Effect of Prophylactic Intraocular Pressure-Lowering Medication on Intraocular Pressure Spikes After Intravitreal Injections

Max P. C. Frenkel; Shamim A. Haji, MD; Ronald E. P. Frenkel, MD

Objective: To determine if prophylactic use of intraocular pressure (IOP)-lowering medication is effective in reducing the IOP spikes after intravitreal injections of pegaptanib, bevacizumab, and ranibizumab.

Methods: Seventy-one patients with exudative age-related macular degeneration received intravitreal injections of 1 of 3 anti–vascular endothelial growth factor medications: 30 patients received pegaptanib (0.09 mL), 47 patients received bevacizumab (0.05 mL), and 42 patients received ranibizumab (0.05 mL). Intraocular pressure–lowering medication, 1 hour prior to the injection, was used 63%, 74%, and 66% of the time in eyes that received pegaptanib, ranibizumab, and bevacizumab, respectively. Intraocular pressure was measured prior to injection, within 1 minute after injection, and every 5 to 10 minutes until the pressure was reduced to a safe level.

Results: All 3 intravitreal injections caused significant initial IOP spikes (mean [SD] IOP of 38.5 [11.56] mm Hg in the pegaptanib group, 37.75 [8.36] mm Hg in the ranibizumab group, and 34.88 [10.45] mm Hg in the bevacizumab group). The IOP reduced to less than 30 mm Hg in all 3 groups within 20 minutes. Prophylactic medication did not prevent postinjection IOP spikes. Patients with and without glaucoma showed a similar rate of IOP normalization over time in all 3 groups.

Conclusion: Intraocular pressure spikes after intravitreal injection of pegaptanib, ranibizumab, and bevacizumab are common and in most cases transient. Routine prophylactic use of IOP-lowering medications is essentially ineffective in preventing IOP spikes after intravitreal injection of pegaptanib, ranibizumab, and bevacizumab and therefore not necessary before the injection.

Arch Ophthalmol. 2010;128(12):1523-1527

AGE-RELATED MACULAR DEGENERATION (AMD) is a leading cause of severe irreversible visual loss in developed countries. Most of the severe vision loss results from the neovascular or exudative form of AMD. Intravitreal injection of various anti–vascular endothelial growth factor (VEGF) drugs to treat the neovascular or exudative form of AMD has gained immense popularity around the world. Bevacizumab (Avastin), ranibizumab (Lucentis), and pegaptanib (Macugen) are among the most common anti-VEGF intravitreal injections used to treat exudative AMD. Bevacizumab is used usually as a 0.05-mL (1.25-mg) intravitreal injection with the frequency determined by the ophthalmologist; ranibizumab, as a 0.05-mL (0.5-mg) intravitreal injection every 4 weeks; and pegaptanib, as a 0.09-mL (0.3-mg) intravitreal injection every 6 weeks.

Increased intraocular pressure (IOP) after intravitreal injections is common, can be quite high, and can occur with all currently used intravitreal agents. We showed that a pronounced spike in IOP was observed in patients administered pegaptanib intravitreal injections. The mean (SD) IOP immediately postinjection was 38 (14) mm Hg. Falkenstein et al reported a mean (SD) IOP of 36.27 (5.1) mm Hg after bevacizumab intravitreal injection, which resolved spontaneously to a mean (SD) of 24.56 (5.9) mm Hg at 10 minutes. Most studies that measure IOP after anti-VEGF injections do so no sooner than 30 minutes postinjection. Although following long-term pegaptanib intravitreal injections, there has been no reported evidence of sustained IOP elevation, Hariprasad et al reported a mean (SD) mild short-term increase in IOP of 8.74 (7.23) mm Hg approximately 30 minutes following pegaptanib intravitreal injections. In the VISION trial, IOP was also measured at 30 minutes postinjection of pegaptanib and was found to be increased by an average of 2 to 4 mm Hg.
with IOP rising to 35 mm Hg or greater in approximately 10% of the patients.6

Topical IOP-lowering medications like brimonidine, 0.2%, and apraclonidine, 1.0%, have been shown to be effective in preventing IOP spikes after argon laser trabeculoplasty.7,8 To our knowledge, no topical or systemic medication has been studied to see if it can prevent IOP spikes after intravitreal injections. The need for paracentesis before or after intravitreal injections is still controversial.9 In the series of Bakri et al,10 no patient required paracentesis after intravitreal injection over time in the ranibizumab group. There was no statistically significant difference in IOP reduction at any interval except one.

