The Literature

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EFFECT ON INTRAOCULAR PRESSURE IN PATIENTS RECEIVING UNILATERAL INTRAVITREAL ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR INJECTIONS

Hoang QV, Mendonca LS, Della Torre KE, et al[1]

ABSTRACT SUMMARY

Hoang et al studied the frequency and risk factors of increased IOP in patients receiving unilateral intravitreal injections for age-related macular degeneration (AMD).[1] The investigators retrospectively reviewed the charts of 207 consecutive patients with neovascular AMD who had been treated unilaterally with three or more injections of ranibizumab (Lucentis; Genentech) and/or bevacizumab (Avastin; Genentech) between February 1 and July 31, 2010. The inclusion criteria included follow-up for at least 9 weeks. The exclusion criteria included patients with a diagnosis of glaucoma, which was defined as a baseline IOP greater than 21 mm Hg.

The investigators did not perform anterior chamber paracenteses or IOP measurements immediately after the procedure. Instead, they measured IOP at baseline and before pupillary dilation at each follow-up visit. Patients were divided into approximately four equal groups based on the number of injections received (group 1, 3-12 injections; group 2, 3-21 injections; group 3, 22-28 injections; group 4, more than 29 injections). The primary outcome was an IOP greater than 5 mm Hg above baseline for at least two consecutive visits. The contralateral, untreated eye served as the control.

The IOP was 5 mm Hg above baseline for at least two consecutive follow-up visits for 11.6% of eyes that received intravitreal injections compared with 5.3% of control eyes ($P = .02$). Eyes with increased IOP received more injections than eyes without an elevation in IOP (mean total injections, 24.4 [95% CI, 20.9-28] vs 20.4 [95% CI, 18.9-21.8]) and were monitored for a longer time period (183 weeks [95% CI, 157.2-208.8] vs 144.1 weeks [95% CI, 133.2-154.9]). Eyes in group 4 had an odds ratio (OR) of increased IOP 5.75 times that of group 1 ($P = .03$). Of the various clinical factors assessed for association with increased IOP—including age, sex, history of diabetes or hypertension, history of glaucoma, lens status, mean interval between injections, or previous procedures such as intravitreal steroids or pegaptanib (Macugen; Eyetech), peripheral iridotomy or ocular surgery other than cataract surgery—only the total number of intravitreal injections of ranibizumab or bevacizumab was associated with an increase in IOP.

DISCUSSION

What have previous studies reported regarding intravitreal antivascular endothelial growth factor (anti-VEGF) injections and IOP?

Hoang et al noted that multiple studies demonstrated that transient increases in IOP lasting less than 60 minutes are not uncommon with intravitreal anti-VEGF injections. Although a sustained elevation of IOP was not directly noted as a complication of ranibizumab in the ANCHOR and MARINA trials,[2,3] a post hoc analysis by Bakri et al demonstrated a higher likelihood of in IOP of 25 mm Hg or higher in eyes that received ranibizumab compared with controls.[4]

Choi et al performed a retrospective chart review of 127 patients who received anti-VEGF injections for AMD.[5] Although the mean IOP of injected eyes that did not achieve an IOP greater than 25 mm Hg was 15.2 mm Hg ±2.4 as compared with 14.9 mm Hg ±2.6 for noninjected eyes, 14 injected eyes (9.4%) developed an IOP greater than 25 mm Hg, and of these, 9 eyes (5.5%) had a sustained increase of IOP above 25 mm Hg and required glaucoma eye drops or surgery. In a retrospective chart analysis of 215 patients with AMD receiving anti-VEGF injections, Good et al found that patients with preexisting glaucoma had a higher prevalence of increased IOP than the nonglaucoma group (33% vs 3.1%; $P < .001$) despite receiving fewer injections on average.[6] In addition, patients who received bevacizumab had higher rates of increased IOP than those who received ranibizumab (9.9% vs 3.1%; $P = .049$).

What are the proposed mechanisms for how intravitreal anti-VEGF injections may lead to elevated IOP?

