Short and long term Intraocular Pressure Alterations After Intravitreal Injection of Ranibizumab for the Treatment of Choroidal Neovascularization Secondary to Age-related Macular Degeneration

Yaşa Bağlı Makula Dejenerasyona Sekonder Gelişen Koroidal Neovaskülarizasyonunun Tedavisi İçin Kullanılan İntavitreal Ranizbizumab İnjeksiyonu Sonrası Kısa ve Uzun dönem Göz İçi Basınç Değişimleri

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ABSTRACT

Purpose: To report changing in intraocular pressures (IOP) after intravitreal injection of ranibizumab for the treatment of choroidal neovascularization secondary to age-releated macular degeneration and to assess its safety.

Materials and Methods: The study included 95 intravitreal injections of 88 eyes of 69 patients who received intravitreal injections of 0.05 ml (0.5 mg) ranibizumab. The effect of intravitreal injections of ranibizumab on IOP was performed. IOP was measured 2, 45, 120 minutes, 24 hours, 1 week and 4 weeks after injection.

Results: The mean preinjection IOP was 15.70±3.71 mmHg (mean±SD) (range, 13 to 20 mmHg). The mean postinjection IOP 2, 45, 120 minutes after injection was 40.64±7.43 mmHg (range, 12 to 60 mmHg), 28±6.80 mmHg (range, 13 to 38 mmHg), 19. 10±4.18 mmHg (range, 14 to 30 mmHg), respectively. The mean postinjection IOP 24 hours after injection was 16.04±4.43 mmHg (range, 12 to 24 mmHg). At 1-week follow-up, the average IOP was 15.98±3.02 mmHg (range, 14 to 21 mmHg). At 4-week follow-up, the average IOP was 15.86±2.88 mmHg (range, 14 to 20 mmHg).

Conclusions: Our study shows that 0.05 ml (0.5 mg) ranibizumab intravitreal injections cause transient IOP elevation with in immediately after injection but does not cause a marked increase in IOP at the 120 minutes after the procedure. Ranibizumab injection is safe in terms of elevation of IOP.

Key Words: Intravitreal ranibizumab injection, intraocular pressure.

ÖZ

Amaç: Yaşa bağlı maküla dejeneresansına sekonder koroidal neovaskülarizasyon tedavisi amacıyla yapılan intravitreal ranibizumab enjeksiyonunun ardından göz içi basıncı (GİB) değişimlerini bildirmek ve ajanın güvenilirliğini değerlendirmek.

Gereç ve Yöntem: Çalışma intravitreal 0.05 ml (0.5 mg) ranibizumab enjeksiyonu yapılmış 80 hastanın 90 gözünü içermektedir. Enjeksiyon sonrası 2, 45, 120 dakika, 24 saat, 1 ve 4 haftalık GİB ölçümleriyle intravitreal ranibizumab enjeksiyonunun GİB'e etkisi analiz edilmiştir. Glokom hastaları çalışa dışı bırakılmıştır.

Bulgular: Enjeksiyon öncesi ortalama GİB 15.70±3.71 mmHg'dir (ortalama±SD) (13-20 mmHg aralığında). Enjeksiyon sonrası 2, 45, 120. dakikalarda alınan GİB ölçümleri ortalama 40.64±7.43 mmHg (12-60 mmHg aralığında), 28±6.80 mmHg (13-38 mmHg aralığında), 19. 10±4.18 mmHg (14-30 mmHg aralığında) olarak bulunmuştur. Enjeksiyon sonrası 24. saat ortalama GİB 16.04±4.43 mmHg'dir (12-24 mmHg aralığında), 1. hafta ortalama GİB 15.98±3.02 mmHg (14-21 mmHg aralığında) olup 4. hafta ortalama GİB 15.86±2.88 mmHg'dir (14-20 mmHg aralığında).

Sonuç: Çalışmamız 0.05 ml (0.5 mg) intravitreal ranibizumab enjeksiyonunun hemen enjeksiyon sonrasında oluşan fakat 120. dakikada belirgin olarak devam etmeyen geçici bir GİB artışına neden olduğunu ortaya koymuştur. İntavitreal ranibizumab enjeksiyonunun GİB artışı açısından güvenli olduğu sonucuna varılmıştır.

Anahtar Kelimeler: İntravitreal ranibizumab enjeksiyonu, göz içi basıncı.