In the current study, we wanted to determine if prophylactic use of IOP-lowering medication was effective in reducing the IOP spikes after intravitreal injections of pegaptanib, bevacizumab, and ranibizumab. Also, as opposed to waiting for 30 minutes, we evaluated the IOP within 1 minute of intravitreal injection and at several intervals postinjection.

A retrospective medical record review was performed on consecutive series of patients who received anti-VEGF intravitreal injections. The inclusion criterion was having received anti-VEGF intravitreal injections for exudative AMD. The exclusion criterion was having received anti-VEGF intravitreal injections for conditions other than exudative AMD. In patients who received multiple injections of the same anti-VEGF medication, only the first injection was selected for the study. Injections of the fellow eye were also excluded from the study. A total of 71 patients (mean [SD] age, 80 [8] years; all white; 39 women and 32 men) qualified for the medical record review. Of the total 71 patients, 30 patients received pegaptanib, 42 received ranibizumab, and 47 received bevacizumab. Some patients received all 3 anti-VEGF medications and some only received 1 of the 3 medications. Considering that patients were enrolled from a practice that manages patients with glaucoma as well, a large number of patients who received intravitreal injections had glaucoma. Eleven patients (36.6%) in the pegaptanib group, 14 patients (33.3%) in the ranibizumab group, and 10 patients (21.2%) in the bevacizumab group were diagnosed with glaucoma. Administration of IOP-lowering medication, 1 hour prior to the injection, was done 63%, 74%, and 66% of the time in the patients who received pegaptanib, ranibizumab, and bevacizumab, respectively. The topical IOP-lowering medications used were timolol maleate, brimonidine tartrate, apraclonidine hydrochloride, dorzolamide hydrochloride, and brinzolamide. In some patients, oral acetazolamide (300 mg) was used as a prophylactic IOP-lowering medication, which was given 2 hours prior to the injection. Patients received between 0 and 2 medications prior to intravitreal injection. When multiple topical medications were given, they were given 5 minutes apart.

All the injections were performed in an office-based setting using a sterile technique. A 30-gauge needle was used to perform intravitreal injection of 0.05 mL of ranibizumab or bevacizumab and a 27-gauge needle was used to perform intravitreal injection of pegaptanib. A cotton-tip applicator was used to provide counterpressure after withdrawing the needle from the globe.

The IOP was measured before the prophylactic IOP-lowering medication was given prior to the injection, within 1 minute after injection, and every 3 to 10 minutes until the pressure was reduced to a safe level. This was routine practice, based in part on the significant number of patients who had glaucoma. A single Tono-Pen 2 (BioRad, Santa Ana, California), which had been calibrated each day as per the manual, was used to determine the mean IOP; the reading was accepted when the 5% bar was displayed. The IOP was measured prior to IOP-lowering medication administration. Visual acuity was evaluated immediately after the injection as counting fingers, light perception, or no light perception (NLP). Absence of NLP was used as a measure to confirm optic nerve head perfusion. Only patients whose visual acuity became NLP received a paracentesis. All the patients were examined with indirect ophthal-
mortality after the intravitreal injection. Patients were evaluated on subsequent visits for any IOP spikes.

RESULTS

All 3 types of drug injections caused significant initial IOP spikes. Mean (SD) IOP spike at 0 to 1 minute for the pegaptanib group was 38.5 (11.56) mm Hg; for the ranibizumab group, it was 37.75 (8.36) mm Hg; and for the bevacizumab group, it was 34.88 (10.45) mm Hg. The IOP was reduced to less than 30 mm Hg in 100% of injections by 20 minutes (Figures 1, 2, and 3). Mean (SD) IOP postinjection at 11 to 20 minutes was 24.47 (8.15) mm Hg, 23.90 (7.43) mm Hg, and 21.37 (9.69) mm Hg for all the patients who received pegaptanib, ranibizumab, and bevacizumab, respectively. Seventeen patients (56%) in the pegaptanib group, 20 patients (48%) in the ranibizumab group, and 15 patients (32%) in the bevacizumab group had a postinjection IOP spike greater than 40 mm Hg. Of these eyes that had an IOP spike greater than 40 mm Hg, 7 patients (23.3%) in the pegaptanib group, 7 patients (16.6%) in the ranibizumab group, and 3 patients (6.3%) in the bevacizumab group had glaucoma, which was fairly equal to the patients without glaucoma (7 of 11 vs 10 of 19 in the pegaptanib group, 7 of 14 vs 13 of 28 in the ranibizumab group, and 3 of 10 vs 12 of 37 in the bevacizumab group). In these patients with an IOP spike greater than 40 mm Hg, 5 of the 7 patients in the pegaptanib group and all the eyes in the ranibizumab and bevacizumab groups were given IOP-lowering medication.

