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Comparison of Intravitreal Bevacizumab Alone Versus Combined Bevacizumab and Macular Photocoagulation in Diabetic Macular Edema

Diyabetik Maküler Ödemde İntravitreal Bevacizumab İle Kombine Bevacizumab ve Maküler Fotokoagülasyon'un Karşılaştırılması

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ABSTRACT Objective: To compare the efficacy of intravitreal bevacizumab with combined bevacizumab followed by sequential macular laser photocoagulation in the treatment of diabetic macular edema. **Materials and Methods:** Thirty-one eyes injected with intravitreal bevacizumab and 30 eyes with combined therapy of bevacizumab injection and macular laser photocoagulation were included in this retrospective study. The main outcome measures were visual acuity, central macular thickness and the number of injections. **Results:** Each participant completed at least 6 months of follow-up. Baseline best-corrected visual acuity and central macular thickness values of the bevacizumab monotherapy group were similar to those of the combination group (P=0.64 and P=0.15, respectively). In bevacizumab monotherapy group, baseline best-corrected visual acuity (0.91 ± 0.65 logMAR) improved to 0.73±0.55 logMAR at 3 months and to 0.68±0.53 logMAR at 6 months of follow-up (P=0.03). Baseline central macular thickness decreased from 431.65 ± 108.19μm to 381.77 ± 113.29μm at 3 months and to 366.82 ± 105.13μm at 6 months (P=0.03). In the combination group, baseline best-corrected visual acuity improved from 0.84±0.63 logMAR to 0.55±0.48 logMAR at 3 months and to 0.41±0.46 logMAR at 6 months (P=0.01), while baseline central macular thickness decreased from 400.77 ± 119.05μm to 287.10 ± 67.99μm at 3 months and to 265.24 ± 81.48μm at 6 months following the treatment (P=0.02). **Conclusion:** Both treatment modalities were effective in improving visual acuity and reducing central macular thickness. Adding macular laser to intravitreal bevacizumab appeared to be superior to bevacizumab alone in eyes with diabetic macular edema.

Keywords: Macular edema; bevacizumab; intravitreal injections

ÖZET Amaç: Diyabetik makula ödemi tedavisinde intravitreal bevacizumab ile kombine bevacizumab ve ardışık maküler lazer ışık koagülasyon etkinliğinin karşılaştırılması. **Gereç ve Yöntemler:** İntravitreal bevacizumab enjekte edilen 31 göz, kombine bevacizumab enjeksiyonu ve maküler lazer ışık koagülasyon tedavisi uygulanan 30 göz bu retrospektif çalışmaya dahil edildi. Görme keskinliği, santral makula kalınlığı ve enjeksiyon sayısı temel sonuç ölçütleri olarak kabul edildi. **Bulgular:** Her katılımcı en az 6 aylık izleme peryodunu tamamladı. Bevacizumab monoterapi grubunun başlangıçtaki en iyi düzeltilmiş görme keskinliği ve santral makula kalınlık değerleri kombinasyon grubundakine benzerdi (sırasıyla P=0.64 ve P=0.15). Bevacizumab monoterapi grubunda, başlangıçtaki en iyi düzeltilmiş görme keskinliği (0.91 ± 0.65 logMAR), 3. ayda 0.73±0.55 logMAR' a, 6. ayda 0.68±0.53 logMAR'a kadar iyileşmiştir (P=0.03). Başlangıçtaki santral makula kalınlığı 431.65 ± 108.19 μm'den 3. ayda 381.77±113.29 μm'ye ve 6. ayda 366.82±105.13 μm'ye düşmüştür (P = 0.03). Kombinasyon grubunda başlangıçtaki en iyi düzeltilmiş görme keskinliği 0.84 ± 0.63 logMAR' dan'den 3. ayda 0.55±0.48 logMAR'a, 6. ayda 0.41±0.46 logMAR'a kadar iyileşmiş (P=0.01); baslangıçtaki santral makula kalınlığı da 400.77±119.05 μm'den 3. ayda 287.10±67.99 μm'a ve 6. ayda 265.24 ± 81.48 μm'ye (P = 0.02) düşmüştür. **Sonuç:** Her iki tedavi modeli de görme keskinliğini iyileştirmede ve santral makula kalınlığını azaltmada etkili olmuştur. Diyabetik makula ödemi olan hastalarda, intravitreal bevacizumaba maküler lazer eklenmesi bevacizumabın tek başına olan etkisinden daha üstün bulunmuştur.

