

# Immediate Intraocular Pressure Changes and Subconjunctival Reflux After Intravitreal Bevacizumab Injection: Comparison Between 27-Gauge and 30-Gauge Needle

## Intravitreal Bevacizumab Enjeksiyonu Sonrası Ani Göz İçi Basıncı Değişiklikleri ve Subkonjonktival Reflü: 27-Gauge ve 30-Gauge İğne Karşılaştırılması\*

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### ABSTRACT

**Purpose:** Intravitreal injections may cause intraocular pressure (IOP) elevation and subconjunctival reflux. In this study we aimed to investigate the effect of the bore size of the needles used for intravitreal bevacizumab (IVB) injections on acute IOP changes and subconjunctival reflux.

**Materials and Methods:** Data from 93 consecutive IVB injections were reviewed retrospectively. Eighty seven patients who underwent 2.5 mg/0.1 ml injection of IVB were enrolled in this study. The main outcome measures were the postinjectional IOP, IOP mean elevation rate and reflux grade. All measures were compared according to the bore size of the needles used (27-gauge versus 30-gauge).

**Results:** A significant elevation in IOP was observed immediately after injection in all eyes. The IOP elevation rate was greater in 30 gauge group when compared with 27-gauge group (Medians: 167% vs 83%, respectively, p=0.001). The reflux grade with 27-gauge needles was greater than that with 30-gauge needles. The medians of the reflux grade were 1 (0-3) (corresponding to a minimal reflux) and 0 (0-3) (corresponding to no reflux), respectively.

**Conclusion:** A higher IOP elevation is expected if a small-gauge needle is used for IVB injection. Clinicians should be cautious about bore size related IOP spikes, especially in eyes with already compromised perfusion status such as advanced glaucoma and macular ischemia.

**Key Words:** Intravitreal injection, bevacizumab, intraocular pressure, subconjunctival reflux.

### ÖZ

**Amaç:** Intravitreal enjeksiyonlar göz içi basıncı (GİB) artışına ve subkonjonktival reflüye neden olabilmektedir. Bu çalışmada intravitreal bevacizumab (IVB) için kullanılan iğnelerin iç çap boyutlarının ani GİB değişiklikleri ve subkonjonktival reflü üzerine olan etkisini incelemeyi amaçladık.

**Gereç ve Yöntemler:** Ardışık yapılan 93 IVB enjeksiyonun kayıtları retrospektif olarak incelenmiştir. Bu çalışmaya 2.5 mg/0.1 ml IVB enjeksiyonu yapılan 87 hasta dahil edilmiştir. Temel olarak değerlendirilen parametreler; enjeksiyon sonrası GİB, GİB ortalama artış oranı ve reflü derecesidir. Tüm ölçümler kullanılan iğne çap boyutlarına göre karşılaştırılmıştır (27-gauge ile 30 gauge).

**Bulgular:** Enjeksiyon sonrası tüm gözlerde ani olarak GİB'de anlamlı yükselme olduğu gözlemlendi. GİB artış oranı 27 gauge grubu ile karşılaştırıldığında 30 gauge grubunda daha yüksek idi (median değerler sırasıyla %83 ile %167, p=0,001). 27 gauge iğneler ile saptanan reflünün derecesi 30 gauge iğnelere göre daha fazlaydı. Ortanca reflü dereceleri sırasıyla 1 (0-3) (minimal reflü varlığı) ve 0 (0-3) (reflü yok) idi.

**Sonuç:** IVB enjeksiyonunda küçük çapta iğne kullanılır ise GİB'de yükselmenin daha fazla olması beklenmektedir. Klinisyenlerin iğne ucu ile ilişkili GİB artışları konusunda özellikle ileri glokom ve makuler iskemi gibi perfüzyonun sınırlı olduğu durumlarda daha dikkatli olmaları gerekmektedir.

**Anahtar Kelimeler:** Intravitreal enjeksiyon, bevacizumab, göz içi basıncı, subkonjonktival reflü.

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## INTRODUCTION

Intravitreal anti-vascular endothelial growth factor (VEGF) agents have become increasingly popular in the treatment of various retinal disorders. Before ranibizumab received FDA approval, ophthalmologists had started to use bevacizumab (Avastin, Genentech, Inc), a recombinant humanized full-length anti-VEGF antibody, which was originally licensed for colorectal carcinoma treatment. Due to its relatively lower cost, intravitreal bevacizumab (IVB) injection has been widely used in recent years for the treatment of exudative age-related macular degeneration (AMD), neovascular glaucoma and macular edema resulting from diabetic retinopathy (DRP) and retinal vein occlusions (RVO).<sup>1,2</sup>