There was no statistically significant IOP reduction seen whether IOP-lowering medication was used or not before intravitreal injection except at 1 interval (3-10 minutes, 0 medications vs 2 medications) in the pegaptanib group (Table). There was no clinically significant difference between IOP preinjection and at the 1-week follow-up visit.

Patients with and without glaucoma who received IOP-lowering medications showed a similar rate of normalization over time in the ranibizumab and bevacizumab groups, except at 1 interval (3-10 minutes, 0 medications vs 2 medications) in the pegaptanib group (Figure 4 and Figure 5). The IOP of patients treated with bevacizumab tended to diminish more rapidly, although the difference was not statistically significant. In the pegaptanib group, the patients with glaucoma who received IOP-lowering medications showed a similar rate of normalization over time compared with those who did not receive IOP-lowering medications except for at 1 interval (3-10 minutes; \( P = .004 \)) (Figure 6).

No light perception visual acuity, immediately after intravitreal injection, was only seen in the pegaptanib group (2 of 30 patients [6.6%]). Of these 2 patients, 1 patient had glaucoma. The initial IOP in the patients with

<table>
<thead>
<tr>
<th>Group</th>
<th>Medications</th>
<th>Before IVT Injection</th>
<th>After IVT Injection, min</th>
<th>Follow-up Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegaptanib (n=30)</td>
<td>0 (n=10)</td>
<td>14 (3)</td>
<td>38 (18)</td>
<td>33 (10)</td>
</tr>
<tr>
<td></td>
<td>1 (n=11)</td>
<td>13 (2)</td>
<td>36 (8)</td>
<td>31 (8)</td>
</tr>
<tr>
<td></td>
<td>2 (n=9)</td>
<td>14 (5)</td>
<td>43 (7)</td>
<td>39 (8)</td>
</tr>
<tr>
<td>Ranibizumab (n=42)</td>
<td>0 (n=11)</td>
<td>12 (4)</td>
<td>35 (9)</td>
<td>27 (9)</td>
</tr>
<tr>
<td></td>
<td>1 (n=13)</td>
<td>14 (4)</td>
<td>38 (8)</td>
<td>28 (4)</td>
</tr>
<tr>
<td></td>
<td>2 (n=18)</td>
<td>14 (3)</td>
<td>38 (8)</td>
<td>27 (9)</td>
</tr>
<tr>
<td>Bevacizumab (n=47)</td>
<td>0 (n=16)</td>
<td>14 (3)</td>
<td>33 (12)</td>
<td>29 (8)</td>
</tr>
<tr>
<td></td>
<td>1 (n=15)</td>
<td>14 (3)</td>
<td>37 (9)</td>
<td>26 (12)</td>
</tr>
<tr>
<td></td>
<td>2 (n=16)</td>
<td>14 (2)</td>
<td>35 (9)</td>
<td>25 (10)</td>
</tr>
</tbody>
</table>

Abbreviations: IOP, intraocular pressure; IVT, intravitreal.

