Retina Ven Dal Tıkanıklığında İntravitreal Ranibizumab ve Dexametazonun Etkinliğinin Karşılaştırılması

Comparison of Effectiveness of Intravitreal Ranibizumab and Dexamethasone in Branch Retinal Vein Occlusion

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ÖZ

Amaç: Retina ven dal tıkanıklığı(RVDT) hastalarında intravitreal ranibizumab(IVR) ve dexametazonun(IVD) etkinliğinin karşılaştırılması

Gereç ve Yöntemler: RVDT ve makula ödemi nedeniyle IVR ve IVD tedavisi ve takibi yapılan 55 hastanın dosyaları retrospektif olarak incelendi.32 hastaya IVR (Grup 1), 23 hastaya IVD (Grup 2) uygulandı.Gruplar yaş,cinsiyet,iskemi,ödem sonrası başvuru süresi,uygulanan intravitreal enjeksiyon sayısı açısından karşılaştırıldı.Göziçi basıncı(GİB),santral makular kalınlık(SMK) ve logaritmik görme keskinliği (LGK) değerleri enjeksiyon öncesi,enjeksiyon sonrası 1.ay,3.ay,6.ay incelendi.İstatistiksel analizde SPSS 16.0 programı kullanıldı.

Bulgular: Grup 1 de 16 erkek,16 kadın hastanın yaş ortalaması 60,9±9,95 yıl, grup 2 de 12 erkek 11 kadın hastanın yaş ortalaması 60,19 ±10,06 yıldı.(p=0,804) Şikayet başladıktan sonra hekime başvuruya kadar geçen süre grup 1 de 3,4± 2,34 ay, grup 2 de 1,77 ±1,67 aydı.(p=0,006) İskemi grup 1 de 8 hastada varken grup 2 de 13 hastada vardı.(p=0,005) Ortalama enjeksiyon sayısı grup 1 de 2,41±1,15 iken grup 2 de 1,66±0,48 di.(p=0,007) GİB değerleri grup 1 de enjeksiyon öncesi ile sonrası 1. ay(p=0,93) ve 3.ay(p=0,12) ölçümleri arasında istatistiksel farklılık olmamasına rağmen 6. ayda (p=0,018) istatistiksel olarak anlamlı derecede yüksek izlendi.Grup 2 de ise enjeksiyon öncesi ile sonrası 1. ay (p=0,12) ve 6.ay(p=0,066) ölçümleri arasında istatistiksel farklılık olmamasına rağmen 3. ayda (p=0,049) istatistiksel anlamlı derecede yüksek izlendi.

Grup 1 de LGK 0 değeri ile LGK 1,LGK 3 ve LGK 6 arasında istatistiksel anlamlı farklılık vardı. (sırasıyla p değerleri 0,001,0,002,0,002) Enjeksiyon sonrası LGK 3 ile LGK 6 arasında istatistiksel farklılık yoktu.(p=0,238) ,diğer değerlerde enjeksiyon öncesinden itibaren 6. aya kadar giderek artan istatistiksel olarak anlamlı derecede (p değerleri 0,024, 0,001) yüksek görme seviyesi mevcuttu .Grup 2 de LGK 0 değeri ile LGK 1,LGK3 ve LGK 6 arasında istatistiksel anlamlı farklılık vardı.(p değerleri 0,001) LGK 1 değeri ile LGK 3 arasında istatistiksel farklılık yoktu (p=0,097), ancak LGK 6 arasında istatistiksel anlamlı farklılık vardı.(p=0,017) LGK 3 ile LGK 6 arasında ise istatistiksel farklılık olmamasına(p=0,397) rağmen enjeksiyon öncesinden itibaren 6. aya kadar giderek artan görme seviyesi mevcuttu.

