Intraocular Pressure Changes after Different Types of Intravitreal Injections for the Treatment of Macular Edema

Maküla Ödemi Tedavisinde Kullanılan İntravitreal Enjeksiyonların Göz İçi Basıncına Etkisi*

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ABSTRACT

Purpose: To evaluate the effects of intravitreal triamcinolone acetonide (IVTA), bevacizumab (IVB), and the combination of IVTA/IVB on the intraocular pressure (IOP) change in a 6-month follow-up period.

Materials and Methods: Two hundred and seven eyes of 194 consecutive patients (113 male, mean age 61±10 years) that received an intravitreal injection between January 2007 and January 2008 for the treatment of macular edema were evaluated retrospectively. Group 1 consisted of 100 eyes of 94 patients treated with 4 mg IVTA injection, Group 2 consisted of 32 eyes of 27 patients treated with 1.25 mg IVB, and Group 3 consisted of 75 eyes of 73 patients treated with a combination of 2 mg TA and 1.25 mg bevacizumab. The primary outcome measures of the study were change in IOP and the number of eyes with elevated IOP requiring glaucoma treatment.

Results: The initial IOP was similar in all groups (p=0.413). However, in all follow-up examinations the difference between the groups was significant (p value for all visits <0.05). Treatment for elevated IOP was required in 21% eyes following IVTA injection and in 4% eyes following IVTA/IVB injection (p=0.001). None of the eyes that received IVB required glaucoma treatment. IOP rise was highest at one month following IVTA injection and at one week following IVTA/IVB injection.

Conclusion: A significant relation between the steroid dose and IOP elevation was found. Reduction of steroid dose resulted in less frequent IOP elevation.

Key Words: Intraocular pressure, intravitreal bevacizumab, intravitreal injection, intravitreal triamcinolone acetonide.

ÖZ

Amaç: İntravitreal triamsinolon asetonid (İVTA), intravitreal bevacizumab (İVB) ve kombine İVTA/İVB uygulamalarının göz içi basıncına (GİB) olan etkisini 6 aylık takip süresince incelemek.

Gereç ve Yöntem: Maküla ödemi nedeniyle Ocak 2007-Ocak 2008 tarihleri arasında intravitreal enjeksiyon yapılan 194 ardışık hastanın (113 erkek, ortalama yaş 61±10 yıl) 207 gözü geriye dönük olarak incelendi. Grup 1 4 mg İVTA uygulanan 94 hastanın 100 gözünü, Grup 2 1.25 mg IVB uygulanan 27 hastanın 32 gözünü, Grup 3 ise kombine 2 mg IVTA ile 1.25 mg IVB uygulana 73 hastanın 75 gözünü kapsamaktaydı. Temel çalışma parametreleri GİB değişimi ve tedavi gerektiren GİB yükselmesi ile seyreden hasta sayılarıydı.

Bulgular: Başlangıç GİB üç grupta benzerdi (p=0.413). Kontrol muayenelerinin hepsinde ise gruplar arası fark anlamlı idi (tüm vizitler için p<0.05). Çalışma süresince İVTA uygulanan hastalarda %21, İVTA/İVB uygulanan hastalarda ise %4 oranında tedavi gerektiren GİB yükselmesi görüldü (p=0.001). İVB uygulanan gruptan hiçbir göze tedavi gerekli olmadı. İVTA uygulaması sonrası GİB artış en fazla 1. ayda gözlenirken, İVTA/İVB sonrası GİB artışı en fazla 1. haftada gözlendi.

Sonuç: Steroid dozu ile GİB artışı arasında önemli bir bağlantı mevcuttu. Steroid dozunun azaltılması ile GİB yükselmesi daha az sıklıkta izlenmiştir.

Anahtar Kelimeler: Göz içi basıncı, intravitreal bevacizumab, intravitreal enjeksiyon, intravitreal triamsinolon asetonid.