Table. IOP Before and After IVT Injection Over Time in All 3 Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Medications</th>
<th>Before IVT Injection</th>
<th>After IVT Injection, min</th>
<th>Follow-up Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pegaptanib (n=30)</td>
<td>0 (n=10)</td>
<td>14 (3)</td>
<td>38 (18)</td>
<td>33 (10)</td>
</tr>
<tr>
<td></td>
<td>1 (n=11)</td>
<td>13 (2)</td>
<td>36 (8)</td>
<td>31 (8)</td>
</tr>
<tr>
<td></td>
<td>2 (n=9)</td>
<td>14 (5)</td>
<td>43 (7)</td>
<td>39 (8)</td>
</tr>
<tr>
<td>Ranibizumab (n=42)</td>
<td>0 (n=11)</td>
<td>12 (4)</td>
<td>35 (9)</td>
<td>27 (10)</td>
</tr>
<tr>
<td></td>
<td>1 (n=13)</td>
<td>14 (4)</td>
<td>38 (8)</td>
<td>28 (4)</td>
</tr>
<tr>
<td></td>
<td>2 (n=18)</td>
<td>14 (3)</td>
<td>38 (8)</td>
<td>27 (9)</td>
</tr>
<tr>
<td>Bevacizumab (n=47)</td>
<td>0 (n=16)</td>
<td>14 (3)</td>
<td>33 (12)</td>
<td>29 (8)</td>
</tr>
<tr>
<td></td>
<td>1 (n=15)</td>
<td>14 (3)</td>
<td>37 (9)</td>
<td>26 (12)</td>
</tr>
<tr>
<td></td>
<td>2 (n=16)</td>
<td>14 (2)</td>
<td>35 (9)</td>
<td>25 (10)</td>
</tr>
</tbody>
</table>

Figure 4. Mean intraocular pressure (IOP) before and after intravitreal (IVT) injection in patients with and without glaucoma in the ranibizumab group. All the patients received prophylactic medications.

Figure 5. Mean intraocular pressure (IOP) before and after intravitreal (IVT) injection in patients with and without glaucoma in the bevacizumab group. All the patients received prophylactic medications.
Intravitreal injection has become one of the most common medical procedures performed in the United States. With the increasing longevity of our patient population and with the fastest growing age segment in the United States being those older than 85 years, the incidence of AMD is expected to rise as will the use of intravitreal injections. Because the number of intravitreal injections is growing, it is very important to make sure these injections are safer for our patients. There have been numerous published reports of IOP spikes after intravitreal injections. These IOP spikes are common and thought to be transient; on the other hand, it is unknown whether repeated IOP spikes may cause damage in predisposed eyes.

In our series, we found that all 3 types of intravitreal injections resulted in IOP spikes between 0 to 2 minutes postinjection and our data concur with that of Falkenstein et al (mean [SD] at 3 minutes, 36.27 [5.1] mm Hg), Kim et al15 (at time zero was 44 mm Hg), and Hollands et al10 (mean at 2 minutes, 36.1 mm Hg). In all of our patients, IOP was reduced to less than 30 mm Hg within 20 minutes, which is similar to that reported by Bakri et al10 (at 10 minutes, 87% of eyes had an IOP of <35 mm Hg), Falkenstein et al11 (IOP dropped spontaneously to a mean [SD] of 24.56 [5.9] mm Hg at 10 minutes), Kim et al15 (IOP was reduced to <30 mm Hg in 96% of injections by 15 minutes and in 100% by 30 minutes), and Hollands et al10 (only 3 patients [2.9%] had an IOP of 25 mm Hg or higher at 30 minutes). However, our results differ from others because 2 of our patients (6.6%) who received pegaptanib intravitreal injection developed NLP visual acuity and it normalized after these patients underwent immediate anterior chamber paracentesis. The literature is controversial regarding the need for paracentesis in these patients to prevent IOP spikes. Additionally, if paracentesis is to be performed, it is unclear if it should be done preinjection or postinjection. Perhaps certain high-risk patients, who after previous intravitreal injections developed high IOP spikes, are the best candidates for this procedure. Paracentesis is not without risk. Clearly, this is an unnecessary procedure for most patients.

In the current study, we wanted to determine if prophylactic use of IOP-lowering medication was effective in reducing the IOP spikes after intravitreal injections of pegaptanib, bevacizumab, and ranibizumab. Most publications do not report whether IOP-lowering medication was used or not prior to intravitreal injection. In our series, the use of IOP-lowering medication prior to injection of pegaptanib, ranibizumab, or bevacizumab had little effect on the IOP spike. No matter how we analyzed the data, whether by which anti-VEGF drug was given, how many IOP-lowering medications were given, or whether patients had glaucoma, the apparent volume-mediated effect was the overwhelming factor that affected the IOP. After review of the literature, we were not able to find any previous studies to compare our results. Failure of prophylactic medication to substantially reduce IOP appears to be due to the inability of these medications to counteract the apparent volume-mediated mechanism of action of the IOP spikes after intravitreal injections. However, lowering IOP before intravitreal injection may have some theoretical benefit.

