Combined Ranibizumab and Subtenon Triamcinolone Injection for Macular Edema Secondary to Branch Retinal Vein Occlusion

Retinal Ven Dal Tıkanıklığına İkincil Makula Ödemi Tedavisinde Kombine Ranibizumab ve Subtenon Triamsinolon Enjeksiyonu

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ABSTRACT

Purpose: To evaluate the outcomes of combined intravitreal ranibizumab (IVR) and posterior subtenon triamcinolone acetonide (STTA) injection for the treatment of macular edema (ME) secondary to branch retinal vein occlusion (BRVO).

Methods: Nineteen eyes of 19 patients with BRVO and cystoid ME were examined in this retrospective study. Nine eyes were treated with IVR and STTA, and afterwards with *pro re nata* (PRN) IVR (combined group) and 10 eyes received PRN IVR (control group). The outcome measures were: changes in the central macular thickness (CMT), best corrected visual acuity (BCVA), intraocular pressure (IOP), and number of injections.

Results: The mean initial CMT was 541±103µm in the combined and 475±57 µm in the control group (p=0.14). The median baseline BCVA was 1.0 (0.60-1.15) LogMAR in the combined group and 0.75 (0.47-1.07) LogMAR in the control group (p=0.5). In both groups, CMT was significantly reduced and BCVA was significantly improved at the 1st and 3rd months and at the 1st year. In the first 3 months, the combined group received a single dose, whereas the control group was treated with a median number of 2.5 (2-3) injections (p< 0.001). Nevertheless, the number of additional injections after the 1st injection wasn't significant between the groups [combined group: median 3 (1.5-3), control group: median 3 (1.75-4] p=0.34). No IOP elevations or other injection-related complications were encountered.

Conclusions: Combined IVR and STTA therapy seems to be comparable to IVR monotherapy in improving both CMT and BCVA in BRVO, with similar additional injection numbers.

Key Words: Vein occlusion, Ranibizumab, Subtenon triamcinolone.

ÖZ

Amaç: Retinal ven dal tıkanıklığına (RVDT) ikincil makula ödemi (MÖ) tedavisinde kombine intravitreal ranibizumab (İVR) ve arka subtenon triamsinolon asetonit (STTA) enjeksiyonunun sonuçlarını değerlendirmek.

Gereç ve Yöntem: Bu retrospektif çalışmada RVDT ve kistoid MÖ'lü 19 hastanın 19 gözü incelendi. Dokuz göz İVR ve STTA, sonrasında ise *pro re nata* (PRN) İVR (kombine grup) ile tedavi edildi ve 10 göze PRN İVR (kontrol grubu) uygulandı. Santral makula kalınlığı (SMK), en iyi düzeltilmiş görme keskinliği (EİDGK) ve göz içi basıncındaki (GİB) değişimler ve enjeksiyon sayısı değerlendirildi.

Bulgular: Ortalama başlangıç SMK kombine grupta 541±103μm ve kontrol grubunda 475±57 μm idi (p=0.14). Ortanca başlangıç EİDGK kombine grupta 1.0 (0.60-1.15) LogMAR ve kontrol grubunda 0.75 (0.47-1.07) LogMAR idi (p=0.5). Her iki grupta da 1. ve 3. aylarda ve 1. yılda SMK anlamlı olarak azaldı ve EİDGK iyileşti. İlk 3 ayda kombine gruba tek bir doz uygulanırken, kontrol grubu ortanca 2.5 (2-3) enjeksiyon ile tedavi edildi (p< 0.001). Bununla birlikte, ilk enjeksiyondan sonra uygulanan ek enjeksiyon sayısı gruplar arasında anlamlı değildi [kombine grup: ortanca 3 (1.5-3), kontrol grubu: 3 (1.75-4)] (p=0.34). Göz içi basıncı artışı ya da diğer enjeksiyonla alakalı komplikasyonlara rastlanmadı.