Grup 1 de SMK 0 değeri ile SMK1,SMK3 ve SMK6 arasında istatistiksel anlamlı farklılık vardı.(p değerleri 0,001) SMK 3 ile SMK 6 arasında istatistiksel farklılık olmamasına (p=0,238) rağmen enjeksiyon sonrası diğer SMK değerleri arasında istatistiksel farklılık vardı(sırasıyla p değerleri 0,004, 0,003) ve enjeksiyon öncesinden itibaren 6. aya kadar giderek azalan santral makuler kalınlık seviyesi mevcuttu.Grup 2 de SMK 0 değeri ile SMK1,SMK3 ve SMK6 arasında istatistiksel anlamlı farklılık vardı. (p değerleri 0,001) SMK 1 ile SMK3 arasında istatistiksel anlamlı farklılık varken(p=0,031),hem SMK 1 ile SMK 6 arasında hem de SMK 3 ile SMK 6 arasında anlamlı farklılık yoktu. (sırasıyla p değerleri 0,985, 0,414)

Sonuç: GİB IVR grubunda 6.ay, IVD grubunda 3.ay yüksek bulundu.LGK değerleri her iki grupta 6.aya kadar giderek azalıyordu.SMK, IVR grubunda 6. aya kadar giderek azalırken IVD grubunda 1.ayda azalıp 3.ayda artan ve 6.ayda azalan bir seyir izlemiştir,bu değişim IVR grubunda daha tatmin edici bulunmuştur.

Anahtar Kelimeler: İntravitreal enjeksiyon, dexametazon implant, ranibizumab, ven dal tıkanıklığı.

**Daha önce başka bir dergiye gönderilmemiştir. **Çalışmayı maddi olarak destekleyen kişi ve kuruluş yoktur.*

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ABSTRACT

Purpose: Comparison of intravitreal ranibizumab (IVR) and dexamethasone (IVD) effectiveness in branch retinal vein occlusion (BRVO)

Materials and Methods: Fifty-five patients with BRVO and macular edema were treated with IVR (Group 1) in 32 patients and IVD (Group 2) in 23 patients. Groups were compared regarding age, gender, ischemia, duration of post-edema application, number of intravitreal injections. Intraocular pressures (IOP), central macular thickness (CMT) and logarithmic visual acuity (LVA) values were evaluated before injection and at months 1, 3 and 6 after injection. Statistical analyses were performed by SPSS 16.0.

Results: Ischemia was present in 8 patients in group 1 and 13 patients in group 2 ($p = 0.005$). The mean number of injections was 2.41 ± 1.15 in group 1 and 1.66 ± 0.48 in group 2 ($p = 0.007$). The IOP was significantly higher at month 6 in group 1 ($p = 0.018$) and at month 3 in group 2 ($p = 0.049$). There was no statistical difference between LVA 3 and LVA 6 in group 1 ($p=0.238$). Among other parameters, there was significantly higher visual acuity level ($p <0.05$) with improvements up to 6 months. Although there was no statistical difference between LVA 1 and LVA 3 ($p = 0.097$) and between LVA 3 and LVA 6 ($p = 0.397$) in group 2, the visual acuity was progressively improved until month 6. There was statistically significant difference among other CMT values ($p <0.05$), although there was no statistical difference between CMT 3 and CMT 6 in Group 1 ($p = 0.238$). In group 2, there was no significant difference between CMT 1 and CMT 6 or CMT 3 and CMT 6 (p values 0.985, 0.414) but there were significant differences among other CMT values w ($P<0.05$).

Conclusion: The intraocular pressure was found to be elevated in IVR group at month 6 and in IVD group at month 3. LVA remained low until month 6. While CMT was progressively decreased in the IVR group until month 6, it was decreased at month 1 followed by elevation at month 3 and further decreased at month 6 in the IVD group.

