• Clinical Research •

Effect of different lens status on intraocular pressure elevation in patients treated with anti-vascular endothelial growth factor injections

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Abstract

● **AIM:** To assess the effect of lens status on sustained intraocular pressure (IOP) elevation in patients treated intravitreally with anti-vascular endothelial growth factor (VEGF) agents.

● **METHODS:** Data were retrospectively collected for all patients treated with intravitreal injections of anti-VEGF medication at a tertiary medical center in July 2015. Findings were analyzed by lens status during 6 months' follow-up. The main outcome measure was a sustained increase in IOP (≥21 mm Hg or change of ≥6 mm Hg from baseline on ≥2 consecutive visits, or addition of a new IOP-lowering medication during follow-up).

● **RESULTS:** A total of 119 eyes of 100 patients met the study criteria: 40 phakic, 40 pseudophakic, and 39 pseudophakic after Nd:YAG capsulotomy. The rate of sustained IOP elevation was significantly higher in the post-capsulotomy group (23.1%) than in the phakic/pseudophakic groups (8.1%; *P*=0.032), with no statistically significant differences among the 3 groups in mean number of injections, either total (*P*=0.82) or by type of anti-VEGF mediation (bevacizumab: *P*=0.19; ranibizumab: *P*=0.13), or mean follow-up time (*P*=0.70).

● **CONCLUSION:** Nd:YAG capsulotomy appears to be a risk factor for sustained IOP elevation in patients receiving intravitreal anti-VEGF injections. This finding has important implications given the growing use of anti-VEGF treatment and the irreversible effects of elevated IOP.

● **KEYWORDS:** anti-VEGF injections; cataract surgery; intraocular pressure; Nd:YAG capsulotomy
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INTRODUCTION

The overexpression of vascular endothelial growth factor (VEGF) has been identified as a cornerstone of the pathologic process leading to vascular leakage and neovascularization. Accordingly, intravitreal injection of anti-VEGF inhibitors is the main mode of treatment for exudative age-related macular degeneration and other retinal vascular diseases characterized by macular edema and neovascularization including diabetic macular edema and retinal vein occlusion[1-3]. Several anti-VEGF agents are currently available: bevacizumab (Avastin; Genentech, Inc., South San Francisco, CA, USA), a recombinant full-length humanized monoclonal antibody; ranibizumab (Lucentis; Genentech), a humanized monoclonal antibody fragment; and aflibercept (Eylea; Regeneron Pharmaceuticals, Tarrytown, NY, USA), a soluble decoy receptor fusion protein[4-6]. The drugs have a favorable safety profile, with only rare reports of adverse vision-threatening events such as endophthalmitis, vitreous hemorrhage, retinal detachment, and retinal tears, despite their widespread use[7].

A known immediate effect of any intravitreal injection is a transient elevation of intraocular pressure (IOP). In the majority of cases, the spikes normalize within 30min without further intervention[8-9]. However, the occurrence of sustained ocular hypertension in this setting is controversial, with only sparse reports in the recent literature. Both the MARINA trial (anti-VEGF antibody ranibizumab in the treatment of neovascular age-related macular degeneration) and the ANCHOR Trial (ranibizumab versus verteporfin for neovascular age-related macular degeneration), which investigated the effect of ranibizumab treatment in patients with minimal classic or occult neovascularization, reported an absence of long-term effects of monthly injections on mean IOP[10]. Similar findings were noted in a phase III study on the use of aflibercept for neovascular age-related macular degeneration[6]. Wehrli *et al*[11]

conducted a large retrospective study of 302 eyes treated with bevacizumab and/or ranibizumab, with 226 untreated fellow eyes serving as the control group. No between-group difference was noted in the rate of delayed ocular hypertension.

By contrast, several reports in recent years have provided evidence that IOP elevation may be a long-term adverse effect of anti-VEGF drugs[12-15]. Among them is a post-hoc data analysis of the MARINA and ANCHOR trials comparing the anti-VEGF-treated eyes with eyes treated with sham injections or photodynamic therapy. The authors found that the study group had a statistically significant increase in the number of eyes with an elevation of 6 mm Hg or more in IOP from baseline or an IOP equal to or greater than 25 mm Hg on at least 2 consecutive visits[16].