Anahtar Kelimeler: Makula ödemi; bevacizumab; intravitreal enjeksiyon

Article in Press

Diabetic retinopathy is the leading cause of blindness in the working-age population and macular edema is a major cause of central vision impairment in patients with diabetic retinopathy.[1] Although the exact etiology is unknown, diabetic macular edema (DME) results from retinal microvascular changes. Hypoxia produced following compromise of the blood-retinal barrier may stimulate the production of vascular endothelial growth factor (VEGF).[2] VEGF plays a key role in the pathogenesis of DME by mediating vascular permeability and accumulation of intracellular and extracellular fluid.[3] The pathogenesis of diabetic macular edema is also related to other inflammatory and angiogenic cytokine levels that can be suppressed by corticosteroids.[4]

In the Early Treatment Diabetic Retinopathy Study (ETDRS), laser photocoagulation in eyes with macular edema reduced the risk of moderate visual acuity loss by approximately 50% through a 3-year follow-up; however, visual improvement is uncommon (3-14.5%) in DME.[5] Thus, the goal of treatment in DME is to "maintain" visual acuity. Laser photocoagulation may have various side effects, such as an increase in dark adaptation time, paracentral scotoma, choroidal neovascularization, and sub-retinal fibrosis.[6] Moreover, refractory DME does not respond to repeated laser treatments despite a good metabolic control. Although laser photocoagulation was the gold standard treatment in DME, the limitations and side effects of laser photocoagulation have prompted interest in other treatment modalities, including intravitreal steroids, anti-VEGF agents and a combination of these treatment options.[7-9]

The present study aimed to assess the short-term safety and effect of intravitreal bevacizumab (IVB), either alone or in combination with macular laser photocoagulation (MLP), in the treatment of DME.

MATERIALS AND METHODS

PARTICIPANTS

A retrospective and comparative study was conducted at a tertiary eye care center. The patients were followed for at least 6 months (range: 6–8 months). The study was conducted in accordance with the principles of the Declaration of Helsinki and approval from the local medical ethics committee was received. Written informed consent was obtained from each participant. Overall, 61 eyes from 52 patients (mean age: 58.5±9.7 years) were recruited into the present study. The data was collected from the participants' medical records between December 2011 and March 2013. Thirty-one eyes from 31 patients with DME were treated with IVB injections alone and 30 eyes from 21 patients with DME were treated with a combined IVB injection and MLP. Following a full comprehensive ophthalmic examination, clinician has decided to type of mono- or combination therapy according to clinical condition of the patients. The study was designed retrospectively, so the patients assigned to IVB alone and combination treatments were selected randomly among medical records. Inclusion criteria were a diagnosis of DME with fundoscopic examination and confirmed by fundus fluorescein angiography (FFA) and optical coherence tomography (OCT), central macular thickness (CMT) greater than 300 microns (μm) and best-corrected visual acuity (BCVA) better than 20/200 and worse than 20/40. Exclusion criteria were refractory DME, aphakia, any ocular inflammation, prior ocular surgery, laser or injection within the last 6 months and a history of uncontrolled glaucoma.