Key Words: Intravitreal injection, dexamethasone implant, ranibizumab, branch vein occlusion

GİRİŞ

Retinal vein occlusion (RVO) is a common vascular disorder of retina. In developed countries, it is the second most common cause of vision loss following diabetes mellitus.[1] Macular edema (ME) is most frequent complication occurring in both branch and main retinal artery occlusions.[2,3] In previous studies, the ME was attributed to hydrostatic influences caused by increased venous pressure and release of inflammatory cytokines such as vascular endothelial growth factor (VGEF) and interleukin-6 (IL-6) triggered by ischemia resulting from vascular occlusion. As such, increased vascular permeability, vasodilatation and impairment in inner blood-retina barrier occur.[4-6]

There is no established treatment protocol for ME caused by retinal vein occlusion.[7] Currently, intravitreal triamcinolone (IVTA), intravitreal anti-VGEF and recently introduced intravitreal dexamethasone implant are being used in the treatment of RVO. In this study, we aimed to compare effectiveness of intravitreal ranibizumab (IVR) and intravitreal dexamethasone (IVD) therapies used in BRVO-related ME during 6 months follow-up regarding IOP, CMT and LVA values.

MATERIAL-METHOD

We retrospectively reviewed files of 55 patients who had been followed in ophthalmology departments of Karabük University, Medicine School and Yıldırım Beyazıt University, Medicine Scholl between November, 2914 and November, 2015. The patients with glaucoma, those previously underwent ocular surgery, and those on topical medication were excluded.

In the study, 32 patients (group 1) underwent IVR therapy with 0.50 mg/0.05 ml ranibizumab (Lucentis, Novartis), while 23 patients (group 2) underwent IVD therapy with dexamethasone intravitreal implant (0.7 mg; Ozurdex, Allergan, Inc., Irvine, CA). Re-treatment decision was determined based on re-appearance of fluid on OCT accompanying to first- order loss of visual acuity. In IVR group, the patients were re-treated in case of recurrence after 3 monthly injections; however, there were patients could not complete first 3 treatments. In IVD group, the patients were re-treated in case of recurrence following injection. No patient received laser therapy at baseline or during follow-up. The groups were compared regarding age, gender, ischemia, time to presentation after edema development and number of intravitreal injections. The intraocular pressure (IOP) was assessed by applanation tonometry while central macular thickness (CMT) by Cirrus HD spectral-domain OCT (Carl Zeiss Meditec, Dublin, CA) and ischemia by Canon CF-1 fundus fluorescein angiography (FFA) (Digital Mydriatic Retinal Camera. Canon Inc., 30 Tokyo, Japan). The visual acuity was recorded as logarithmic visual acuity (LVA). The IOP, CMT and LVA parameters were assessed at baseline and months 1, 3 and 6.

Statistical analyses were performed by SPSS 16.0 (Statistical Package for Social Sciences-SPSS, Inc., Chicago, Il- linois). The Chi-square test was used to compare gender distribution between groups. The Student's t test was used to compare quantitative variables between groups. The Friedman variance analysis was used to assess presence of differences between measurements obtained on day 1, 7 and 30. The Wilcoxon paired sample test was used for post hoc assessment following variance analysis. All tests were 2-tailed. The significance level was set as $p=0.05$.

FINDINGS

The group 1 included 16 men and 16 women with mean age of 60.9 ± 9.95 (40-83) years while the group 2 included 12 men and 11 women with mean age of 60.19 ± 10.06 (39-82) years.($p=0.804$) .The time from

onset of complaints to presentation was 3.4± 2.34 months in group 1 and 1.77 ±1.67 months in group 2 (p=0.006). Ischemia was defined as area greater than 5 disc diameter on FFA. The ischemia was detected in 8 patients (25%) in group 1 and 13 patients (56.5%) in group 2 (p=0.005). Mean number of injections was 2.41±1.15 in group 1 and 1.66±0.48 in group 2 (p=0.007). The IOP was detected as 16.30± 1.95 mmHg at baseline, 16.30±1.69 mmHg at month 1, 16.65±1.46 mmHg at month 3 and 16.90±1.83 mmHg at month 6 after injection in group 1. Although there was no significant difference baseline IOP value and those obtained at months 1 (p=0.93) and 3 (p=0.12), there was significant difference between baseline values and those obtained at month 6 (p=0.018). In group 2, the IOP was detected as 16.21± 2.12 mmHg at baseline, 16.63±1.95 mmHg at month 1, 16.84±1.80 mmHg at month 3 and16.74±1.94 mmHg at month 6 after treatment. Although there was no significant difference between baseline IOP values and those obtained at months 1 (p=0.12) and 6 (p=0.066), there was significant difference between IOP values obtained at baseline and month 3 (p=0.049).