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Sonuç: Retinal ven dal tıkanıklığında SMK'yı ve EİDGK'yı düzeltmede kombine İVR ve STTA tedavisinin İVR monoterapisine, benzer ek enjeksiyon sayısı ile kıyaslanabilir olabileceği görülmektedir.

Anahtar Kelimeler: Ven tıkanıklığı, Ranibizumab, Subtenon triamsinolon.

INTRODUCTION

Branch retinal vein occlusion (BRVO) is a common, sight-threatening retinal vascular disorder that often leads to macular edema (ME), which is the most frequent cause of visual impairment in such patients.[1]

The ME due to BRVO can resolve itself spontaneously, but it can also last for a long time and can lead to photoreceptor damage and functional loss.[2] Several treatments have been developed to improve visual function and to facilitate anatomic recovery from ME due to BRVO. The efficacy of certain treatments has been presented; these treatments include grid laser photocoagulation, vitrectomy with arteriovenous sheathotomy, intravitreal anti-vascular endothelial growth factor (anti-VEGF), intravitreal and/or subtenon injection of triamcinolone acetonide (STTA), and intravitreal dexamethasone implant as well as a combination of the aforementioned therapies for ME due to BRVO.[3-8]

Combination of these treatments might achieve more successful results, in that different treatments influence the different pathways of BRVO. Combination therapies might provide an advantage by multiplying the efficacy, creating additive effects and reducing the treatment time and cost. In this study, we aimed to evaluate the benefit and outcomes of combined posterior STTA and intravitreal ranibizumab (IVR) treatment in eyes with cystoid macular edema (CME) due to BRVO.

METHODS

Medical records were retrospectively reviewed concerning 19 eyes of 19 patients with CME and BRVO, who received either a combination treatment of IVR/STTA injections and afterwards IVR injections or IVR injections at our hospital between 2014 and 2016. Informed consent forms were signed by all patients. The study was conducted in accordance with the tenets of the Declaration of Helsinki. This study was approved by the institutional review board.

The outcome measures of the present study were: changes in the central macular thickness (CMT), best corrected visual acuity (BCVA), intraocular pressure (IOP), and the number of injections. All patients received complete eye examinations, including BCVA measurement with Snellen's chart, biomicroscopy, fundoscopy, Goldmann applanation tonometry, fluorescein angiography (FFA; VISUCAM 500; Carl Zeiss Meditec), and spectral-domain optical coherence tomography (OCT) (RTVue-100; Optovue, Inc.).

In our clinical practice, we performed as initial therapy combined STTA and IVR therapy for patients with BRVO and ME who demanded fewer injection numbers due to social or economic reasons. Inclusion criteria were: (1) CME secondary to BRVO; (2) CMT >300 µm. Exclusion criteria were: (1) increased IOP; (2) vitreomacular surface anomalies; (3) history of prior vitrectomy; (4) visual loss as a result of other diseases; (5) intravitreal and/or subtenon injection of anti-VEGF or steroids within the last 3 months; (6) laser treatment within the previous 3 months.

Injections were done under sterile conditions in the operating room. Topical 0.5% proparacaine hydrochloride was used for anesthesia, and 5% povidone iodine was used for endophthalmitis prophylaxis. In the combination treatment group, after the conjunctiva and Tenon's capsule were cut 8 mm posterior to the limbus at the superotemporal quadrant, 1.0 mL (40 mg/mL) TA (Kenacort- A; Bristol-Myers Co.) was administered to the subtenon area. Then, 0.5mg IVR (Lucentis; Novartis Pharma AG, and Genentech, Inc.) was injected with a 30-gauge needle at the superotemporal pars plana.

After the operation, 0.3% moxifloxacin eye drops were used 4 times per day for 5 days. Follow-up examinations were done the first day, the first week, and the 1st, 2nd, and 3rd months after the operation. Examinations of BCVA and OCT were repeated monthly.