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INTRODUCTION

Vascular endothelial growth factor (VEGF) plays a critical role in both adult and developmental blood vessel growth. Because VEGF is such a crucial regulator of angiogenesis, it has become an attractive target for pharmacologic manipulation to treat cancers and ophthalmic diseases.[1-4] Intravitreal injections of agents blocking the actions of vascular endothelial growth factors (VEGF) have become common in the treatment of various vascular disorders of the eye in the vitreoretinal clinic or ophthalmic surgical environment. To date, no significant toxicity has been reported after intravitreal anti-VEGF injections, but limited safety data are available.[3,4] Although reportedly low, complications of these procedures include raised intraocular pressure, hyphema, vitreous hemorrhage, and retinal detachment.[2-5] In prior reports the potential complications of intraocular pressure (IOP) after intravitreal injections especially IVTA injection have been identified.[6-10] Rosenfeld and colleagues reported that ranibizumab (Lucentis, Novartis, Switzerland) had no long-term effect on IOP as determined by monthly measurements during the 2-year MARINA study. [5] As far as we know there are only a few studies about the short-term effect of intravitreal injection of ranibizumab treatment on IOP in literature. The purpose of our study was to determine the short and long term effect of intravitreal ranibizumab on IOP in 2, 45, 120 minutes, 24 hours, 1 week and 4 weeks after injection.

MATERIAL AND METHODS

A retrospectıve case review was performed to identify all patients who received an intravitreal injection of ranibizumab in our retina deparment. Data from 95 consecutive intravitreal injections to 88 eyes of 69 patients were analyzed. Glaucoma patients have not been enrolled in this study. The study protocol was complied with the provisions of the Declaration of Helsinki. The patients underwent complete ophthalmic examination, including corrected visual acuity measurement using the ETDRS chart, slit lamp biomicroscopy with a 90 diopter precorneal lens and a Goldmann three-mirror contact lens, color fundus photography, fluorescein angiography and OCT. Visual acuity was also measured before and after treatment. Intravitreal ranibizumab was administered after discussing the risks and benefits of different treatment regimens with the patients. Informed consent was obtained from each patient. Topical proparacaine hydrocholoride was applied to the ocular surface followed by preparation with 5% povidone iodine. All patients included in this series received ranibizumab injection as directed by the instructions provided in the package insert (0.5 mg ,volume 0.05 mL). Ranibizumab in a syringe with a 30-gauge needle was then injected through the pars plana into the vitreous cavity inserted through the sclera 3 to 4 mm posterior to the limbus. After injection, the injection site was occluded temporarily and was massaged with a sterile cotton-tipped applicator as the needle was withdrawn from the eye. Postinjection light perception was assessed and the intraocular pressure (IOP) was monitored. Anterior chamber (AC) paracentesis was not performed in any of the injections. None of patients have received antiglaucoma medication for IOP elevation. All pressures were measured using the Goldmann applanation tonometry. IOPs were measured before sterile preparation (baseline IOP) and immediately after injection (within 2 minutes) and were reassessed 45, 120 minutes, 24 hours, 1 week and 4 weeks thereafter.

After the prosedure, the patient was instructed to apply topical antibiotics to the injected eye 4 times a day for 7 days. There were no episodes of inflammation or severe vision decrease immediately after an injection. During examination, there were no cases of endophthalmitis, retinal detachment, or lens damage. Research data, frequency, percentage, mean and standard deviations are presented in the form.

RESULTS

The mean age of patients was 72.5 years (range, 51 to 88 years), with 42 men and 53 women. Fifty eyes were phakic and 45 eyes were pseudophakic. Patients received intravitreal injections of ranibizumab for choroidal neovascularization secondary to age-releated macular degeneration. The mean preinjection IOP was 15.70±3.71 mmHg (mean±SD) (range, 13 to 20 mmHg). The mean postinjection IOP 2, 45, 120 minutes after injection was 40.64±7.43 mmHg (range, 12 to 60 mmHg), 28±6.80 mmHg (range, 13 to 38 mmHg), 19. 10±4.18 mmHg (range, 14 to 30 mmHg), respectively. The mean postinjection IOP 24 hours after injection was 16.04±4.43 mmHg (range, 12 to 24 mmHg). At 1-week follow-up, the average IOP was 15.98±3.02 mmHg (range, 14 to 21 mmHg). At 4-week follow-up, the average IOP was 15.86±2.88 mmHg (range, 14 to 20 mmHg). Seventy-eight eyes (82.1%) had IOP elevation immediately after 2 minute, 53 (55.7%) eyes had IOP elevation after 45 minute, 5 (5.2%) eyes had IOP elevation after 120 minute. Only 3 eyes (3.1%) had IOP elevation 24 hours after injection. None of the 88 eyes experienced an IOP rise to greater than 21 mmHg as measured one and four weeks after ranibizumab injection. The main outcome measure was an IOP increase, defined by absolute value of IOP elevation (5 mmHg or higher) of baseline. There were no patients with a diagnosis of preexisting glaucoma. None of patients have received antiglaucoma medication for IOP elevation. In 34 injections (37.7%), IOP at 2 minutes was 50 mmHg or higher. Nevertheless, all eyes except 2 had at least hand movement vision and a perfused optic nerve visualized with indirect ophthalmoscopy. In two patient, light perception was not noted immediately after injection but became apparent within one minute after the injection with careful observation for

optic nerve perfusion with indirect ophthalmoscope. After the optic nerve became perfused, the patient saw light.