In group 1, LVA was measured as 0.76 (0.61-1.05) at baseline (LVA0), 0.52 (0.40- 0.70) at month 1 (LVA1), 0.41 (0.26-0.61) at month 3 (LVA3) and 7 (0.22-0.52) at month 6 (LVA6) after injection while CMT was detected as 591 µm (522-672) at baseline (CMT0), 361 µm (291-442) at month 1 (CMT1), 261 µm (210-323) at month 3 (CMT3) and 242.5 µm (217-285) at month 6 (CMT6) after treatment. (Figure 1,2)

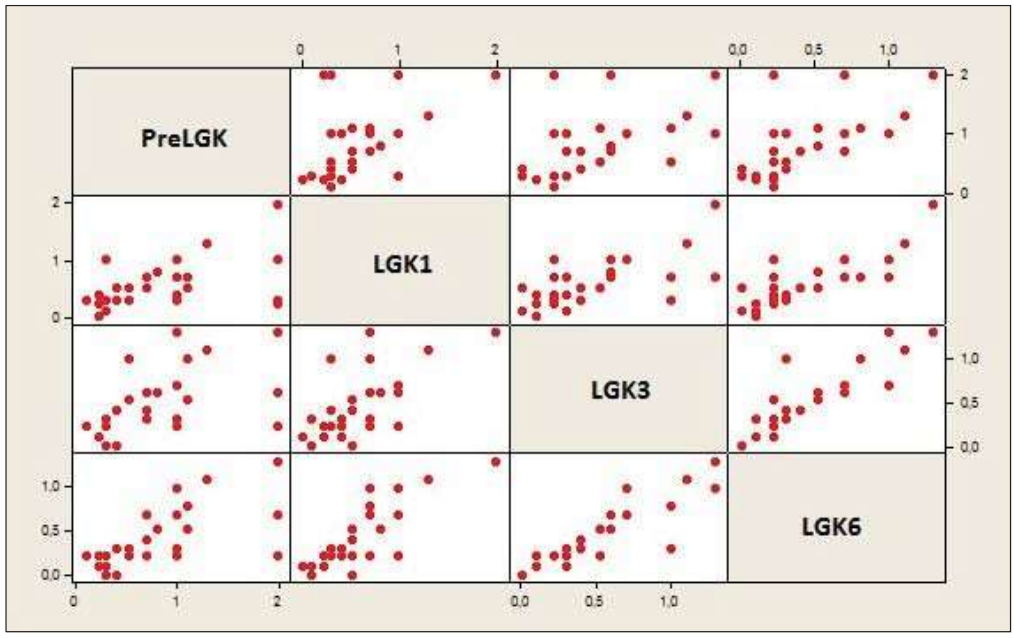

Figure 1: *Distribution of logarithmic visual acuity values in IVR group*

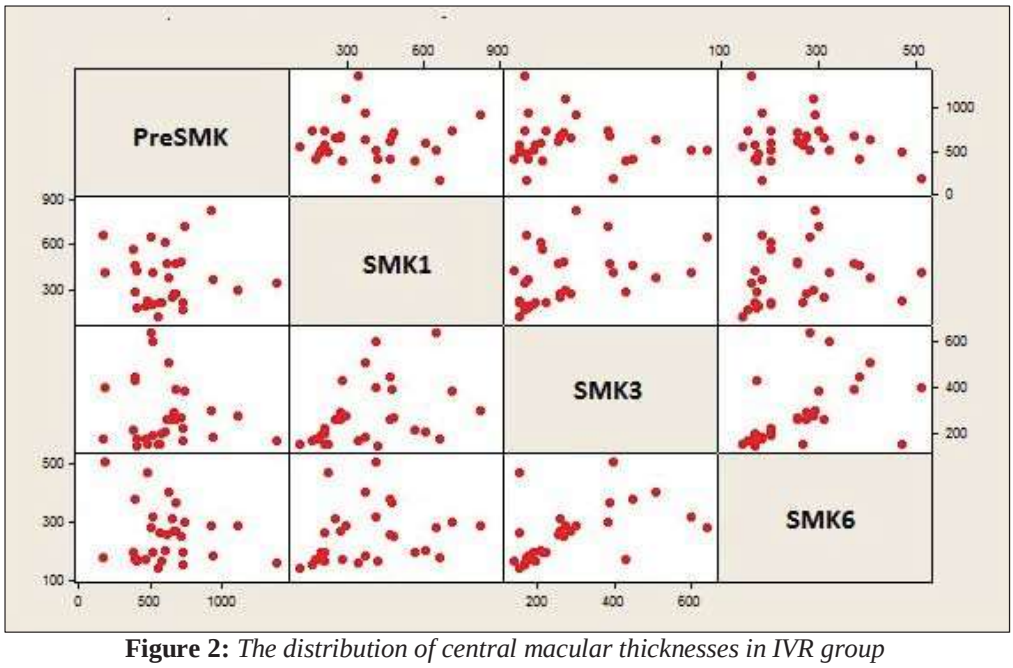

Figure 2: *The distribution of central macular thicknesses in IVR group*

In group 2, LVA0 was found as 1.00 (0.70-1.35), LVA 1 as 0.65 (0.40- 0.90), LVA3 as 0.52 (0.35-0.70) and LVA6 as 6, 0.50 (0.35-0.70) while CMT0 was measured as 590 µm (491-779), CMT1 as 280 µm (238-382), CMT3 as 344 µm (295- 409) and CMT6 as 292 µm (236- 390) (Figure 3,4).

In group 1, there was significant difference between LVA0 and LVA1, LVA3 and LVA6 (p values: 0.001, 0.002, and 0.002, respectively). While there was significant difference between LVA1, LVA3 and LVA6 values (p values: 0.024 and 0.001, respectively) there was no significant difference between LVA3 and 6 (p: 0.238). The visual acuity level was progressively improved from baseline to month 6.

In group 2, there was significant difference between LVA0 and LVA1, LVA3 and LVA6 (p values: 0.001 for each). There was no significant difference between LVA1 and LVA3 (p=0.097); however, there was significant difference between LVA1 and LVA6 (p=0.017). No significant difference was detected between LVA3 and LVA6 (p=0.397). The visual acuity level was progressively improved from baseline to month 6.

In group 1, there was significant difference between CMT0 and CMT1, CMT3 and CMT6 (p values: 0.001 for each). There was significant difference between CMT1 and both CMT3 and CMT6 (p values: 0.004 and 0.003, respectively) while there was no significant difference between CMT3 and CMT6 (p:0.238)