The risk factors contributing to the sustained IOP elevation remain unclear owing to differences among the studies in the number of injections[11,13-15] and type of anti-VEGF agent used[13-14], and the inclusion of patients with pre-existing glaucoma[14-15,17] or prior use of topical or intravitreal steroids[12,15,17].

Besides the medication, there is evidence pointing to the contribution of the cataract extraction itself[18], alone or with the performance of neodymium doped yttrium aluminum garnet (Nd:YAG) capsulotomy[19], and Nd:YAG capsulotomy itself[20]. The present study sought to shed further light on this issue. The aim of the study was to assess the effect of lens status, in particular after Nd:YAG capsulotomy, on sustained IOP elevation.

SUBJECTS AND METHODS

Ethical Approval The study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of Rabin Medical Center. Informed consent was waived due to the retrospective nature of the study.

The database of the Retina Clinic of Rabin Medical Center, a tertiary university-affiliated hospital, was retrospectively reviewed for all patients with retinal vascular disease who were treated with an intravitreal injection of anti-VEGF agent in July 2015. It is our departmental policy in these cases to start with bevacizumab (1.25 mg/0.05 mL) and switch to ranibizumab (0.5 mg/0.05 mL) on the basis of the patient response. Therefore, none of the patients received only ranibizumab. We included only patients for whom the pre-injection (baseline) IOP value and all IOP values during a minimum of 6 months' follow-up from the first injection were available. Exclusion criteria were a change in lens status during follow-up (cataract surgery or Nd:YAG capsulotomy), intraocular lens implantation outside the bag, receipt of intravitreal corticosteroid treatment during follow-up, and any intraocular surgery other than cataract surgery prior to or during follow-up, with the exception of glaucoma surgery (trabeculectomy, glaucoma drainage devices or laser trabeculoplasty) during follow-up.

The following data were collected from the medical files: patient age and sex, reason for treatment, number of anti-VEGF injections, type of injection, follow-up time (defined as the time from the first injection until the last follow-up), lens status prior to and throughout treatment, IOP prior to treatment and at every follow-up visit, diagnosis of glaucoma, and medications for glaucoma before anti-VEGF injection and throughout follow-up.

IOP was measured by Goldmann applanation tonometry. Measurements were performed before every injection and at every office visit.

The main outcome measure was a sustained increase in IOP, defined as IOP≥21 mm Hg or a change from baseline of ≥6 mm Hg, recorded on at least 2 consecutive visits, or the addition of a new IOP-lowering medication after the start of anti-VEGF treatment for 45d or more, during follow-up. These criteria were selected to rule out normal IOP fluctuations and represent a clinically significant IOP elevation.

Continuous variables are presented as means and standard deviation, and nominal variables, as number and percentage. Continuous data were checked for normality (Shapiro-Wilk test). One-way analysis of variance (ANOVA) with Bonferroni post hoc test or the Kruskal-Wallis nonparametric test was used to compare variables by lens status. Unpaired Student's *t*-test or the nonparametric Mann-Whitney test was used to compare variables by the presence or absence of sustained IOP elevation. A P value of <0.05 was considered statistically significant. All statistical analyses were performed using the SPSS v. 3.

RESULTS

A total of 119 eyes of 100 patients met the study criteria. The patient characteristics and clinical data are shown in Table 1.

Division by lens status during follow-up yielded 3 groups: 40 phakic eyes, 40 pseudophakic eyes, and 39 pseudophakic eyes following Nd:YAG capsulotomy. There was no significant difference among the groups in the rate of pre-treatment glaucoma (phakic, 7.5%; pseudophakic, 2.5%; post-capsulotomy, 12.8%; P=0.22) or mean pre-treatment IOP [14.6±2.3 mm Hg (range 10-20), 14.2±2.1 mm Hg (10-18) and 14.3±2.6 mm Hg (10-22), respectively; P=0.76]. All patients with pre-treatment glaucoma had primary open angle glaucoma, were followed by an ophthalmologist for their glaucoma prior to their retinal disease and were at their target pressures under topical treatment (2.11±1.27 medications). There was also no difference among the groups in the diseases for which they were treated (P=0.13). Patients with phakic eyes were significantly younger than patients with pseudophakic eyes (73.2±14.5, 82.6±7.9, and 82.9±8.5y, respectively; P<0.001).

The association of lens status with IOP elevation is shown in Table 2.