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INTRODUCTION

Triamcinolone acetonide (TA) is increasingly used for the treatment of numerous macular disorders that are associated with diabetic retinopathy,[1-3] retinal vein occlusion,[3,4] choroidal neovascularization,[5] and uveitis. Intravitreal triamcinolone acetonide (IVTA) minimizes the side effects associated with systemic steroid therapy. However, intravitreal injection of TA is associated with increased risks of ocular complications, including vitreous hemorrhage, retinal detachment, bacterial endophthalmitis, and intraocular pressure (IOP) elevation, which can often result in serious visual loss.[6-8]

Bevacizumab has especially emerged as a novel therapeutic strategy for age-related macular degeneration providing promising results.[9] As with other VEGF inhibitors, bevacizumab has repeatedly been reported to be suitable and safe for intravitreal injection.[10]

According to various reports, one can assume that intravitreal VEGF inhibition will also be applicable in other retinal diseases, such as retinal vein occlusion, uveitis, and diabetic maculopathy.[11,12] Injection related complications such as subconjunctival hemorrhage, hyphema, infectious endophthalmitis, vitreous hemorrhage, retinal detachment, and traumatic cataract may occur at a frequency of about 0.15% after intravitreal bevacizumab (IVB).[13,14]

Topical, intravitreal, and systemic corticosteroid therapy can induce IOP elevation, which can lead to glaucoma.[6,7,15] Acute IOP rise following intravitreal bevacizumab administration was reported,[14] whereas glaucoma development in long term follow-up was not described.

In this study we aimed to evaluate the effects of intravitreal 4 mg triamcinolone acetonide, 1.25 mg bevacizumab, and the combination of 2 mg triamcinolone with 1.25 mg bevacizumab on IOP levels in a 6-month follow-up period and to define the incidence of IOP elevation following the injections.

MATERIALS AND METHODS

In this retrospective study, 207 eyes of 194 consecutive patients who received an intravitreal injection between January 2007 and January 2008 for the treatment of macular edema secondary to either diabetic retinopathy or retinal vein occlusion were evaluated. The intravitreal injections were analyzed in three different groups: Group 1 consisted of 100 eyes of 94 patients treated with 4 mg 0.1 ml IVTA injection, Group 2 consisted of 32 eyes of 27 patients treated with 1.25 mg 0.05 ml IVB, and Group 3 consisted of 75 eyes of 73 patients treated with a combined intravitreal injection of 2 mg 0.05 ml (a half dose) TA and 1.25 mg 0.05 ml bevacizumab.

Data collection was performed retrospectively from the patient charts. The demographic data of the patients, any history of systemic disease, and the etiology for macular edema in the pre-injection period were recorded.

The following data were noted at each visit: IOP as measured by Goldmann applanation tonometer, any complication occurring as a result of intravitreal injection, as well as any medication used or surgical procedure undergone to lower IOP. Patients were included in the study if they had received intravitreal injection only once during the study period and had been followed for at least 3 months. The eyes with previous injections of less than 6 months' duration were not included in the study. Only subjects with macular edema due to diabetic retinopathy or retinal vein occlusion were assessed. Patients with glaucoma, a history of steroid-induced ocular hypertension, or high initial IOP levels were excluded from the study. Other exclusion criteria were neovascularization in fluorescein angiography, presence of rubeosis iridis on biomicroscopic examination, and a history of previous vitreoretinal surgery. As a routine practice, topical glaucoma medications were initiated in cases of steroid-induced ocular hypertension if IOP was more than 21 mmHg. The initial treatment regimen constituted a monotherapy usually with a topical β-blocker agent. If IOP was measured between 26 and 30 mmHg, a combination of topical β-blocker agent and a topical carbonic anhydrase inhibitor (CAI) was prescribed. An α2 agonist was added to the topical β-blocker/CAI combination in cases when IOP exceeded 30 mmHg and a systemic CAI was further added if IOP exceeded 35 mmHg. The subjects with high IOP levels were scheduled for more frequent examinations as required, while the initial treatment medications were modified according to the response. The primary outcome measures of the study were change in IOP and the number of eyes with elevated IOP requiring glaucoma treatment during the study period.

Injection Technique

All injections were performed under sterile operating room conditions. Topical anesthesia with 0.5% proparacaine hydrochloride (Alcaine, Alcon) was applied to all eyes before the injection. A sterile drape was used following the eyelid and periorbital scrubbing with 10% povidone-iodine solution using the standard sterile technique. A sterile lid speculum was placed and 5% povidone-iodine was applied to the conjunctiva and fornices for 3 minutes and irrigated with BSS thereafter. With the aid of a strabismus compass the place of injection was determined at 3.5 mm distance from the limbus in phakic eyes and 3 mm in pseudophakic eyes. The superior temporal quadrant was chosen for the procedure.