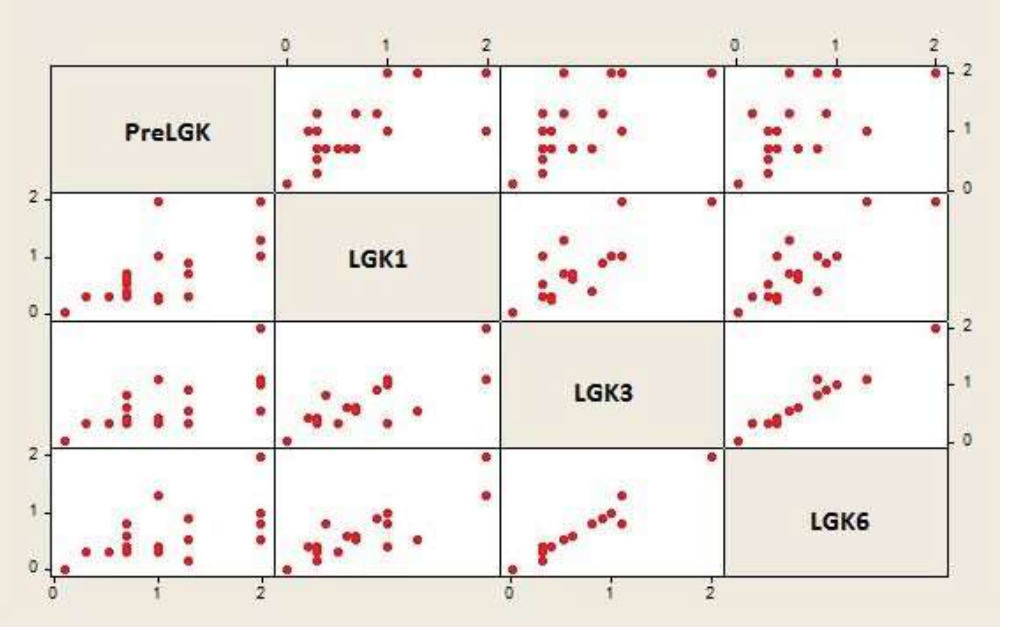

Figure 3: *Distribution of logarithmic visual acuity values in IVD group*

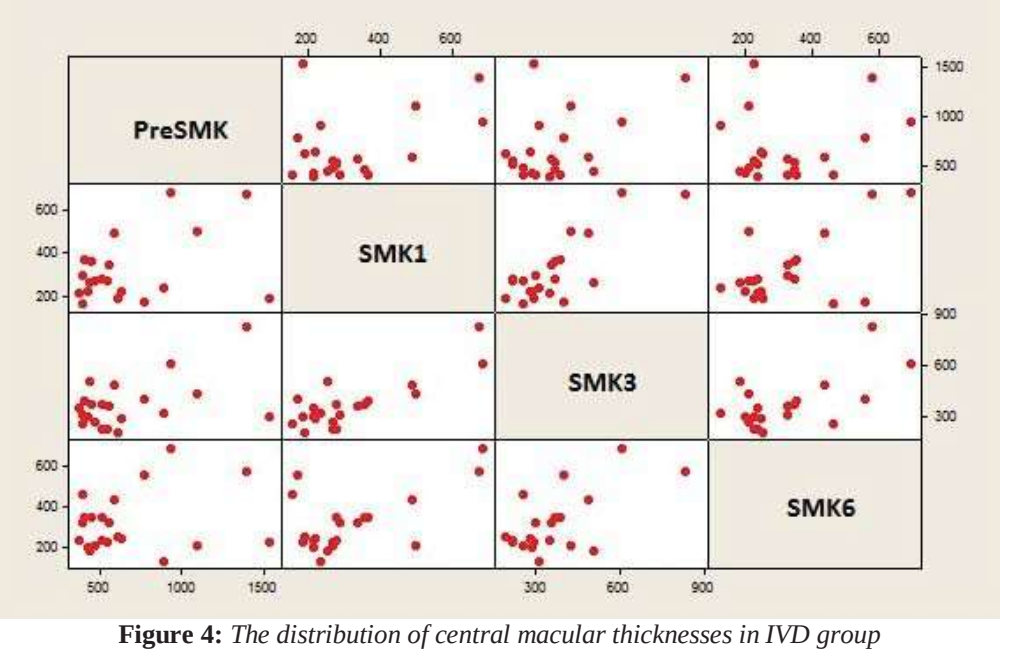

Figure 4: *The distribution of central macular thicknesses in IVD group*

The central macular thickness was progressively decreased from baseline to month 6.

In group 2, there was significant difference between CMT0 and CMT1, CMT3 and CMT6 (p values: 0.001 for each). There was significant difference between CMT and CMT3 (p: 0.031) but not between CMT1 and CMT or CMT3 and CMT6 (p values: 0.985 and 0.414, respectively). The CMT increased at month 3 was decreased at month 6 after injection.