Table 1 Baseline demographic and clinical characteristics of patients treated with anti-VEGF agents, by lens status *n* (%)

Characteristics	Phakic eyes	Pseudophakic eyes	Post-capsulotomy eyes	*P*
No. of eyes	40	40	39	
Males	21 (52.5)	8 (20)	14 (35.9)	0.01[a]
Age (y)	73.2±14.5	82.6±7.9	82.9±8.5	<0.001[a]
Laterality (right eye)	18 (45)	15 (37.5)	19 (48.7)	0.59
Diagnosis				
Exudative AMD	25 (62.5)	31 (77.5)	27 (69.2)	
Diabetic macular edema	13 (32.5)	6 (15)	5 (12.8)	0.13
Others[b]	2 (5)	3 (7.5)	7 (18)	
Number of injections				
Bevacizumab	10.2±3.5	9.9±4.0	8.7±4.3	0.19
Ranibizumab	2.0±3.1	1.8±3.1	3.3±4.3	0.13
Total	12.2±3.2	11.7±3.7	11.9±4.5	0.82
Follow-up (d)	701.3±80.1	710.4±100.0	735.7±301.9	0.70
Pretreatment glaucoma	3 (7.5)	1 (2.5)	5 (12.8)	0.22

AMD: Age-related macular degeneration. [a]Statistically significant (post-capsulotomy *vs* phakic/pseudophakic); [b]Others indication for anti-VEGF treatment included myopic choroidal neovascularization, peripapillary choroidal neovascularization, central retinal vein occlusion and branch retinal vein occlusion.

Table 2 Sustained IOP elevation criteria by study groups *n* (%)

Criterion	Phakic eyes	Pseudophakic eyes	Post-capsulotomy eyes	*P*
≥6 mm Hg increase on 2 consecutive visits	3 (7.5)	3 (7.5)	5 (12.8)	0.64
		6 (7.5)	5 (12.8)	0.35
≥21 mm Hg on 2 consecutive visits	0	0	0	
New IOP lowering medication	0	2 (5)	4 (10.3)	0.11
		2 (2.5)	4 (10.3)	0.09
Total	3 (7.5)	4 (10)	9 (23.1)	0.09
		7 (8.8)	9 (23.1)	0.03[a]

IOP: Intraocular pressure. [a]*P*<0.05.

The overall rate of sustained IOP elevation was 13.4%. The rate was significantly higher in the post-capsulotomy group than in the phakic+pseudophakic groups (23.1% *vs* 8.8%; *P*=0.03). There were no statistically significant differences among the 3 groups (Table 1) in mean number of injections, either total (phakic: 12.2±3.2; pseudophakic: 11.7±3.7; post-capsulotomy: 11.9±4.5; *P*=0.82) or by type of anti-VEGF medication (bevacizumab, 10.2±3.5, 9.9±4.0 and 8.7±4.3, respectively, *P*=0.19; ranibizumab, 2.0±3.1, 1.8±3.1 and 3.3±4.3, respectively, *P*=0.13). Mean follow-up time was similar in all 3 groups (701.3±80.1, 710.4±100.0, and 735.7±301.9d, respectively; *P*=0.70) as was the interval between the beginning of treatment and IOP elevation (247.0±158.0, 251.0±11.7 and 445.1±259.1, *P*=0.23). IOP in the three groups ranged between 8-23 mm Hg in the phakic group, 10-30 mm Hg in the pseudophakic group and 10-28 mm Hg in the post-capsulotomy group.

Sustained IOP elevation rate remained significantly higher in the post-capsulotomy group following further analysis of the data using multivariable logistic regression that included total number on injections and pre-existing glaucoma (*P*=0.047). When separately analyzing bevacizumab and ranibizumab, significance remained with the former while there was a trend toward significance with the latter (*P*=0.045 and 0.073, respectively).

Two patients with pre-treatment glaucoma had sustained IOP elevation (12.5% of all patients with sustained IOP elevation and 22.2% of patients with pre-treatment glaucoma), both were in the post-capsulotomy group. Their initial IOP elevation occurred 10 and 13mo after beginning treatments and after receiving 9 and 10 injections, respectively. Their IOP was stable until that point and restabilized after adding topical treatments (two and one IOP lowering drops, respectively).