Despite the therapeutic benefits of this agent, ocular complications such as endophthalmitis, uveitis, retinal detachment or tear, vitreous hemorrhage, and retinal vascular events related to injection have been reported.<sup>3</sup> It is also well described that administration of intravitreal therapy may cause immediate or sustained intraocular pressure (IOP) elevation.<sup>4-7</sup> However, little is known about the probable factors such as ocular anatomical features, the volume of injected fluid, amount of reflux after injection, size of the injecting needle, injection modalities (scleral tunnel or straight injection) and whether the injection site is tamponed or not after injection. All these factors may play a role in the immediate IOP elevation after intravitreal injection. A correlation between the introduced fluid volume into the vitreous cavity and immediate rise in the IOP would be expected; however, the relationship between IOP spike and the bore size of the needles used has not been studied.

Reflux and subconjunctival bleb formation are other possible events following intravitreal injection.<sup>8,9</sup> Boon et al.,<sup>10</sup> suggested that reflux may decrease the amount of effectively injected drug volume, which can be significant as the volume of drug injected is quite small (0.05 to 0.09 ml). They designed a study to determine the composition of the reflux fluid by adding 1% sodium fluorescein to injected bevacizumab. They found that in 10 patients (35.5%) the reflux fluid was clear (liquefied vitreous), in two patients (7%) there were traces of fluorescein and in a single patient (3.5%) the reflux was almost entirely fluorescein-labeled drug. However, whether needle bore size affects the incidence and amount of reflux or not has not been investigated.

Therefore, in this study we aimed to investigate the acute IOP changes and subconjunctival reflux after intravitreal bevacizumab injection, and the effect of needle bore-size on these parameters.

## MATERIAL AND METHODS

Data from 93 consecutive intravitreal bevacizumab injections (2.5 mg/0.1 ml) of 87 patients -with either 27 or 30 gauge needles- were analyzed. The indications for anti-VEGF injection were exudative AMD, DME, RVO, central serous chorioretinopathy (CSCR) and other retinal diseases. Patients with uncontrolled glaucoma, high myopia or hypermetropia, and a history of prior vitrectomy were excluded.

All injections were performed by the same physician (HAT) in the operating room with a uniform protocol. All patients were positioned supine and IOP (baseline IOP) was measured with Tono-Pen (Tono-Pen AVIA® Applanation Tonometer, Reichert Technologies, USA) under topical anesthesia. The eyelids and periorbital skin were sterilized with 10% betadine. The ocular surface including eye lashes and conjunctiva were sterilized with 5% betadine for 3 minutes. A lid speculum was placed and the injection was performed through the superiotemporal pars plana (3.5 mm posterior to the limbus) with directly straight needle insertion. After the removal of the needle, a cotton tipped applicator was softly placed on the incision site for 3-5 seconds, and the surgeon inspected the eye for subconjunctival reflux. The amount of reflux was estimated visually and graded into four categories: no reflux (0), minimal reflux (1), moderate reflux (2) and marked reflux (3) as described by Lorenz et al.,<sup>11</sup> Minimal reflux was estimated to be less than one third of the injected volume, moderate reflux corresponded to a regurgitation between one third and two thirds of the injected substance, and marked reflux was estimated to be more than two thirds of the injected volume. IOP was measured by Tono-Pen immediately after the cotton tip applicator was withdrawn (Postinjection IOP). Central retinal artery perfusion was approved by confirming that the visual acuity was hand motion or better.

The statistical analysis was performed by using the SPSS software version 16.0 (SPSS Inc, Chicago, Illinois, USA). Kolmogorov-Smirnov test was used to evaluate the normality of the distribution of the data. Reflux grading, IOP values and IOP elevation rates were given as median (and minimum-maximum), demographic and clinic categorical variables (gender, pre-existing glaucoma and lens status) were shown as rates, and age was shown as mean  $\pm$  standard deviation. IOP elevation rate was described as (postinjection IOP - preinjection IOP)  $\times$  100. Gender, pre-existing glaucoma and lens status were examined using the Chi-square test with Fisher-Freeman-Halton Exact Test and Yates' Continuity Correction. Age was analyzed with the t test. The differences between baseline IOP values (27 vs 30-gauge) and IOP elevation rates of groups (presence of glaucoma and

lens status) were compared with Mann-Whitney U test. The baseline and postinjection IOP values of 27 and 30 gauge groups were compared with Wilcoxon Rank test. A multivariable logistic regression analysis was used to investigate the influence of cataract and glaucoma on increased IOP and subconjunctival reflux. A p value of less than 0.05 was considered statistically significant.