The injection was into the vitreous cavity using a 30 gauge needle. As soon as the needle was drawn back continuous pressure was applied with a cotton tip at the injection site to prevent vitreous or injected material reflux and subconjunctival hemorrhage. After the completion of the injection, the light perception of the eye was asked. A topical antibiotic agent was prescribed four times daily for one week duration and the patient was asked to present to the emergency department in case of a sudden visual loss, pain, or redness in the eye.

Table1: Change in the mean IOP±SD (mm Hg) in each group compared to baseline.

	Baseline	1 Day	1 Week	1 Month	3 Months	6 Months
Group 1	15.3±1.8	16.6±3.0*	17.1±2.9*	17.5±3.6*	16.7±3.2*	17.2±4.3*
Group 2	14.7±2.0	14.2±2.4	15.4±1.9	14.8±1.3	15.3±1.7	15.5±1.7
Group 3	15.2±2.5	15.8±4.3	16.1±2.9*	15.9±2.7	15.1±1.9	15.4±2.0

* Statistically significant compared to baseline ($p<0.05$)

Following the injection subjects were examined at 1 day, 1 week, and 1 month, and then at the discretion of the treating physician. At each visit, besides measuring IOP, a biomicroscopic examination was performed and any complication was noted.

Statistical Analysis

All data were collected and analyzed using SPSS 15.0 (Statistical Package for the Social Sciences) for Windows. The normality of the data was confirmed using the Kolmogorov-Smirnov test ($p>0.05$); thus parametric tests were performed for analysis. Mean±standard deviation (SD) was calculated. One-way analysis of variance (ANOVA) was performed to analyze the difference in IOP measurements among the three groups and Paired Samples t-test was applied for repeated IOP measurements in each group. To compare the rate of subjects with elevated IOP between the groups Fisher's exact test was performed. P value <0.05 was considered statistically significant. Because only a few patients had follow-up for more than 6 months, statistical analysis was not performed for the follow-ups after 6 months.

RESULTS

Intravitreal injections were performed in 207 eyes of 194 subjects (113 male, 81 female). The mean age was 61±10 years, and for each group the mean age was 62±10 years, 60±14 years, and 60±9 years, respectively ($p=0.23$). The mean follow-up was 7.1±3.3 months (range 3 to 18 months). All patients had macular edema due to vascular pathologies. Diabetic retinopathy was present in 108 (52%) eyes and retinal vein occlusion in 99 (48%) eyes.

The diabetic retinopathy/retinal vein occlusion ratio in each group was 51/49, 17/15, and 40/35, respectively ($p>0.05$). The results of the study showed no difference in the initial IOP measurements among the groups ($p=0.413$). However, in all follow-up examinations the difference among the three groups was significant. P values for 1 day, 1 week, and 1, 3, and 6 months were 0.003, 0.002, 0.009, 0.005, and 0.001, respectively. The mean IOP change in each group is given in Table 1.

In subgroup analysis, in Group 1 there was a significant IOP increase in all post-injection visits compared to initial measurements (p value for all visits ≤ 0.001). No significant change in IOP was observed in Group 2 patients (p value for all visits >0.05). In Group 3, compared to initial IOP significant elevation was present at 1 week after the injection ($p=0.026$), while the change was non-significant at all other visits ($p>0.10$), (Table 1).

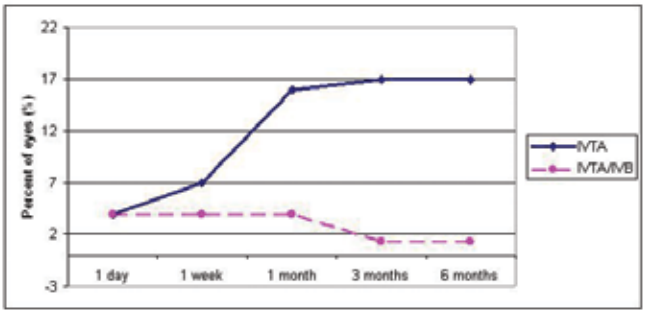
One day after the injection, 4 eyes in Group 1 (4%) and 3 eyes in Group 3 (4%) showed elevation in IOP, whereas none of the eyes in Group 2 had elevated IOP. A topical β-blocker agent or a combination of β-blocker/CAI was prescribed for the 4 eyes in Group 1 and for 2 eyes in Group 3 (Table 2). One eye in Group 3 with IOP>40 mmHg received maximal glaucoma therapy that consisted of a topical β-blocker/CAI, a topical α2 agonist, and a systemic CAI agent for initial treatment. The systemic CAI was abandoned following IOP regulation.