Comparison of the patients with and without a sustained IOP elevation (Table 3) revealed that the group with a consistently high IOP had a significantly lower baseline IOP (13.3 mm Hg *vs* 14.5 mm Hg, *P*=0.04). However, there were no between-group differences in the number of injections, either total (11.8±3.9 *vs* 12.9±3.4; *P*=0.3) or by type of medication (bevacizumab: 9.1±4.1 *vs* 9.7±4.0; *P*=0.56; ranibizumab:

Table 3 Comparison between patients with sustained IOP elevation and patients without sustained IOP elevation *n* (%)

Characteristics	Sustained IOP elevation	No IOP elevation	*P*
Eyes	16	103	
Males	6 (37.5)	37 (35.9)	0.90
Age (y)	81.3±7.6	79.3±12.1	0.53
No. of injections			
Bevacizumab	9.1±4.1	9.7±4.0	0.56
Ranibizumab	3.8±4.5	2.1±3.4	0.16
Total	11.8±3.9	12.9±3.4	0.30
Baseline IOP (mm Hg)	13.3±2.7	14.5±2.2	0.04[a]
Diagnosis			
Exudative AMD	10 (62.5)	73 (70.9)	
Diabetic macular edema	3 (18.8)	21 (20.4)	0.46
Others	3 (18.8)	9 (8.7)	
Follow-up (d)	778.8±170.0	705.8±188.4	0.15
Pretreatment glaucoma	2 (12.5)	7 (6.8)	0.42

AMD: Age-related macular degeneration; IOP: Intraocular pressure. [a]*P*<0.05.

3.8±4.5 *vs* 2.1±3.4; *P*=0.16), or in mean follow-up time (778.8±170.0 *vs* 705.8±188.4d; *P*=0.15).

DISCUSSION

The present study suggests that Nd:YAG capsulotomy is a risk factor for sustained IOP elevation in patients treated with anti-VEGF injections. This finding in important given the increasing use of anti-VEGF injections and the potentially irreversible damage caused by elevated IOP.

Several leading theories have been proposed to explain the mechanism underlying long-term IOP elevation after anti-VEGF injection. Some authors suggested that microparticles from the medication's packaging or delivery equipment may obstruct the trabecular meshwork. This assumption is based on reports of a different aggregate high-molecular-weight protein concentration in repackaged samples of bevacizumab and a higher prevalence of sustained IOP elevations in patients attending centers using repackaged bevacizumab than in patients treated in centers receiving bevacizumab in its original package[14,19].

It is also possible that the high-molecular-weight drugs themselves, especially bevacizumab (MW 150 kDa; ranibizumab, 48 kDa), obstruct the outflow channels. Support for this assumption was provided by findings of a higher prevalence of sustained elevated IOP in studies of patients receiving bevacizumab[12]. Moreover, in a recent experimental study, bevacizumab was found in the trabecular meshwork and Schlemm's canal after injection into a rat model[21].

A third theory suggests that recurrent episodes of transient post-injection IOP elevation chronically damage the aqueous outflow channels, eventually causing sustained IOP elevation[22]. Alternatively, inflammation, whether recurrent inflammation, post- injection subclinical inflammation, or chronic drug-induced trabeculitis or uveitis, may induce scar formation and fibroblast proliferation which gradually obstruct aqueous outflow[9,23].

Although cataract surgery is generally thought to lower IOP to some degree[18], in the setting of intraocular anti-VEGF injections, lens extraction and, especially, opening of the posterior capsule during Nd:YAG capsulotomy, may promote the introduction of the injected proteins and molecules into the trabecular meshwork, thereby increasing IOP[19]. Supporting evidence to this theory could be drawn from several animal studies showing increased clearance of bevacizumab and ranibizumab after lensectomy, vitrectomy or both. The improved clearance is attributed, at least in part and specifically in the aphakic eyes, to increased role of the trabecular meshwork[24-26]. It is possible that posterior capsulotomy increases the evacuation through the trabecular meshwork in a similar manner, which in turn increases the risk for sustained elevated IOP. Our finding of higher prevalence of increased IOP in patients after Nd:YAG capsulotomy supports this assumption. Interestingly, if increased clearance does exist after posterior capsulotomy, this may be an indication for more frequent anti-VEGF injections in these patients. Further studies are needed to shed light on this matter. Two previous studies focused on the effect of lens status on sustained IOP elevation. In the first, Hoang *et al*[15] reported no association between these factors. However, they included only the final lens status at the last injection in the analysis. In a subsequent study, the same group found, in accordance with our results, that phakic lenses are apparently protective against sustained IOP elevation. Both of the earlier studies, however, by contrast to ours, included only a minimal number of patients who had undergone Nd:YAG capsulotomy (3.9% and 6%, respectively). The 13.4% total incidence of a sustained increase in IOP in the present study was higher than reported by Bakri *et al*[16] on post hoc analysis of the ANCHOR and MARINA trials (5.4% for 0.3 mg ranibizumab and 4.5% for 0.5 mg ranibizumab), and higher than in the studies of Hoang *et al*[15,17] (7.2% and 11.6%), and Good *et al*[14] (6%). The discrepancy may be attributable to our high percentage of post-capsulotomy patients. The high number of bevacizumab injections may also have played a role, as bevacizumab has been found to be a risk factor for sustained IOP elevation[14]. Bevacizumab was not used at all in the ANCHOR and MARINA trials, and was used in only a relatively low percentage of eyes in the studies of Hoang *et al*[15,17] (34.1% and 32.4%) and Good *et al*[14] (55.3%). The incidence of increased IOP in the post-capsulotomy group in our study is higher than attributed to the procedure in the literature (23.1% *vs* 1%-6%, respectively)[20,27-28], possibly