Statistical analyses were conducted using SPSS software version 16 for Windows (SPSS Inc., Chicago, IL, USA). Kolmogorov-Simirnov/Shapiro-Wilk's tests were used to evaluate whether or not the variables are normally distributed. The nonparametric tests were used to compare BCVA, CMT, and IOP (non-normally distributed parameters). Pre- and post-treatment serial comparisons (not normally distributed) were performed using Wilcoxon matched pairs nonparametric test. Comparison of variables between the groups was performed using the Mann-Whitney U test. Fisher's exact test was used to compare the proportions in different groups. Best corrected visual acuities were converted to the logarithm of minimal angle of resolution (LogMAR) for statistical analysis. A result with a p level lower than 0.05 was accepted as a statistically significant result.

RESULTS

Nine eyes were treated with a single dose of ranibizumab and STTA and afterwards with pro renata (PRN) ranibizumab (combined group) and 10 eyes received only ranibizumab (control group). The patients in the control group were injected with *pro re nata* (PRN) IVR after the 1st IVR dose. Both groups were followed-up 1 year, with monthly

monitoring. Reinjection criteria for the combined group after the 3 rd month and for the control group after the 1 st month were; CMT>300 µm and/or a decrease in BCVA ≥1 Snellen line from the last visit. None of the patients received laser treatment during the first 3-months.

Two patients in combined and 2 patients in control groups received laser treatment during the 1 year follow-up. In none of the patients cataract progressed requiring phacoemulsification surgery. There was no significant difference between the groups in terms of gender, age, location of BRVO (superior or inferior), baseline CMT, BCVA, and IOP. In the combined group 44.4 % of the eyes and in the control group 10 % of the eyes were pseudophakic. Three eyes (33.3%) in the combined group and 1 eye (10%) in the control group received prior intravitreal injection at least 3 months before our therapy (p=0.012). Fundus fluorescein angiography was performed in all cases; 33.3% of the eyes in the combined group and 30% of the cases in the control group had ischemic type of BRVO (p=0.10). Demographic characteristics of the patients are shown in Table 1.

In the combined group, mean initial CMT was reduced from 541±103 µm to 290±86 µm (p=0.008) in the 1st month, to 334±69 µm (p=0.008) in the 3rd month and to 285±59 µm (p=0.08) in 1st year. In the control group, mean baseline CMT decreased from 475±57 µm to 316 ±71µm (p=0.005) after the 1st month, and to 289±71 µm (p=0.005) after the 3rd month and to 298±46 µm (p=0.05) after the 1st year. Figure 1 shows the changes in CMT after therapy. The greatest CMT decrease in the combined group was achieved in the 1st month after the operation. At the 1st month follow-up, the mean CMT decrease was 251±101 µm in the combined group and 159±58 µm in the control group; this difference was significant (*p*=0.025). At the 3rd month follow-up, the mean decrease in CMT compared to baseline CMT was 206±95 µm in the combined group and 186±84 µm in the control group; however, this difference was not significant

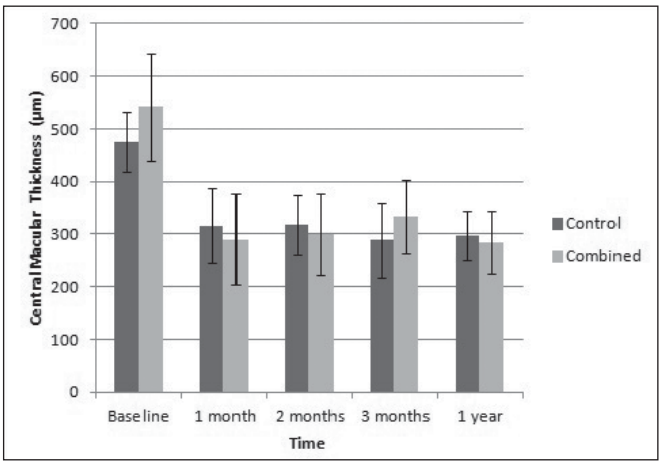

Figure 1. *The changes in CMT after theraphy.*

(*p*=0.68). The mean number of injections during the first three months was a median of 2.5 (2-3) in the control group, and it was significantly greater in comparison to the one injection in the combined group (*p*<0.001). Nevertheless, the number of additional injections after the 1st injection wasn't significant between the 2 groups (combined: median 3 (1.5-3), control: median 3 (1.75-4); p=0.34).