One week after the injection, in Group 1, the medication was discontinued in 1 eye while the 4 other eyes developed elevation in IOP. In Group 3, there was no need to start glaucoma medication in any of the eyes (Table 2). None of the eyes had elevated IOP at 1 week in Group 2.

Table2: The treatment regimen in eyes with elevated IOP.

		1 Day [N, (%)]	1 Week [N, (%)]	1 Month [N, (%)]	3 Months [N, (%)]	6 Months [N, (%)]
Group 1	Category A	2 (2)	3 (3)	6 (6)	6 (6)	6 (6)
	Category B	2 (2)	3 (3)	9 (9)	11 (11)	10 (10)
	Category C	0	1(1)	1(1)	0	1(1)
	Category D	0	0	0	0	0
Group 3	Category A	1 (1.3)	1(1.3)	1(1.3)	0	0
	Category B	1(1.3)	1(1.3)	1(1.3)	1(1.3)	1(1.3)
	Category C	0	1(1.3)	1(1.3)	0	0
	Category D	1(1.3)	0	0	0	0

Category A: Topical one agent medication, Category B: Topical two-agent medication, Category C: Topical three-agent medication, Category D: Topical three-agent medication+systemic CAI



Graphic: Percent of eyes on glaucoma medication in each visit after the injections. IVTA: intravitreal triamcinolone acetonide, IVTA/IVB: intravitreal triamcinolone acetonide/intravitreal bevacizumab.

At the end of the first month, in Group 1, there were 9 more eyes with elevated IOP, which were managed either by a topical β-blocker agent or by a combination of topical β-blocker/CAI agent and the glaucoma medication of one eye with previously elevated IOP was discontinued. Thus, in Group 1 a total of 16 eyes (16%) were receiving glaucoma medication at the end of 1 month. There was no change in the regimen in the treated eyes in Group 3 (Table 2). In Group 2, none of the eyes had elevation in IOP requiring medication at the end of the first month.

At 3 months, the treatment was terminated in one eye in Group 1, whilst 2 other eyes required glaucoma medication. A total of 17 eyes were being treated for elevated IOP. In Group 3, only the eye with IOP>40 mm Hg at the 1st day continued the previous treatment.

At 6 months in Group 1, the glaucoma medication of 2 eyes with previously elevated IOP was discontinued while glaucoma medication was initiated in 2 other eyes developing elevated IOP 6 months after the IVTA injection. In Group 3, no eye required glaucoma treatment.

In the 6-month follow-up period, following IVTA injection, a total of 21 (21%) eyes, 11 of them with diabetic retinopathy and 10 with retinal vein occlusion, received treatment for elevated IOP. When the steroid dose was halved (2 mg) in the combined injection of IVTA/IVB only 3 eyes, that 2 of them with diabetic retinopathy and 1 of them with retinal vein occlusion, required treatment ($p=0.001$, Fisher's exact test).

On the other hand, none of the eyes in Group 2 showed an increase in IOP requiring treatment during the study period. After 6 months, the numbers of eyes still receiving medication in Group 1 and Group 3 were 17 (17%) and 1 (1.3%), respectively ($p<0.001$, Fisher's exact test). The onset of pressure elevation occurred mostly within a month in the IVTA injected group, while patients receiving IVTA/IVB experienced an acute IOP rise that was transient and normalized at follow-up periods (Graphic, Table 2).

During the study period all eyes received medical glaucoma treatment whenever required and no glaucoma surgery was performed. None of the eyes required hyperosmotic agents.

DISCUSSION

Steroid-induced ocular hypertension is a significant problem after intravitreal administration of steroids in posterior segment pathologies such as age-related macular degeneration, diabetic macular edema, retinal vein occlusion, and posterior uveitis.[6,7,15,16] IVTA-related IOP increase depends on glaucoma predisposition of the patient, follow-up time, corticosteroid dose applied, pre-injection ocular hypertension, and the number of repeated injections.[17,18] Steroids induce biochemical and ultrastructural changes in the trabecular meshwork and triamcinolone crystals accumulate in aqueous outflow pathways occluding the meshwork thereby resulting in elevated IOP.[19-20] Various studies reported 17% to 52% IOP elevation rates following IVTA injections.[6,21-23] In the current study, a significant relation was present between the triamcinolone acetonide dose and IOP elevation. After combined IVTA/IVB injection in which the steroid dose was half of the standard IVTA dose, the rate of IOP elevation decreased by 5-fold. None of the eyes injected with IVB developed high IOP levels requiring treatment. Thus the total rate of elevated IOP in the IVTA/IVB group may be attributed to the steroid content of the injection.