DISCUSSION

VEGF inhibition is becoming an important modality in the treatment of AMD and other neovascular disease.[1-5] Within the last years, anti-VEGF drugs such as ranibizumab have increasingly been applied at multiple centers as an intravitreally treatment option for various intraocular neovascular, edematous and proliferative ocular disorders. Despite the therapeutic benefits of these agents, repeat injections often are required. [2-5] As intravitreal injections become an increasingly common method of treatment, investigating the need for monitoring IOP after injection is important for patient safety, increased patient satisfaction despite need for repeated injections.[11-15] The MARINA study also shows that monthly ranibizumab injections are safe in terms of its effect on long-termIOP.[5] For immediate short-term after injection, intravitreal injections were well tolerated by patient in this study. This is in agreement with previous studies.[5,16,17] To our knowledge, this is the first study that IOP has been evaluated immediatly after intravitreal ranibizumab injection in the treatment of retinal diseases in Turkish literature.

It is important that IOP monitoring and then to identify patients at high risk for delayed normalization of IOP immediately after intavitreal injection. The guidelines for intravitreal injections recommend, monitoring of IOP after injection and providing therapy when elevated IOP warrants intervention.[11,12] However, when to best monitor IOP is debatable. In clinical trials with ranibizumab and pegaptanib, IOP was measured up to one hour after injection.[5,6] A series on pegaptanib injections has demonstrated short-term safety from an IOP standpoint when patients were evaluated at 30 minutes and five to seven days later and questioned the need for an IOP check 30 minutes after injection.[6] Although some studies of IOP trends immediately after intravitreal injections of bevacizumab, triamcinolone, or pegaptanib concluded that monitoring of postinjection IOP may not be necessary,[6,16,17] others suggest checking once at five to 10 minutes after injection, [9,10] whereas others recommend IOP checking after injection but do not give guidance as to when or for how long. [8,10,13] Some studies recommend performing paracentesis, whereas others do not.[6,8,18]

Benz and associates reported that IOP changes within the initial 30 minutes after intravitreal triamcinolone acetonide injection correlate with the presence of vitreous reflux.[13] In their study, patients who were noted to have no vitreous reflux after injection had a marked increase in mean IOP, which normalized within 30 minutes. Patients who were noted to have vitreous reflux did not have an increase in mean IOP within 30 minutes of the injection. Their study was limited to cases where 0.1 ml intravitreal triamcinolone acetonide was given with a 27-gauge needle and excluded eyes with a history of glaucoma. Whereas 30 gauge needle was used in our study. Although reflux was not noted in a prospective manner in our study, nor would it be possible to quantify accurately the amount of reflux, their findings support findings in our study. We also found that IOP almost normalized over 120 minutes. We found that the incidence of IOP elevation immediately after injection was significantly higher with smaller bore needle size, despite the smaller volume injected with these needles. This is most likely because of less reflux through a smaller injection opening, whereas larger-bore needles allowing more reflux. Kim and co-workers found that IOP normalized over 30 minutes.[16] They also sugessted that in addition to reflux and volume injected, other factors such as the size of the globe and scleral rigidity also may play a role in IOP spike after intravitreal injection. It was asserted that in this study if more than 0.05 ml were to be injected with a small-gauge needle, which does not allow for much reflux, or if reflux does not occur when a larger volume is injected with a larger-bore needle, even higher IOP immediately after injection may be expected than that observed in their series, and these eyes should be monitored more closely with further caution. Majica et al. adduced that IOP returns to baseline at the 1-week, 2-week and 4-week follow-up visits and intravitreal injection of ranibizumab results in an expected mild transient elevation of IOP immediately after injection.[17] In contrast to our results, Yorgun et al. demostrated that, early changes in IOP after intravitreal bevacizumab injection as an another anti-VEGF were not noted by GAT and PDCT.[19] Nonetheless, the ocular pulse amplitude (OPA) measured by pascal dynamic tonometer was significantly increased 30 minutes after the injection in this study. The authors suggested that this increase in OPA may be caused by early effects of bevacizumab on choroidal blood flow. Our series reveals that intravitreal injection of ranibizumab results in an expected modarate or severe transient elevation of IOP immediately after injection. However, the IOP normalises to baseline within 120 minutes without employing therapy for IOP control and AC paracentesis was not required. Limitations to our study include not having patient with glaucoma. Also, we did not analyze our data based on refractive error of eyes and axial lenght.

In conclusion, the current study reveals that ranibizumab injection is safe in terms of elevation of IOP in a short and long-term setting. All eyes in our series achieved almost normalization of IOP within 120 minutes without need for any immediate intervention, such as paracentesis. Therefore, in most cases, repeated or prolonged IOP monitoring for normalization after intravitreal injections may not be necessary on the day of injection. Anterior chamber paracentesis immediately after injection is not recommended. Furher investigation are needed to better understanding of the effect of intavitreal injection on IOP.

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