The median baseline BCVA was 1.0 (0.60-1.15) LogMAR in the combined group and 0.75 (0.47-1.07) LogMAR in the control group (*p*=0.50). The median baseline BCVA of the combined group improved to 0.50 (0.35-1.0) LogMAR (*p*=0.040) in the 1st month, to 0.70 (0.30-1.0) LogMAR (*p*=0.017) in the 3rd month and to 0.40 (0.30-0.75) LogMAR (*p*=0.018) in the 1st year. In the control group, the median initial BCVA increased to 0.50 (0.27-0.82) LogMAR (*p*=0.007) in the 1st month and to 0.35 (0.20-0.60) LogMAR (*p*=0.005) in the 3rd month and 0.35 (0.18-0.62) LogMAR (*p*=0.008) in the 1st year. Figures 2 show the visual acuity changes after the treatments of the two groups.

In the combined group, the changes in the mean IOP in the 1st (19.2±1.7 mmHg) and 3rd (18±2.2mmHg) months

Table 1. *Demographic characteristics of the patients.*

	Combined	Control	P value
Number (n)	9	10	
Age (mean±SD)	60± 11	58±13	0.51
Gender (F/M)	3/6	5/5	0.65
Location of occlusion (S/I)	6/3	7/3	1
Baseline IOP (mmHg) (mean±SD)	18.4±2	16.3 ±2.3	0.052
Baseline CMT (µm) (mean±SD)	541±103	475± 57	0.14
Baseline BCVA (logMAR) (median, IR)	1.0 (0.60-1.15)	0.75 (0.47-1.07)	0.5

BCVA: best-corrected visual acuity; **CMT**: central macular thickness; **S**: superior; **I**: inferior; **logMAR**: logarithm of the minimum angle of resolution, **IOP**: Intraocular pressure, **IR**: interquantal range, **SD**: Standart Deviation

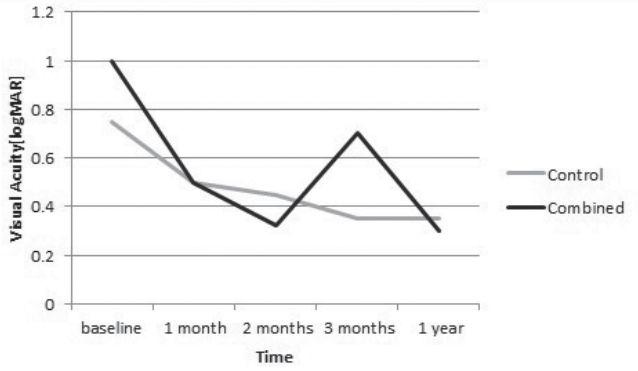

Figure 2. *The visual acuity changes after therapy of the two groups.*

and at the 1st year (18.7±1.7mmHg) weren't significantly different than the baseline IOP (p=0.21, p=0.58, and p=0.58, respectively). In the control group, the IOP changes in the 1st (16.3±1.8 mmHg) and 3rd (15.6±1.8mmHg) months and in the 1st year (15.9±1.7mmHg) also weren't significant, in comparison to the baseline measurement (p=1 ,p=0.15, and p=0.15, respectively).

Serious complications which could threaten vision were not encountered in any patient.

DISCUSSION

Vascular endothelial growth factor plays a significant role in the development of ME due to BRVO, by increasing vascular permeability.[5-9] The BRAVO trial demonstrated the effectiveness of IVR in improving BCVA and reducing CMT in BRVOs.[5] However, in addition to VEGF, elevated levels of other inflammatory cytokines including interleukin-6 (IL-6) and interleukin-8 (IL-8) were also found in eyes with BRVO.[10] Administering steroids injection can decrease IL-6 and -8 levels, which cannot be reduced with anti-VEGF therapy.[10]

Application of TA reduces inflammation, stabilizes the blood-retina barrier, and reduces VEGF level and cellular proliferation.[11] Subtenon administration of TA is also known to provide effective drug penetration.[12] Therefore it represents a more reliable alternative to intravitreal use, especially when considering the serious potential complications of glaucoma, cataracts, and retinal detachment.[7,13-15] Hayashi et al. reported that STTA therapy alone might have a limited response to BRVO-related ME, and additional injections would be needed.[15] Thus, STTA can be considered as an adjuvant therapy to intravitreal anti-VEGF treatment.