STUDY DESIGN AND INJECTION TECHNIQUES

The patients were divided into 2 groups for evaluation. The first group-the IVB group- was composed of patients who were only injected with IVB as a monotherapy. This included 31 eyes from 31 patients. The second group-the combined IVB+ MLP group-was composed of patients who were given an IVB injection followed by MLP. This combination group consisted of 30 eyes from 21 patients. The 2.5mg/0.1 mL of bevacizumab was injected into one eye with a 27-gauge needle, 3.5 to 4 mm away from the limbus, where appropriate, by an experienced physician in sterile conditions. After injection, all the patients were examined the next day and prescribed topical moxifloxacin 0.5%

to be taken at 2-hour intervals for 1 week. Patients in the combination group were treated with MLP (The laser was applied in grid fashion) within 4 weeks of their IVB injection. MLP was performed by experienced examiners with a spot size of 100 μm, pulse duration of 100 ms, and a power of 50–100 mW.[6]

Detailed and routine ophthalmic examinations were carried out at baseline, at the 1st week, and at the 1st, 2nd, 3rd and 6th months of the study period. Visual acuity was described as BCVA using the ETDRS scale and converted to Logarithm of the Minimum Angle of Resolution (logMAR) for analysis. The anterior segment was examined with a slit lamp. Intraocular pressure (IOP) was measured by Goldmann applanation tonometry. A fundus examination was performed using indirect ophthalmoscopy and a +90 diopter lens. FFA (Canon CF-60DS, Canon Inc., New York, NY, USA) was performed at 3-month intervals after the baseline. OCT (Cirrus HD-OCT 4000 model, software version 5.1.1.6 Carl Zeiss Meditec, Dublin, CA, USA) was performed at all visits except in the 1st week. PRN retreatment criteria were defined as follows: essential supplements of IVB injections were performed during follow-up visits in patients with CMT values greater than 300μm and which did not decrease more than 50μm in comparison to the previous value, at least a 6-week interval was also considered before giving the booster doses of IVB injections. None of the patients in the combined IVB-MLP group were given injections during the 1st month of the study period when MLP (LIGHTLas TruScan, Lightmed, San Clemente, CA, USA) was applied. Data obtained at the baseline, 3rd and 6th months of the follow-up period were noted in order to compare the BCVA, CMT and IOP parameters in a statistical analysis.

STATISTICAL ANALYSIS

The statistical analysis of the data was performed using the program SPSS (version 18.0; IL, CA). Continuous variables were expressed as 'mean ± standard deviation' and frequency data were expressed as numbers (%). Intra-group repeated measurements were analyzed by an 'analysis of variance' test and inter-group statistical differences were subjected to an 'independent **t**-test'. The significance level was set to ≤ 0.05.

RESULTS

IVB GROUP

The mean age of the 31 patients in this group was 59.9± 9.5 years (range: 51–66 years). Of them, 38.7% were male and 61.3% were female. BCVA improved from0.91 ± 0.65 (logMAR) to 0.73 ± 0.55 at the 3rd month and to 0.68 ± 0.53 at the 6th month of the follow-up period (P=0.03). CMT decreased from 431.65 ± 108.19μm to 381.77 ± 113.29μm at the 3rd month and to 366.82 ± 105.13μm at the 6th month after the treatment (P=0.03). Baseline IOP (16.0 ± 2.6mmHg) changed neither at 3 months (16.5 ± 3.2mmHg) nor at 6 months (16.3 ± 4.1mmHg) after the injection (P=0.62). A significant improvement of BCVA and a significant decrease in the mean CMT was noted throughout the study period (P=0.03 and P=0.03, respectively) (Table 1).

COMBINED IVB AND MLP GROUP

The mean age of the 30 patients in this group was 56.9 ± 7.3years (range: 49–70 years). Of them, 42.9% were male and 57.1% were female. The baseline BCVA improved from 0.84 ± 0.63 (logMAR) to 0.55 ± 0.48 at the 3rd month and to 0.41 ± 0.46 at the 6th month of the treatment period (P=0.01). CMT decreased from 400.77 ± 119.05μm to 287.10 ± 67.99μm at the 3rd month and to 265.24 ± 81.48μm at the 6th month (P=0.02). The baseline IOP (15.3 ± 3.2mmHg) was similar to the IOP at 3 months (15.4 ± 3.9mmHg) and 6 months (15.5 ± 3.5mmHg) after the treatment (P=0.72). The improvement in BCVA and the decrease in the CMT was statistically significant during the study period (P=0.01 and P=0.02, respectively) (Table 1).

