.[7]In the current study, VA was observed to increase significantly within all the months, and peak increases were obtained particularly with the long-term follow-up with repeated injections particularly in months 2 and 12 (Figure 1). In another study again with repeated dexamethasone implantation whenever required, marked improvements were observed in BCVA within the treatment period and increase in BCVA ≥2 lines was seen in 47% of the patients while an increase in BCVA ≥3 lines was seen in 36% of the patients.[16]In the GENEVA study, the increase in BCVA was more rapid in the CRVO group compared to the BRVO group. Accordingly in SOLO study there was an increase of three lines in BCVA in CRVO group whereas there was an increase of two lines in BCVA in BRVO group in forth week.[17] Arifoğlu et al reported that there are not any differences between two groups in terms of increase in BCVA.[18] This study showed that the increase rates were similar according to the VA increase plot for CRVO and BRVO (Figure 4). But the visual outcomes at the final visit had increased after repeated injections more significantly in the BRVO group compared to the CRVO group.

In GENEVA study, while the percentages of patients with ≥15 letters improvement from baseline in the 0.7 mg-group were 21.2% at month 1, 29% at month 2 and 22% at month 3, the percentages of patients with ≥15 letters improvement from baseline in the current study group were 34.8% at month 1, 69.6% at month 2, 47.8% at month 3, 68% at month 6, 65.2% at month 9, 61.1% at month 12, 45.5% at month 15 and 56% at the final visit. However, while the patients in GENEVA study were followed up for 6 months with one single implant, the mean follow-up period in the current study was 14.6±5.5 (6-27) months, and there were also patients with re-implantation within 6 months at minimum intervals of 3 months. This can explain the achievement of ≥15 letters improvement from baseline in the current study with higher ratios. In REMIDO study, the percentage of patients with ≥15 letter improvement was 58.6%, those with ≥10 letters improvement was 64.3%, and the percentage of patients with ≥5 letter increase was 75.7%.[19]

It has been shown in many studies that intravitreal dexamethasone implant significantly decreases the macular thickness.[7,11,19,20] In REMIDO study, significant MMI decreases of 300 µm were observed at month 3 following each injection.[19] In the current study however, significant decreases were seen in CMT at months 1, 2, 3 and 6, with the most prominent decrease in month 2.

The rate of cataract was 31% in GENEVA study, %32 in another study[21] but 54.3% in the current study, which could be related to the number of patients who received 2 or more implants in the current study. Again in another study evaluating repeated injections of dexamethasone implants it was seen that cataract progression necessitating surgery was seen in 29.3% of the patients, and of those, 73% were operated on before the 4th injection.[20] With regard to complications, vitreous hemorrhage was seen in 1 (4%) patient in the current study and in 2.4% of patients in GENEVA study.[7]

The mean IOP was seen to peak in month 2 in the current study, as in other studies, and ≥25 mmHg was seen in 2%, which responded to medical treatment. Previous studies have shown the most frequent adverse effect to be the IOP increase.[16,19,20] In a study by Capone et al., while ≥10 mmHg intraocular pressure increase was seen in 32.6% of the patients, 29.1% of the cases could be controlled with anti-glaucomatous therapy, and incisional glaucoma surgery was required only in 1.7%.[20]

Another question which the current study attempted to answer was the period of effectiveness and the intervals required for repeating the injections. The number of implants administered in this study was 2.6±1.5 (1-6) within the mean follow-up time of 14.6±5.5 (6-27) months. The mean number of implants administered to CRVO cases within the mean follow-up time of 14.7±6.3 (6-27) months, was 2.6±1.7(1-6), and 2.6±1.3 implants were administered to BRVO cases within the mean follow-up time of 14.6±4.9 (6-23) months (1-6).In a study by Eter et al, the mean period between the 1st and 2nd injections was calculated as 155±47 days, while between the 2nd and 3rd injections it was 166±61 days, thus injections were required less frequently compared to the current study.[16]

In another single-center study, dexamethasone implants were placed in 33 eyes with macular edema secondary to RVO, and the results of treatment, re-implantation intervals and adverse effects were analyzed.[15]Cases were followed for a mean period of 16.9±10.5 (7-48) months, and re-implants were required after a mean period of 4.7±1.1 months following the 1st implant, and 5.1±1.5 months after the 2ndimplant. Likewise, the interval after the 1st implant was 5.3 ± 1.6 month (3-9) and the interval after the 2nd implant was 4.1 ± 0.6 months (3-5) in the current study and the interval for re-implantation was found to be <6 months. Significant VA increases were seen after a mean period of 1.4±0.7 months following the 1st implant and 1.8±0.8

months following the 2nd implant in the previous study, and this increase was similar in the current study. Based on all these results, the ideal repeat interval for intravitreal dexamethasone treatment must be shorter than 6 months and patients must be examinedat certain intervals before the end of 6 months.

Retinal neovascularization was seen in 20% in the current study. However, previous studies have shown that steroids have also anti-angiogenic effects through VEGF inhibition, and it was shown in GENEVA study that dexamethasone implant significantly decreased the retinal neovascularization rate through its effect on the progression of the disease and ischemia. İn another study there was no ischemic transformation in follow up so this study supported that neovascular change secondary retinal ischemia was reduced with dexamethasone treatment.[22] However, in SCORE study, it was demonstrated that the retinal neovascularization rate was not reduced with intravitreal triamcinolone in the long term.[3,5] Neovascularization outside the retina was not seen in the current study. Furthermore, in another study, the rate of transformation from non-ischemic venous occlusion to ischemic venous occlusion was 9.4 %within 6 months, and 12.6% within 18 months.[23] In the current study however, this rate was 10% within the follow-up period of 11.3±4.3 months.In another study, improvements were seen in all the visual functions except for contrast sensitivity after dexamethasone implant in cases with macular edema secondary to retinal vascular disease.[24] In our study as well it was seen that contrast sensitivity decreased significantly.

This study had some limitations, primarily that it was resrospective, uncontrolled and evaluated a relatively small study population. Nevertheless, the findings provide useful comparisons with the results from other studies.

In conclusion, dexamethasone implant treatment has positive effects on VA increase and CMT decrease in macular edema related to RVO. Long-term effects are provided through continuous intraocular release from the dexamethasone implant and this decreases the need for injections. While treatment is provided with a mean number of 2 to 4 dexamethasone implantations annually, more implantations are required in the anti-VEGF group, and this makes dexamethasone superior to ranibizumab, which is an anti-VEGF agent. However, patients must be under close follow-up with regard to potential adverse effects like cataract and intraocular pressure increase.

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Not applicable

Conflict of interest:

Allauthors have no financial interests to disclose. This study was not funded by any organisation

Ethics:

Our retrospective study conducted in accordance with the Declaration of Helsinki

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