The major advantage of combined therapy is a rapid resolution of ME, leading to an quicker functional improvement. Anti-VEGF combined with STTA has been reported to be effective for the treatment of diabetic ME.[16,17] However, to the best of our knowledge, only one report deals with the results of combined anti-VEGF and STTA injections for therapy of ME due to BRVO.[7]

We studied the outcomes of combined posterior STTA and IVR therapy in eyes with ME secondary to BRVO. The ME was significantly resolved after the 1st and 3rd months following the therapy; a dramatic CMT decrease was obtained in the 1st month, which might account for the adjunctive effect of the triamcinolone. The effect of anti-VEGF is reported to occur in the 1st month, whereas the effect of STTA is seen in the initial two months.[18-20] The significant decrease in CMT was obtained with a median number of 2.5 injections in 3 months in the control group, in comparison to the combined group's single injection. This might be explained by the synergistic effect of IVR with the STTA. In our study, we remarked that combined group patients' VA increased in the 1 st month but then decreased in the 3 rd month, whereas the VA increase continued in the control group in the 3 rd month. This might be due to the effect of STTA in the initial 2 months.

Moon et al. presented their outcomes of combined intravitreal bevacizumab (IVB) with a single STTA injection for therapy of ME due to BRVO. They achieved successful results, finding BCVA increase and CMT decrease in both groups. These outcomes are similar to our results concerning macular thickness and visual acuity. They reported that, although combined therapy did not affect the visual results compared with monotherapy, it had the advantage of decreasing the number of additional doses. Their results indicated a longer lasting duration of combined treatment in comparison to monotherapy, and they reported that combining the drugs could postpone or decrease the recurrence rate of ME associated with BRVO.[7] They found a stastistically significant difference in the number of additional IVB injections after the 1 st IVB injection at 6 months (IVB group 0.96±0.83, IVB/STTA group 0.44±0.70). These results are in contrast to our study regarding the additional number of injections, as we found no significant difference between the groups at 1 year follow-up. The aforementioned study reported results with bevacizumab and STTA and did not specifically evaluate the effect of a single dose. We studied not only the effect of the single dose of STTA and IVR in the short term, but also the benefit of this combined dose to the 1 year treatment response.

Hayashi et al. found a rate of IOP elevation due to STTA injection of 8%.[15] We did not encounter significant IOP increase in our patients. This could be due to the small patient group and relatively short follow-up. Moon et al. also reported no IOP elevation requiring medical or surgical intervention.[7] Although one single STTA injection didn't lead to a remarkable change in IOP, repeated STTA injections were reported to result in IOP elevation, and this should be keep in mind.[7,14]

Limitations of the present study are: its retrospective design, small patient group, short follow-up, and the lack

of ultrasonographic imaging to search whether STTA could reach the target.

At the 1st month, the mean CMT decrease was significantly higher in the study group than the control group. The combined therapy of IVR and STTA might provide an advantage in achieving a more remarkable and faster CMT decrease in the first 2 months.. Quicker resolution of ME could also provide a safer laser therapy when needed. It can also reduce the number of injections, the complications, and the therapy costs in short term. Although the injection numbers were significantly less in the combined group compared to the control group in the first 3 months, the number of additional injections after the 1 st injection wasn't significant between the groups.

In conclusion, combined IVR and STTA therapy seems to be comparable to IVR monotherapy in improving ME in BRVO, with similar additional injection numbers. . However, more studies with larger sample sizes are required to evaluate the efficacy and safety of this treatment.

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