RESEARCH ARTICLE

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Evaluation of Photodynamic Therapy-Combined Intravitreal Bevacizumab in Age-Related Macular Degeneration

Yaşa Bağlı Makula Dejenerasyonunda Fotodinamik Tedavi ile Kombine İntravitreal Bevacizumabın Değerlendirilmesi

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ABSTRACT

Aim: *It was aimed to compare treatment results of photodynamic therapy (PDT) and PDT-combined intravitreal bevacizumab injection (PDT+IVB) in patients with age-related macular degeneration (AMD).*

Materials and Methods: *63 eyes of 55 patients with neovascular AMD were included. Group 1 consisted of 40 eyes of 35, Group 2 consisted of 23 eyes of 20 patients. Visual acuity (VA), intraocular pressure measurement and fundus examination were performed. Pattern Electroretinography P50 amplitude and edema map values (EMV) were mea-sured with Heidelberg Retina Tomograph (HRTII).*

Results: *VA increased in 14 (35%), remained unchanged in 17 (42.5%), and decreased in 9 (22.5%) eyes in Group 1 (PDT). The PERG P50 amplitudes were compared with values of pre-treatment, and found to increased at 10.6%, 11.98%, and 8.46% and HRTII EMV were 5.86%, 4.88%, and 11.22% at 1st, 3rd, and 6th months, respectively. In Group 2 (PDT+IVB), VA improved in 9 (39.13%), remained unchanged in 8 (34.78%), and decreased in 6 (34.78%) eyes. PERG P50 amplitudes were reduced to 10.15%, 5.8%, and 0.1% and HRTII EMV were reduced to 13.07%, 12.17%, and 14.87% at 1st, 3rd, and 6th months, respectively.*

Conclusion: *Verteporfin and PDT are effective and safe methods that preserve VA in subfoveal choroidal neovascular membranes due to neovascular AMD.*

Keywords: *Age-related macular degeneration, photodynamic therapy, intravitreal injection, bevacizumab, vascular endothelial growth factor, early diagnosis*

ÖZET

Amaç: *Yaşa bağlı makula dejenerasyonu (AMD) olan hastalarda fotodinamik tedavi (PDT) ve PDT ile kombine intravitreal bevacizumab enjeksiyonu (PDT+IVB) tedavi sonuçlarının karşılaştırılması amaçlandı.*

Gereç ve Yöntemler: *Neovasküler YBMD'li 55 hastanın 63 gözü dahil edildi. Grup 1 35 hastanın 40 gözü, Grup 2, 20 hastanın 23 gözü içermekteydi. Görme keskinliği (VA), göz içi basıncı ölçümü ve göz dibi muayenesi yapıldı. Patern Elektroretinografi P50 genliği ve ödem haritası değerleri (EMV) Heidelberg Retina Tomografi (HRTII) ile ölçüldü.*

Bulgular: *Grup 1'de (PDT) 14 (%35) gözde VA arttı, 17 (%42.5)'sinde değişmedi, 9 (%22.5)'unda azaldı. PERG P50 amplitüdleri tedavi öncesi değerlerle karşılaştırıldı ve 1., 3. ve 6. aylarda sırasıyla %10.6, %11.98 ve %8.46 artmış ve HRTII EMV %5.86, %4.88 ve %11.22 bulundu. Grup 2'de (PDT+IVB) 9 (%39.13)'unda VA düzeldi, 8 (% 34.78)'inde değişmedi, 6 (%34.78)'sında azaldı. PERG P50 amplitüdleri 1., 3. ve 6. aylarda sırasıyla %10.15, %5.8 ve %0.1, HR-TII EMV %13.07, %12.17 ve %14.87 azaldı.*

Sonuç: *Verteporfin ve PDT, neovasküler AMD'ye bağlı subfoveal koroidal neovasküler membranlarda VA'yı koruyan etkili ve güvenli yöntemlerdir.*

Anahtar Kelimeler: *Yaşa bağlı makula dejenerasyonu, fotodinamik tedavi, intravitreal enjeksiyon, bevacizumab, vasküler endotelyal büyüme faktörü, erken tanı*

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INTRODUCTION

Age-related macular degeneration (AMD) has been defined as a progressive decrease in central visual acuity (VA) and described as a macular neurodegenerative disease (1). In developed countries, it is the most common cause of central vision loss in patients 65 and over age (2).