related to the role of anti-VEGF injections in this pathology.

The present study did not identify other major risk factors for sustained IOP elevation. Hoang *et al*[15,17] found total number of anti-VEGF injections to be a risk factor, but their patients received a much higher mean number of injections (20.8 and 21.1, respectively) than ours (11.9). Good *et al*[14] noted an association of pre-existing glaucoma with a high frequency of sustained IOP elevation (33%). In our study, the number of patients with pre-existing glaucoma (n=9) may have been too small to achieve statistical significance, although a relatively high percentage of the patients with sustained IOP elevation had a pretreatment diagnosis of glaucoma (12.5%). This is certainly an important direction for future research. The lack of a difference in the rate of IOP elevation by type of anti-VEGF agent in our study may be explained by our departmental policy of starting all patients on bevacizumab such that none received only ranibizumab, making it difficult to differentiate the individual effect of the two drugs.

The fact that capsulotomy did not remain a significant risk factor following multivariable analysis using number of ranibizumab injections could result from the smaller size of the molecule. Potentially this enables easier diffusion of the molecule to the anterior chamber even without the opening in the posterior capsule and therefore eliminates its effect.

The patients with a sustained IOP elevation had a lower baseline IOP (13.3 mm Hg) than the other patients (14.5 mm Hg; P=0.04). This finding, although statistically significant, does not seem to have any clinical importance owing to the small difference between the groups. Patients with phakic eyes were significantly younger than patients with pseudophakic eyes, in line with the progression of cataract over the years and the need for cataract-removal surgery at older age.

This study has several limitations. Our sample size was limited, future prospective multi-center studies are needed for the evaluation of this important subject.

Excluding patients whose baseline or follow-up IOP measurements were not available could have created a selection bias assuming these data would not be missing in patients at risk for increased IOP. This may explain the relatively high percentage of patients with pre-existing glaucoma found to have sustained IOP elevations. However, since it is our policy to always measure and document the IOPs, this phenomenon is probably marginal resulting from inattention and was spread evenly between the groups.

As a result of the retrospective nature of this study, the effect of the time frame between the cataract surgery, Nd:YAG capsulotomy and IOP elevation, or Nd:YAG capsulotomy specifications (energy, spot size, number of shots) and IOP elevation could not be assessed. This information is not detailed in most patients' charts. Evaluating these data in future studies could add valuable information.

Another drawback was the higher prevalence of pretreatment glaucoma in the post capsulotomy group. This could have potentially confounded the outcomes of the study, especially since 12.5% of the sustained IOP elevation group did have pre-existing glaucoma. However, since these differences did not reach statistical significance, neither in the 3 study groups nor between the patients with and without sustained IOP elevation, and since the absolute numbers and overall prevalence of pretreatment glaucoma patients were not high, we believe their effect on the results was minimal at most. The effect of pre-existing glaucoma combined with lens status could also be an interesting direction for research.

In conclusion, this study suggests that Nd:YAG capsulotomy is a risk factor for a sustained elevation in IOP in patients treated with anti-VEGF injections. This finding may have clinical implications when capsulotomy is being considered in patients under anti-VEGF treatment. It supports the recommendation for routine monitoring of IOP levels in all patients treated with anti-VEGF drugs, and particularly, patients after capsulotomy.

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