DISCUSSION

Until recently, laser photocoagulation, which was shown to improve visual acuity, was standard approach in macular edema treatment in BRVO.[8] There is no established treatment protocol for macular edema in retinal vein occlusion.[7] In some studies, it was shown that IVTA is effective in reducing macular edema and improving vision outcomes.[9] However, severe complications such as increased IOP, cataract and endophthalmitis were observed with IVTA.[10] In studies using anti-VGEF, it was shown that there was significant improvement in visual acuity by monthly ranibizumab injection and that adverse effects were minimal when compared to IVTA. In BRAVO and CRUISE studies using ranibizumab injection, 15-letters of visual acuity gain was observed within 6 months in 61% of patients in BRVO and in 48% of patients in CRVO while 15-letters of visual acuity gain rate was 15% within 6 months in GENEVA study using intravitreal dexamethasone implant. However, the rate of patients with maculaR edema <3 months was 37-44% in BRAVO and CRUISE studies while it was 14-17% in GENEVA study. The all above-mentioned studies suggested that shorter duration of macular edema resulted in more favorable outcomes regarding visual acuity gain.[11-13]

Brown et al. classified 392 cases with CRVO-related macula edema while Campochiaro et al. classified 397 cases with BVO-related macular edema as follows: those received 0.3 mg ranibizumab, those received 0.5 mg ranibizumab and those received no anti-VGEF injection. Authors detected significant improvement in visual acuity and central macular thickness in groups receiving 0.3 and 0.5 mg ranibizumab at 6-months follow-up when compared to those received no anti-VGEF injection.[14,15] Spaide et al. administered 3 monthly injections to 20 cases with CRVO and followed these patients by additional injections in case of persistent macular edema or de novo retinal hemorrhage in monthly follow-up.[16]

In the MEAD study, authors found improvement in best corrected visual acuity (BCVA) and CMT following intravitreal dexamethasone implantation.[17] In the PLACID study, >2 order visual acuity gain was achieved within first 6 months in patients underwent intravitreal dexamethasone implant plus laser photocoagulation (LPC) when compared to those underwent LPC alone but the gain became insignificant after month 9. [18] In the CHAMPLAIN study, the effect of dexamethasone was investigated in eyes with diabetic macular edema which underwent vitrectomy and authors reported marked decrease in CMT and ≥2 order visual acuity gain in BCVA at weeks 8 and 13 in 30% of cases.[19] In the GENEVA study comparing patients with RVO-related macula edema who underwent 0.7 mg dexamethasone implant and controls, it was found that rate of ≥15-letters visual acuity gain in BCVA was 30% in implant group and 13% in the control group on day 90 while 23% in the implant group and 20% in the control group at month 6. Haller et al. investigated effectiveness of dexamethasone implant in both BRVO-related macular edema and diabetic macular edema by clinical examination and showed improvement in visual acuity. The use of 0.7mg intravitreal dexamethasone, particularly if used in early phase within 3 months, loss of visual acuity could be decreased in long-term and visual acuity gain was always better than patients left untreated. The most rapid improvement in visual acuity and retinal thickness was observed within first 60-90 days.[20]

In this study, we compared 6-months clinical effectiveness of IVD and IVR treatments used in BRVO-related macular edema, particularly in IOP, CMT and LVA. It was found that LVA0 median was 0.76 (min.0.61; max.1.05) and LVA6 median was 0.37 (min.0.22; max.0.52) in 32 patients in IVR group (p=0.002) while LVA0 median was 1.00 (min.0.70,-max.1.35) and LVA6 median was 0.50 (min.0.35;max.0.70) (p=0.001) in 23 patients in IVD group, indicating significant difference in both groups. Visual acuity at baseline is one of criteria that predict prognosis in BRCO. If visual acuity is ≥1 LogMAR, it is considered that prognosis would be poor.[21] ın our study, visual acuity at baseline was about 1 LogMAR in all cases with ischemic type BRVO in both groups. In our study, time to presentation was shorter in IVD group (1.77±1.67 months than IVR group (3.4±2.34 months) and improvement comparable to IVR group could be achieved ın IVD, presumably due to early presentation, although number of patients with ischemia was higher.