IVB VERSUS IVB AND MLP GROUPS

There were no statistically significant differences in the means of the BCVA, CMT and IOP between the 2 groups at baseline (P=0.64, P=0.27, P=0.36). Comparing the combined IVB-MLP group to the

TABLE 1: Data obtained from IVB (n=31) and combined IVB and MLP (n=30) group eyes during the study period.

Parameters	IVB	IVB+MLP	P**
BCVA (logMAR)			
Baseline	0.91 ± 0.65	0.84 ± 0.63	0.64
3 month	0.73 ± 0.55	0.55 ± 0.48	0.36
6month	0.68 ± 0.53	0.41 ± 0.46	**0.04†**
P*	**0.03†**	**0.01†**	
CMT (µm)			
Baseline	431.65 ± 108.19	400.77 ± 119.05	0.15
3 month	381.77 ± 113.29	287.10 ± 67.99	**0.03†**
6month	366.82 ± 105.13	265.24 ± 81.48	**0.02†**
P*	**0.03†**	**0.02†**	
IOP (mmHg)			
Baseline	16.0 ± 2.6	15.3 ± 3.2	0.36
3 month	16.5 ± 3.2	15.4 ± 3.9	0.41
6month	16.3 ± 4.1	15.5 ± 3.5	0.24
P *	0.62	0.72	

P*: results obtained by ANOVA test, **P**:** results obtained by independent sample-t test, † statistically significant, **IVB:** intravitreal bevacizumab, **MLP:** macular laser photocoagulation, BCVA: best-corrected visual acuity, **CMT:** central macular thickness, **IOP:** intraocular pressure.

IVB group, significant differences were observed in the mean of the CMT measurements taken in the 3rd and 6th months (P=0.03 and P=0.02, respectively). Better BCVA values were observed at the 6th month in the combined IVB-MLP group (P=0.04). Similar mean IOP values were noted at the 3rd and 6th months (P=0.41 and P=0.24, respectively) (Table). An IOP of 21 mmHg or higher was observed in 1 eye at the 3rd month in the IVB group, in 2 eyes at the 3rd month in the combined IVB-MLP group and in 1 eye at the 6th month in the combined group. The eyes responded well to topical glaucoma agents.

The mean number of injections was 2.3 ± 0.7 in the IVB monotherapy group and 1.6 ± 0.7 in combined IVB-MLP group (P□0.001).

DISCUSSION

Laser photocoagulation was considered the gold standard in the treatment of DME. However it may induce blood-retinal barrier breakdown and increase retinal thickness.[7] Moreover, some groups of patients do not respond to laser treatment very well. Consequently, clinicians have sought more effective treatment modalities, such as intravitreal anti-VEGFs and corticosteroids.[10,11]

Anti-VEGF agents may be more effective than the laser treatments that are associated with extensive resultant tissue damage.[12] The incidence of complications, such as glaucoma and cataracts, encountered in connection to the intravitreal injection of corticosteroids, can be avoided with the use of anti-VEGF. For these reasons, they are becoming the preferred choice of treatment in cases of DME with coexisting glaucoma and in cases recalcitrant to lasers and intravitreal steroids.[11]

The safety and efficacy of bevacizumab in reducing CMT and improving BCVA has been established in various studies.[13,14] Its recent popularity, greater availability, and the reasonable cost of bevacizumab persuaded us to use this kind of anti-VEGF drug in our study.

In our study, we compared IVB mono-treatment and combined IVB-MLP treatment in patients with DME. Assessing them separately, both treatments had significant effects in improving BCVA and reducing CMT. Although its baseline DME witnessed a statistically significant improvement, the mean CMT was still above 300µm in the IVB monotherapy group at 6 months. Intergroup analysis showed better CMT values at both the 3rd and 6th months, and better visual acuity values at 6

months could be obtained with combined IVB and MLP therapy. Combining laser therapy with IVB also significantly decreased the number of injections needed.