AMD is divided into 2 groups (3). Exudative/neovascular AMD constitutes ~10% of cases characterized by the formation of new vessels developing from choroid. Atrophic/non-exudative AMD constitutes ~90% of cases characterized by a slight decrease in vision over many years, photoreceptor loss and geographic atrophy (3). It is hypothesized that abnormal enzymatic activity of senescent retinal pigment epithelium (RPE) cells causes accumulation of metabolic products. Swelling of RPE cells disrupts their normal cell metabolism, causing them to secrete extracellularly (4). Tears in Bruch's membrane are thought to be responsible for neovascularization from choriocapillaris (5).

Vascular endothelial growth factor (VEGF) is specific to vascular endothelial cells. In the retina, the primer sources are RPE, muller cells, ganglion cells, and pericytes (6). Bevacizumab blocks all biologically active isoforms of VEGF (7).

Photodynamic therapy (PDT) is based on the principle of selective vasoocclusion of neovascular membrane by stimulating it with light following intravenous verteporfin, a synthetic photosensitizer (8).

This study aimed to compare treatment results of PDT and PDT combined with intravitreal bevacizumab injection (PDT+IVB) in patients with AMD.

MATERIALS and METHODS

Ethical Considerations

This prospective study was performed in the Ophthalmology Clinic of Erciyes University Faculty of Medicine. Approval for our research was granted by the Ethics Committee of Erciyes University (approval number: 2009-01/94). Informed consent was obtained from the participants. The principles of the Declaration of Helsinki were observed throughout the research.

Study Design

63 eyes of 55 newly diagnosed neovascular AMD patients treated between 2006 and 2009 were included. Cases with choroidal neovascular membrane due to ocular diseases other than AMD (pathological myopia, angioid streaks, central serous retinopathy, etc), uncontrolled systemic hypertension, impaired bleeding profile, renal dysfunction, thromboembolic history, hyperlipidemia, active diabetic retinopathy, myocardial infarction within 6 months, history of cerebrovascular disease were not included.

Patients were divided into two groups: Group 1 treated with PDT; Group 2 treated with PDT+intravitreal bevacizumab. The largest lesion diameter was determined according to FFA.

The laser spot diameter was calculated using the PDT application method. After verteporfin infusion laser biomicroscope was used. The application was made with a 689 nm diode laser using 50 J/cm² energy and 600 mW/cm² power for 83 seconds. Intravitreal bevacizumab was injected and intraocular pressure was measured. Cases were called for ophthalmological control (VA, intraocular pressure value, slit-lamp, fundus examinations, PERG, HRT and FFA) at 1st, 3rd and 6th months. Recordings were taken with the PERG Primus 2.5 Tomey Primus electrophysiology device. Adjustments were made according to the standards of the International Society of Ocular Clinical Electrophysiology (ISCEV: International Society of Electrophysiology of Vision). Macular edema analysis was performed using the HRT II macular edema module. The edema map value (EMV) was obtained by adapting these measurements to all points, and using them to evaluate in the evaluation of macular edema.

Statistical Analysis

IBM SPSS Statistics version 17.0 was used for statistical analysis. Data of normal distribution was checked. Distribution was defined as mean ± SD. Student's t test was used for age and PDT diameter; the Pearson chi-square test was used for FFA, gender and lesion type; The Mann-Whitney U test was used for HRTII EMV, VA values, and PERG P50 amplitudes. Statistical significance was shown as $p<0.05$.

RESULTS

31 cases were male (56.36%), 24 cases were female (43.64%). Their mean age was 63.85 years (range 53-85 years). Group 1 consisted of cases treated with PDT. 40 eyes of 35 cases were included. 23 (57.5%) cases were male, 12 cases (42.5%) were female. Their mean age was 72.7±8.6 years (range 53-83 years). 23 (67.6%) patients had classically dominant, 14 patients (53.8%) had occult, and 3 patients (7.5%) had minimally dominant lesions. The mean PDT diameter was 4828.75 ± 1255 (2000-7900) microns. Standard PDT was applied according to FFA. VA values, PERG P50 value, and mean EMV were shown in Table 1.

There were no statistically significant differences between mean VA values, PERG P50 value and HRTII EMV detected in pre-treatment and post-treatment controls (for each, $p>0.05$). According to baseline value, mean EMVs after treatment were 5.86% at 1st, 4.88% at 3rd, and 11.22% at 6th month. No statistically significant differences were found between EMVs ($p>0.05$). Maximum reduction in EMV was observed at the 3rd month. There was no significant increase between VA values after treatment and changes in PERG P50 amplitudes. When PERG P50 values were compared with pre-treatment value, we found a rate of 10.6% at 1st, 11.98% at 3rd, and 8.46% at 6th month.