A considerable difference was also observed in the rate of medical treatment discontinuation upon a successful IOP control. In the IVTA group, of 21 eyes receiving glaucoma medication during the follow-up, only in 4 eyes could the treatment be discontinued. At the end of 6 months, 17 eyes still required glaucoma treatment. In the combined injection group, however, IOP elevation was mostly transient, allowing discontinuation of the medical therapy. The other significant finding of the study was the time when the rate of new onset IOP elevated eyes showed a peak. In the standard IVTA dose group the number of eyes with IOP elevation increased considerably until 1 month after the injection and did not change much thereafter, while in eyes with the reduced steroid dose the number of eyes with IOP elevation did not show a change until 1 month and the rate decreased after 1 month (Graphic). The incidence of the steroid-induced IOP elevation was observed to be highest at 1 month among Group 1 subjects, while an acute IOP rise was more common in Group 3.

Kosobucki et al., reported triamcinolone acetonide to be visualized in the vitreous cavity on ophthalmoscopic examination until 102 days in vitrectomized eyes and 191 days in non-vitrectomized eyes following 20 mg IVTA injection.[24] Jonas et al., on the other hand, demonstrated corticosteroids in humor aqueous after 18 months of 20 mg IVTA administration.[25] It is obvious that when the dose of the steroid increases the clearance of the drug from the eye gets slower; therefore higher doses of IVTA will have a longer effect due to a longer period to induce the changes in susceptible subjects. Discontinuation of the steroid is essential to control the IOP in steroid-induced ocular hypertension. In rare cases, however, elevated IOP may persist despite terminating the treatment with steroids.[26]

The duration of steroid therapy may influence the reversibility of the IOP elevation. Espildora et al., reported normalization in pressures in all cases of steroid induced glaucoma when the drug was used for less than 2 months, while the tension remained chronically elevated in all patients using the steroid for more than 2 years.[27] In the case of intravitreal use, a dose-dependent clearance of the steroid increases the importance of using the smallest amount of steroid to minimize the exposure time of the eye to the drug and therefore to minimize the permanent ultrastructural changes in the aqueous outflow pathways. IOP elevation in our study group was among the lowest range compared to the previous studies. The reason for that was primarily that the eyes with established glaucoma, suspected glaucoma, or ocular hypertension were all excluded from the study. The best way to decrease the occurrence of steroid-induced glaucoma is prevention by discrete selection of patients for steroid therapy. In the standard management of steroid-induced glaucoma besides treatment with topical or oral glaucoma medications, laser trabeculoplasty or surgery is applied in required cases.[28,29]

In our study, none of the eyes underwent glaucoma surgery for uncontrolled IOP. Although various studies reported satisfactory results using IVTA or IVB in the treatment of macular edema, 30-32 the best treatment modality remains to be determined. Some studies showed superior results after IVB injections and others after IVTA injections.[30-32] Recently, reports about the effect of combined IVTA/ IVB administration appeared in the literature.[33-35] When used together the additive effect of both agents seemed beneficial on macular edema management.[33-35] In addition, as shown in the current study, the combined use of the agents with lower steroid dose helped to decrease the common side effect of the intravitreal steroids.

Intravitreal triamcinolone administration, as a common treatment modality for macular edema, may cause elevation in IOP that in rare cases also requires a surgical approach. Our results demonstrated a relation between the steroid dose and IOP elevation. The incidence of steroid-induced ocular hypertension decreased significantly when the dose of the steroid was halved in the form of combined IVTA/IVB injection. IOP rise was highest at 1 month following IVTA injection, while patients receiving IVTA/IVB showed mostly an acute IOP increase that returned to normal levels by the end of 1 month. Patients receiving IVB on the other hand did not show any significant change during the study period. Dose reduction of the steroids obviously reduces their IOP elevating effect.

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