Soheilian et al. claimed that up to 12 weeks, IVB primary treatment of patients with DME yielded better visual outcomes than laser photocoagulation alone, although it was not associated with a significant decrease in CMT.[15] Inspired by this, we decided to compare IVB alone with combined therapy of IVB and laser photocoagulation, which will be concluded as the superiority of combined therapy.

Barteselli et al.[16] have indicated that a combined therapy of bevacizumab injections followed by navigated laser treatment for clinically significant DME demonstrated significant visual gain and CRT reduction after bevacizumab treatment and stabilization after navigated laser up to 12 months. They noted a lower number of injections (4.4) were required in 12 months than were reported in previous combination studies. Beyond their study, we noted a more lower requirement number of injections (1.6) at 6 months.

After a 2-year, single-center, prospective, randomized, controlled trial, Rajendram et al. have reported that IVB primary treatment yields better results in BCVA and CMT than primary MLP, and that the median number of treatments over 24 months was 13 for IVB and 4 for MLP.[17] Although they reported the superiority of IVB alone than MLP alone in BCVA and CMT contrary to us, MLP decreased number of treatments, which was also observed in our study.

Lee et al. compared the efficacy of IVB (2.5mg in 0.1mL) and a combined treatment of bevacizumab and MLP in the treatment of DME.[18]Although both treatments were effective, the combined treatment did not yield better BCVA or CMT reduction at 6 months than a bevacizumab injection alone, contrary to our results.[15]

Azad et al. aimed to compare the efficacy of IVB (1.25mg in 0.05mL), intravitreal triamcinolone acetonide (IVT) and macular grid augmentation in the management of DME.[19] They found that both IVB and IVT may be effective in the treatment of refractory DME when compared with macular grid augmentation. We also observed that combined treatment was more effective.

Faghihi et al. compared IVB (1.25mg) alone with a combination of IVB and focal laser, and determined that at 6 months, both regimes had comparable vision improvement and neither dosage was superior to the other, contrary to our results with the exception of laser fashion.[20]

Takamura et al. have shown that after IVB (1.25mg in 0.05mL), CMT decreased temporarily, and the CMT significantly increased at 2 months and thereafter in the IVB group but did not increase significantly in the IVB plus targeted retinal photocoagulation group; the BCVA in the IVB plus laser group was significantly better than that in the IVB group, 5 and 6 months after treatment, similar to our study.[21]

Solaiman et al. have demonstrated that combined therapy with IVB (1.25mg in 0.05mL) and sequential modified grid laser photocoagulation 3 weeks later appears to be superior to laser or IVB alone in reducing macular thickening and improving visual acuity.[22] Six months after treatment, the reduction in the mean CMT was significant in the IVB plus laser group only, and there was no significant improvement in the mean BCVA in all the groups. Whereas in a retrospective multicenter study, Arevalo et al. observed that in a comparison of 3 groups, primary IVB (1.25 mg), primary grid laser therapy and combined IVB-laser, a higher CMT decrease was shown in the primary IVB group than in the other modalities.[23] The former study was parallel to our study other than insignificant improvement in the mean BCVA, whereas the latter one was contrary to our results.

Solaiman et al. have concluded that repeated IVB (1.25 mg) injections could provide a long-term benefit for the treatment of diffuse DME and performing macular grid photocoagulation only 3 weeks' subsequent to the initial IVB injection.[24] This might provide longer disease-free intervals and reduce the burden of more frequent injections. They noted that the mean number of injections was

significantly lower in the combined group (2.36 per eye) than in the IVB group (3.27 per eye). The mean number of injections in both groups (2.3 vs. 1.6) of our study seem to be lower than expected. We think that this might be due to the presence of the patients who were not injected IVB due to a dramatic decrease in CMT.

In conclusion, although our study had some limitations, such as a relatively short period of examination and a small population, we are able to conclude that both IVB monotherapy and combined IVB and MLP therapy showed significant effects on BCVA and CMT in the treatment of DME. Combined treatment was superior to IVB mono- therapy in both improving BCVA and reducing CMT. The need for re-injection also significantly decreased. Both treatment modalities could be initial treatment options in patients with DME, but combination therapy may yield better results at 6 months.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

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