These values were compared with baseline value (p> 0.05). In Group 1, VA improved in 14 (35%), did not change in 17 (42.5%), and decreased in 9 (22.5%) eyes after treatment. Scar development was observed at the rate of 82.9% in FFA and the leakage was 39.3% at 3rd month, while these rates were 80.5% and 31.8% in 6th month, respectively. The differences were statistically significant (p< 0.05).

Group 2 consisted of 23 eyes of 20 subjects. 12 (60%) cases were male, 8 (40%) were female. Their mean age was 76±7.11 years (range 56-81 years). 11 (32.4%) had classically dominant and 12 (46.2%) had occult lesions. There were no classical type in this group. Their mean PDT diameter was 5219±1517 (2500-7900) microns. IVB 1.25/0.05 mg/ml was administered after standard PDT. Mean VA value, PERG P50 value, and HRTII EMVs were shown in Table 1. The difference wasn't statistically significant between mean VA and PERG P50 values of 1st, 3rd, and 6th month controls before and after treatment (p> 0.05). However, difference between HRTII EMVs was statistically significant (p<0.05). According to baseline value, mean EMVs after treatment were 13.07% in1st, 12.17% int 3rd and 14.87% in 6th month. Decreased values were seen in 1st and 3rd months. The difference was statistically significant between 1st and 3rd month EMVs p<0.05). The differences between values of before and after treatment in terms of VA, PERG P50 amplitude and HRTII EMV weren't statistically significant. Compared to pre-treatment value, we found a decrease of 10.15% in 1st, 5.8% in 3rd and 0.1% in 6th month in PERG P50 values. But differences were not statistically significant (p> 0.05).

Table 1. Visual acuity (VA), PERG P50 amplitudes and HRT II EMV of Group 1 and Group 2 before treatment (BT) and at 1st months 3rd months 6th months after treatment (AT). * Shows groups that differ

	BT (mean ± SD)	1.month AT (mean ± SD)	3. month AT (mean ± SD)	6. month AT (mean ± SD)	p
Group 1 (n=40) VA	1.45 ± 0.93	1.45 ± 0.87	1.36 ± 0.74	1.29 ± 0.74	0.47
PERG P50 amplitudes	1.42 ± 0.86	1.27 ± 0.73	1.25 ± 0.76	1.30 ± 1.04	0.28
HRT II EMV	2.05 ± 0.76	1.93 ± 0.65	1.95 ± 0.75	1.82 ± 0.60	0.17
Group 2 (n=23) VA	1.37 ± 0.82	1.29 ± 0.73	1.35 ± 0.78	1.19 ± 0.59	0.46
PERG P50 amplitudes	1.38 ± 0.62	1.24 ± 0.67	1.30 ± 0.56	1.40 ± 0.91	0.59
HRT II EMV	2.22 ± 0.75	1.93 ± 0.54*	1.95 ± 0.56*	1.89 ± 0.63*	0.03*

PERG: *Pattern Electroretinogram,* ***HRT:*** *Heidelberg Retina Tomography* ***EMV:*** *Edema Map Value,* ***BT:*** *Before Treatment,* ***AT:*** *After Treatment,* ***VA:*** *Visual Acuity*

After PDT+IVB, VA values were increased in 9 (39.13%), did not change in 8 (34.78%), and decreased in 6 (26.08%) eyes. Scar development in FFA was 17.1% in 3rd and 19.5% in 6th month (p< 0.05). In this group, leakage in FFA was 60.7% in 3th and 68.2% in 6th month. The difference was statistically significant between these values (p< 0.05).

The differences weren't statistically significant between groups in terms of age, gender, PDT diameter and lesion type. But importantly, when groups were evaluated in terms of scar development and leakage in FFA in 3th and 6th months we saw statistically significant differences (p<0.05). The alterations in VA values after treatments were presented in Table 2.

Table 2. The alterations in visual acuity (VA) after treatment.

	Number of Eyes	Increased VA	Steady VA	Decreased VA
Group 1	40	14 (35%)	17 (42.5%)	9 (22.5%)
Group 2	23	9 (39.13%)	8 (34.38%)	6 (26.08%)

VA: Visual Acuity

VA, PERG values and HRT values of group 1 and 2 before treatment and 1st, 3rd, 6th months after treatment were shown in Figure 1, 2 and 3.