In our series, all the patients who developed NLP visual acuity received pegaptanib (0.9-mL) intravitreal injection. Also, 56% of eyes that received pegaptanib injection had an IOP more than 40 mm Hg as compared with 32% of eyes that received bevacizumab and 48% of eyes that received ranibizumab. However, the difference was not statistically significant. Information on short-term IOP trends after intravitreal injections in eyes with glaucoma is limited and clinical trials on anti-VEGF therapies tend to exclude eyes with glaucoma. When we analyzed the patients who received prophylactic medication before intravitreal injection, the ranibizumab and the bevacizumab groups showed similar rates of IOP normalization over time whether or not patients had glaucoma; the only exception was 1 interval in the ranibizumab group. In these 2 groups, we only analyzed patients who received prophylactic medications to keep the groups comparable. We further analyzed the effect of prophylactic medications in glaucomatous eyes in the pegaptanib group. In this group, the patients with glaucoma who received prophylactic medications before the injection did better at 1 interval (3-10 minutes) than those who did not receive it. We could not compare the patients with glaucoma who received prophylactic medication with those who did not in the ranibizumab and the bevacizumab groups because all the patients in these 2 groups who had glaucoma received prophylactic medications.

Kim et al13 reported that eyes with preexisting glaucoma took significantly longer to achieve an IOP of less than 30 mm Hg compared with eyes without a history of glaucoma, but both groups had normalized IOP to less than 30 mm Hg within 30 minutes. Bakri et al10 reported that at 10 minutes, eyes with glaucoma were less likely to have an IOP less than 35 mm Hg, but this difference became less marked with time. Hollands et al10 found that glaucoma was not a statistically significant variable and patients with glaucoma tend to have higher baseline IOP. The effect of the IOP spikes on the already-compensated in these patients.
promised optic nerve in patients with glaucoma is not known. However, caution may be prudent in patients with advanced glaucoma when repeated injections are indicated. Considering that our study did show lower IOP at the 3- to 10-minute interval in the pegaptanib group in patients who had glaucoma and who received prophylactic medication compared with the patients who did not, it may be beneficial to use prophylactic medications in patients with advanced glaucoma receiving pegaptanib intravitreal injection. However, our sample size was very small. In patients who are deemed to be at high risk of having damage from these recurrent IOP spikes, paracentesis should be considered, because it is an effective therapy. However, because of the increased risk of infection, it must be used judiciously.

The current study has several limitations. It is retrospective in nature, the number of patients who received prophylactic treatment before intravitreal injection was not the same in all 3 groups, and the number of patients with and without glaucoma varied between groups. Some patients received all 3 anti-VEGF medications, but others were only treated with 1 of these medications. Finally, IOP measured with the Tono-Pen may have underestimated the higher IOPs compared with Goldmann tonometry.23 The high incidence of preexisting glaucoma in this study is unusual; however, it is helpful in analyzing the effect of IOP spikes in the patient population that may be at highest potential risk from these injections.

In conclusion, IOP spikes after intravitreal injection of pegaptanib, ranibizumab, and bevacizumab are common and in most cases transient. Our study is retrospective in nature, the number of patients who received prophylactic treatment before intravitreal injection was not the same in all 3 groups, and the number of patients with and without glaucoma varied between groups. Some patients received all 3 anti-VEGF medications, but others were only treated with 1 of these medications. Finally, IOP measured with the Tono-Pen may have underestimated the higher IOPs compared with Goldmann tonometry. The high incidence of preexisting glaucoma in this study is unusual; however, it is helpful in analyzing the effect of IOP spikes in the patient population that may be at highest potential risk from these injections.

Submitted for Publication: August 24, 2009; final revision received March 11, 2010; accepted March 13, 2010.
Correspondence: Ronald E. P. Frenkel, MD, 509 SE Riverside Dr, Ste 302, Stuart, FL 34994 (efeye@aol.com).
Financial Disclosure: None reported.
Previous Presentation: Part of this study was presented at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting; May 11, 2009; Fort Lauderdale, Florida.

REFERENCES

8. Barnes SD, Campagna JA, Dirks MS, Doe EA. Control of intravascular pressure evolutions after argon laser trabeculoplasty: comparison of brimonidine 0.2% to apraclonidine 1.0%. Ophthalmology. 1999;106(10):2033-2037.