When considered regarding CMT, the values were progressively decreased from baseline to month 6 (median 591,361,261,242.5) in IVR group while highest effectiveness was observed at month (median 280) which then increased (median 344) at month 3 and decreased again at month 6 (median 292). CMT was decreased at month owing to repeated injections. In our study, gain in visual acuity was preserved in majority of patients during this period despite increased macular thickness and recurrences.

This confirms pharmacological effects of implant where peak concentration at posterior segment is achieved within 2 months; thereafter, begins to reduce between days 60 and 90 with ongoing effect until day 180.[22]

In their study, Good et al. investigated persistent IOP elevation following intravitreal anti-VGEF injection. The study included 225 eyes of 195 patients. Bevacizumab injection was administered to 101 patients whereas ranibizumab injection to 96 patients and both bevacizumab and ranibizumab injections to 18 patients. Medical therapy was prescribed to patients with IOP>21 mmHg in 2 occasions during 30 days. Medical therapy was initiated in 12 patients while one patient underwent selective laser trabeculoplasty (however, IOP was elevated again and medical therapy was prescribed). The extent of IOP elevation was found to be significantly higher in 2 patients with known glaucoma than other patients. The IOP elevation was observed in 9.9% of patients received bevacizumab and 3.1% of patients received ranibizumab, indicating a significant difference.[23] IOP elevation is anticipated due to accumulation of anti-VGEF proteins within humor aqueous by increasing number and frequency of injections. Another mechanisms leading IOP elevation can be associated to development of immune reaction against drugs; however, it was suggested that there was no finding suggestive of inflammation with normal angles in gonioscopy. In two distinct centers applying bevacizumab, significant difference was found in IOP, indicating that application technique and some other factors, rather than anti-VGEF itself, is involved in IOP elevation. The storage, transport, plastic injectors and lapse can be important in protein aggregation. Thus, storage and transport processes should be handled meticulously.[23] In our study, significant IOP elevation was detected in IVR group at month 6 but no intervention was needed.

In the multicenter GENEVA study involving approximately 1200 patients, IOP<25 mmHg was detected in less than 16% of patients, which was readily recovered with medical therapy. In our study, IOP was found to be elevated in IVR group at month 6 and in IVD group at month 3. Again, in a multicenter study including 290 patients, ≥10 mmHg IOP elevation was detected in 32% whereas ≥25 mmHg in 33% and ≥35 mmHg in 9% of patients; however, approximately 44% of patients had IOP>25 mmHg and 24% were on topical anti-glaucomatous agents before injection.[7] By excluding these patients, of the patients with history of anti-glaucomatous agent use, drug was changed in 11% while 1.4% underwent laser for glaucoma and 1.7% underwent insicioanl glaucoma surgery.[7] As patients with glaucoma were excluded, we had no patient requiring laser or surgical glaucoma treatment after IVD injection.

IVD implant is an effective treatment modality in reducing vision loss caused by macular edema in BRVO and IOP should be meticulously monitored due to its steroid content.[24] We recommend to assess IOP at months 2 and 3 where IOP value peaks regardless of recurrence. Although there was significant IOP elevation in IVD group at month 3 and in IVR group at month 6, no patient required additional laser, surgical or topical anti-glaucomatous therapy. Thus, we think that risk for IOP should not preclude IVD and IVR injection in normotensive eyes.

In conclusion, this study has some limitations including small sample size, short follow-up and retrospective nature. However, BRVO-related macular edema, timely IVR and IVD injections are associated to satisfactory results regarding improvement in visual acuity and macular thickness; in addition, the IOP can also be taken under control. In our study, although the extent of improvement in visual acuity was comparable in both groups, it is striking that CMT results were more satisfactory with IVR injection compared to IVD injections if used with appropriate timing.

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