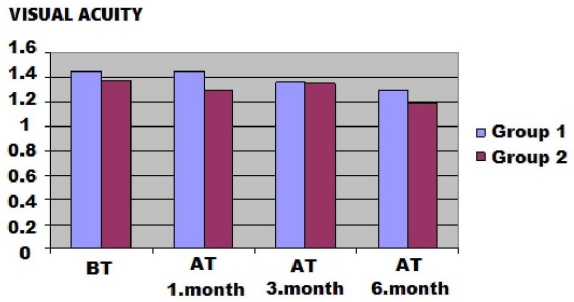

Figure 1. Visual acuity of group 1 and group 2 before treatment (BT) and at lst 3rd 6th months after treatment (AT).

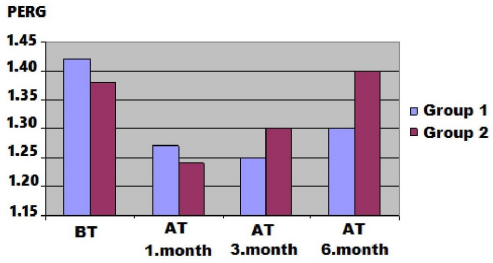

Figure 2. PERG values of group 1 and group 2 before treatment (BT) and at lst 3rd 6th months after treatment (AT).

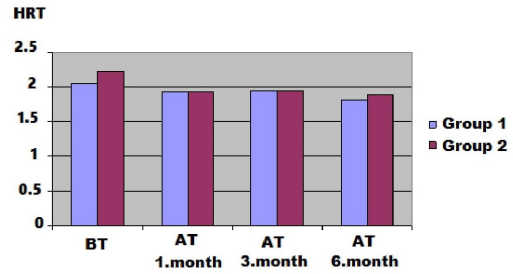

Figure 3. HRT values of group 1 and group 2 before treatment (BT) and at lst 3rd 6th months after treatment (AT).

DISCUSSION

Hemodynamic changes in choroidal circulation play a role in AMD pathophysiology (9). Simultaneous degeneration of elastin and collagen causes calcification and fragmentation of the Bruch membrane (10). Angiogenetic stimulation and VEGF levels increase due to the triggering of relative choroidal ischemia. This cycle ultimately initiates the formation of new vessels from choriocapillaris along the calcified and ruptured Bruch membrane (10).

Vitreous VEGF levels are higher in patients with AMD (11,12). In hypoxia, the release of VEGF increases exaggeratedly and regulates the adhesion of leukocytes to endothelium. Macrophages also facilitate the migration of choroidal capillaries by eroding already thinned bruch membrane with proteolytic enzymes (13). In AMD, increased VEGF was demonstrated in RPE cells (14). VEGF has functions in paracrine signal transmission between RPE and choriocapillaris and in the continuation of fenestrated structure of choriocapillaris (15).

VEGF blockade is provided by intravitreal bevacizumab administration, although there is no significant regression in vessels of the advanced choroidal neovascular membrane (CNVM). Withdrawal of intraretinal, subretinal and subRPE fluid shows that antipermeability effect of the drug is more prominent than the antineovascular effect (16).

Argon laser photocoagulation and PDT are two treatment options for neovascular AMD. PDT is a tissue selective local treatment with superficial action and strong damage effects on microvascular tissues (17). PDT with verteporfin is an essential advance in the treatment of neovascular AMD. It provides a short-lived but potent antiangiogenic effect on CNVM. Verteporfin binds to plasma lipoproteins and accumulates particularly at sites of neovascularization. The laser beam causes an activation, resulting in the release of short-lived singlet oxygen and reactive oxygen radicals that damage to endothelial cells of newly formed vessels and cause the release of procoagulant and vasoactive substances via leukotriene-cyclooxygenase pathway. Then, vascular occlusion occurs (17). Results from clinical studies showed that PDT was effective and safe in reducing vision loss and didn't permanently damage neurosensory retina on the membrane (18).

Chen et al. (19) reported that combined intravitreal ranibizumab with PDT can improve visual acuity, decrease CMT, and reduce the area of macular degeneration of wet AMD patients compared to intravitreal ranibizumab alone. Saviano et al. (20) reported that PDT combined with intravitreal bevacizumab injection is superior to bevacizumab monotherapy in treating macular CNV. Potter et al. (21) performed two doses of PDT in neovascular AMD. The first group received bevacizumab combined with 25J/cm² of PDT (25J/cm²), the second group received bevacizumab combined with 12 J/cm² of PDT, and the third group received bevacizumab monotherapy. The 6th-month results of the study showed that the patients needed 2.8, 2.5, and 5.1 times of bevacizumab injection on average in group I, group II, and group III, respectively, so it can be observed that the frequency of bevacizumab injection decreased with PDT (21).