## RESULTS

We evaluated 93 consecutive 2.5 mg/0.1 ml intravitreal bevacizumab injections to 89 eyes of 87 patients, who received one or more injections using either a 27 or 30 gauge needle. Forty five (48%) injections were performed using 27-gauge needles and 48 injections (52%) were performed using 30 gauge needles. Both groups were similar in terms of age, sex, indication for bevacizumab, history of glaucoma and cataract surgery ( $p=0.37$ ,  $p=0.976$ ,  $p=0.621$ ,  $p=0.525$ ,  $p=0.399$ , respectively). The most common reason for IVB injection was DRP (47%) in the 27-gauge group and AMD (44%) in the 30-gauge group (Table 1).

Median baseline IOP before injection was 16 (6-33) mmHg in the 27-gauge group and 14 (5-26) mmHg in the 30-gauge group ( $p=0.094$ ). A significant elevation in IOP was observed immediately after injection in both groups, with a median postinjection IOP of 31 (10-55) mmHg in the 27 gauge group, and 37 mmHg (11-55) in the 30 gauge group ( $p<0.001$  for both). The

incidence of a postinjection IOP of 30 mmHg or higher was 77% in the 30 gauge group and 55% in 27 gauge group ( $p=0.027$ ) (Table 2). IOP elevation rate was significantly greater in the 30 gauge group than in the 27-gauge group, with median values of 167% (range: 27 to 816%) and 83% (range: 22 to 816%), respectively ( $p=0.001$ ). Multivariable logistic regression analyses showed that IOP increase was independent of sex ( $p=0.767$ ) and age ( $p=0.538$ ).

Eleven patients had preexisting primary open angle glaucoma (PAAG). Among these patients, 4 injections were performed with 27 gauge needles and 7 with 30 gauge needles. There was no significant difference in IOP elevation rate between the eyes with and without glaucoma ( $p=0.535$ ). IOP elevation rate was also similar in pseudophakic and phakic patients ( $p=0.295$ ).

Reflux was noted in %64 of the 27 gauge and %47 of the 30 gauge group ( $p=0.108$ ). The reflux with 27 gauge needles was greater than that with 30 gauge needles; the medians of reflux grade were 1 (0-3) (corresponding to a minimal reflux) and 0 (0-3) (corresponding to no reflux), respectively (Table 2). However, this difference was statistically nonsignificant ( $p=0.127$ ). Multivariable logistic regression analyzes showed that reflux grade was also independent of sex ( $p=0.771$ ), age ( $p=0.395$ ), presence of glaucoma ( $p=0.740$ ) and lens status ( $p=0.839$ ). However, a significant negative correlation between reflux grade and IOP elevation was noted ( $r= -0.673$ ,  $p<0.001$ ).

**Table 1:** Demographics and baseline characteristics of patients.

Data	27-gauge n, (%)	30-gauge n, (%)	p value
Age (years)	67.8±9.3	65.7±12.4	$p=0.37$
Gender			
Male	28 (66)	31 (68)	$p=1.000$
Female	14 (34)	14 (32)	
Diagnosis			
AMD	15 (36)	20 (44)	$p=0.111$
DRP	20 (47)	13 (29)	
BRVO	3 (7)	4 (9)	
CSC	0	5 (11)	
Others	4 (10)	3 (7)	
Glaucoma			
(+)	4 (10)	7 (15.5)	$p=0.601$
(-)	38 (90)	38 (84.5)	
Lens status			
Phakic	32 (76)	30 (67)	$p=0.457$
Pseudophakic	10 (24)	15 (33)	
Total	42	45	

AMD; Age-related Macular Degeneration, DRP Diabetic Retinopathy, RVO; Retinal Vein Occlusion, CSC; Central Serous Chorioretinopathy.

## DISCUSSION

Intravitreal injection of anti-VEGF agents has become an increasingly common intervention in the treatment of retinal diseases. IOP spike is a well-known event after all intravitreal injections. The retinal dysfunction and optic disc changes related to IOP spikes, which may be particularly important in patients receiving recurrent intravitreal injections and patients with glaucoma, has not been well defined. He et al. stated that repeated increases in IOP could cause cumulative dysfunction in the internal retinal layers of rats.<sup>12</sup> Intravitreal injections of dif-

**Table 2:** Comparison of reflux grade frequency among 27- and 30-gauge group.

Data	27-gauge n, (%)	30-gauge n, (%)	
Reflux grade			
0	16 (36)	25 (52)	$p=0.127$
1	16 (36)	14 (29)	
2	6 (13)	5 (11)	
3	7 (15)	4 (8)	
Total	45	48	

ferent anti-VEGF agents consist of different volumes and may be administered with different needle bore sizes. In the current study, we investigated the IOP changes and reflux grade immediately after the IVB injection on the basis of needle bore size.