Although short-term successful results of PDT have been reported, in the Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) trial, there was consistent evidence at both 1 and 2 years that PDT results in less deterioration in visual acuity in the randomized eye than placebo

We applied standard PDT to 63 eyes/55 patients. 23 (67.6%) of 40 eyes/35 patients were dominant classical, 14 of them (53.8%) were occult, 3 of them (7.5%) were minimal classical type. 11 (32.4%) eyes were dominant classical and 12 (46.2%) eyes were occult type in group 2.

We evaluate our cases according to lesion types. Our patients with occult lesions seem to respond better to treatment: VA increased 30.43% in dominant classical lesions and 42.85% in occult lesions.

The point to be considered was the size of the lesion. PDT was recommended in lesion seizes less than four macular photocoagulation study-disk area (MPS-DA), while follow-up was more appropriate for large lesions. PDT was applied again to 8 eyes (20%) in 3rd month. Herein, PDT was applied once to 32 (80%) eyes and twice to 8 (20%) eyes.

Follow-up of lesion size is essential in the evaluation of the amount of progression. In the TAP study, progression of dominant classical lesions was observed. In the 24-month follow-up, lesion size was smaller than 6 MPS-DA in 55% of patients in verteporfin group, while this rate was 25% in placebo group (19). VIP study, the progression of the classical component of the lesion was 45% less in the verteporfin group than in the placebo group in the 24-month follow-up. The rate of being above 9 MPS-DA in pure occult lesion size was 2 times higher in placebo group (22). In TAP and VIP reports, initial lesion size affected visual results of PDT rather than membrane properties of CNVM (22). Their results were worse in lesions with a DA greater than 4 MPS in predominant classical CNVMs.

Angiographic findings provide an independent and objective assessment of outcomes. In our cases, the difference between groups regarding scar development in FFA of 3rd and 6th month measurements were statistically significant ($p<0.05$). Patients with predominant classical CNVM and lesion diameter greater than 4 MPS-DA were

worse in our cases. The most common ocular side effect is transient decrease in VA due to foveal inflammation in first days. In VIP study the frequency decreased after the first two treatments (22). VA loss of more than 4 rows in first 7 days after treatment was reported in 3 patients in TAP study and in 10 patients in VIP study. In our cases, 2 patients had low back pain during infusion, and 2 patients had nausea and vomiting. None of other side effects were observed.

Although short-term successful results of PDT have been reported, the use of PDT was dramatically reduced after the recent anti-VEGF agent in the management of patients with neovascular AMD. Recently, PDT has been performed for specific situations, including the combination treatment of anti-VEGF agents and PDT (23, 24), in patients with a contraindication to the use of intravitreal anti-VEGF agents, and in patients with polypoidal choroidal vasculopathy (25, 26).

Ideal treatment should prevent the formation of new CNV by reducing inflammation and reducing VEGF secretion, as well as eliminating existing CNV. Targeting both vascular and extravascular component of CNV would be the most appropriate treatment. However, it seems difficult for single treatments to provide this process and reliability. Moreover, the need for more than one treatment and inability to obtain sufficient results in studies with monotherapies revealed the need for combination therapy. Verteporfin and PDT damage endothelial cells of newly formed vessels and cause vessel occlusion. With the addition of anti-VEGF therapy, it is planned to prevent the effects of VEGF, which occurs during the pathogenesis of CNV and is induced by PDT with verteporfin.

In our study; there was no statistically significant differences in VA, PERG P50 amplitude and HRT II EMVs during 6-month follow-up period between groups. This can be explained by;1) diameters of PDT performed due to the large lesion diameters of group 2 were also large, 2) VA levels were lower than those in group 1, 3) patients presented at a very late stage.

PDT with verteporfin is an effective treatment modality for preserving current VA in patients with neovascular AMD with progressively declining VA. Early diagnosis of disease is important. There is a correlation between initial and final VA of cases diagnosed early and it reflects positively on treatment results. Bevacizumab is one of the most effective, safe and cost-effective treatment options in the treatment of neovascular AMD.

Ethics Committee Approval: The Ethics Committee of Erciyes University approved the study protocol (approval number: 2009-01/94).
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