Our investigation showed that a 0.1 ml IVB injection causes a significant IOP elevation. The IOP was higher than 30 mm Hg in %66 of all injections, and more than 35% of the injections resulted in an IOP spike above 50 mm Hg. A previous study by Kim et al.,<sup>13</sup> with different doses (0.05, 0.09, 0.1) of anti-VEGF agent and different needle bore sizes (27, 30, 32 gauge) has also reported similar changes. They noted the numbers for IOP greater than 30 and 50 mmHg as %79 and %35, respectively. In our study, patients with an IOP above 50 mmHg were more frequent than in the previous studies. Benz et al. carried out a study on patients without glaucoma, and reported an immediate IOP elevation after 0.1 ml intravitreal triamcinolone acetonide injection with a 27 gauge needle.<sup>11</sup> Furthermore, we found that the rate of IOP elevation immediately after the injection was significantly higher in the 30-gauge group when compared to the 27 gauge group (167% vs 83%). The incidence of IOP above 30 mmHg was also higher with 30 gauge bore size (77% vs 55% with 27 gauge). A previous study reported these values for 32, 30 and 27 gauge needle as 94%, 84% and 47%, respectively.<sup>13</sup>

The second aim of our study was to evaluate the grade of subconjunctival reflux. We observed that reflux appeared less frequently and with less amount with 30 gauge needles, however the difference was statistically non-significant. Our results regarding the incidence and grade of vitreous reflux are mostly similar to those of previous studies. Boon et al.<sup>10</sup> observed that 46% of patients had reflux after IVB injection, whereas in our current study, the reflux rate was 55% for all injections. Various factors such as volume, injection speed, length and direction of the incision, lens status, preinjectional and postinjectional IOP and needle bore size may have an influence on the reflux grade.<sup>14,15</sup> These parameters were similar in the 2 groups in our study. Our results support the hypothesis that smaller-bore needles cause less reflux through a smaller injection orifice, whereas larger-bore needles allow more reflux. Kim et al.<sup>13</sup> also reported that the incidence of IOP elevation immediately after injection was significantly higher with smaller bore needle size, despite the smaller volume injected with those needles.

A significant negative correlation between reflux grade and IOP elevation was observed in our study. In the absence of reflux, a significantly higher IOP

spike can be expected due to a larger volume administered to a closed system.<sup>15</sup> Increased volume of subconjunctival reflux may diminish the effective amount of drug delivered into the eye. Anterior chamber paracentesis may be a suitable option with 0.1 ml intravitreal injections, especially while using 30 gauge needles.

The effect of prior glaucoma on IOP elevation after intravitreal injections remains unclear. Some authors found glaucoma a significant variable, whereas others found that it was not.<sup>5,16</sup> In our study, the presence of glaucoma and the status of the lens (pseudophakic vs phakic) had no influence on IOP elevation rate and reflux grade. Lorenz et al.,<sup>11</sup> also reported a study determining the grade of reflux after injection of 0.1 ml IVB and found that the lens status had no effect on subconjunctival reflux.

The volume we used is twice the volume used by some other clinicians (2.5 mg/0.1 ml vs 1.25 mg/0.05 ml). A greater IOP rise is expected with such a high volume, irrespective of the needle gauge. Such<sup>17,18</sup> an acute elevation has been reported as a potential risk for patients with intraocular circulatory diseases. A smaller IOP spike may be expected with injection of 0.05 ml of drug. However,<sup>16,19</sup> none of our patients needed a paracentesis, although a paracentesis is recommended by some authors when a volume of 0.1 ml is used.

To the best of our knowledge, there is only one study in the literature, which is also retrospective, reporting both IOP changes and reflux grade after intravitreal administration of bevacizumab. Our study includes a reasonable number of patient from our daily practice with minimal exclusion criteria, hence making it relevant to clinical practice. However, the most important limitation of this study is its non-randomized and retrospective design. Another potential limitation may be the lack of the refractive data of the patients, as hyperopic eyes may have higher IOP elevation as a result of their overall smaller size. Additionally, the quantification of vitreous reflux is based on subjective assessment.

In conclusion, a higher IOP elevation is expected if a small-gauge needle, which does not allow for much reflux, is used for IVB injection. Eyes with already compromised perfusion status such as those with advanced glaucoma or macular ischemia should be monitored more closely. The long-term consequences of IOP spikes related to intravitreal injections is remains mostly unknown and may be worthwhile to investigate as most patients require multiple injections in the course of their treatments.

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