Proposed mechanisms include repeated trauma and IOP spikes due to the injection procedure leading to trabecular dysfunction.[1] Glaucoma patients may be particularly susceptible to this stress due to preexist-

ing trabecular compromise.[6] An immunologic reaction induced by anti-VEGF agents leading to inflammation and elevated IOP is also a possible etiology, predicting a larger IOP response for bevacizumab than ranibizumab due to the former's Fc moiety and longer serum and vitreal half-life.[7] Additionally, physical blockage of the trabecular meshwork by anti-VEGF agents or other protein aggregates,[8] silicone oil used to lubricate syringes,[9] or other debris can play a role in elevating IOP.

What new information does this study provide?

This study demonstrated a correlation between the total number of anti-VEGF injections for neovascular AMD and IOP elevation. Because the exclusion criteria included the initiation of glaucoma eye drops prior to a second follow-up visit in patients with an elevated IOP, this study may have underestimated the risk of frequent anti-VEGF medications on IOP.

SUSTAINED ELEVATION OF INTRAOCULAR PRESSURE AFTER INTRAVITREAL INJECTIONS OF BEVACIZUMAB IN EYES WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION

Mathalone N, Arodi-Golan A, Sar S, et al[10]

ABSTRACT SUMMARY

Mathalone et al investigated the prevalence of elevated IOP after an intravitreal injection of bevacizumab (Avastin; Genentech) for neovascular age-related macular degeneration (AMD) and the possible risk factors for IOP elevation.[10] In this retrospective cohort study, consecutive patients with AMD who received intravitreal injections of bevacizumab were assessed for increased IOP. Sustained IOP elevation was defined as an IOP of 22 mm Hg or higher and a change from baseline of 6 mm Hg or more recorded on at least two consecutive visits and lasting at least 30 days. The inclusion criteria consisted of the presence of AMD and recorded IOP values for the baseline and follow-up visits. The exclusion criteria included eyes with retinal vein occlusion, diabetic retinopathy, previous intraocular surgery other than phacoemulsification, previous AMD treatment, or previous use of topical steroids. The investigators did not perform anterior chamber paracenteses. They used Goldmann tonometery to measure IOP values, but dilation status was not reported. Recorded data comprised age, gender, glaucoma and lens status, length of follow-up, total injections and interval between injections, and management for eyes demonstrating increased IOP.

The study included 201 eyes of 174 patients who received at least one intravitreal injection of bevacizumab. Multivariable analysis showed that male gender (odds ratio, 3.1; 95% CI, 1.1, 7.9; $P = .028$) and an interval between injections of less than 8 weeks (odds ratio, 3; 95% CI, 1.1, 8.5; $P = .029$) were associated with IOP elevation, whereas preexisting glaucoma, the number of injections, lens status, and follow-up period were not. Eye drops were started for 21 of the 22 eyes that demonstrated increased IOP; the remaining eye, which had previously been diagnosed with glaucoma, needed additional topical treatment. None of the eyes required laser or incisional glaucoma treatment.

DISCUSSION

What are some significant differences between the two studies in this literature review?

The study by Mathalone et al comprised patients that received only bevacizumab injections, and Hoang et al involved patients who received ranibizumab (Lucentis; Genentech) as well.[1,10] Hoang et al monitored the relationship between the number of intravitreal injections and IOP, including some patients who have received greater than 29 intravitreal injections, whereas patients in the study by Mathalone et al had received fewer than 23 injections. The criteria for sustained, elevated IOP also differed between the two studies.

What treatment modalities are necessary to treat the effects of IOP elevation associated with bevacizumab?

Patients who had an elevated IOP after an injection of bevacizumab were treated with topical therapy. Laser and incisional therapy were not needed. Skalicky et al documented the treatment of IOP elevation in patients receiving intravitreal injections of antivascular endothelial growth factor (anti-VEGF) in a small retrospective case review.[11] Of the six patients whose IOP increased, two had primary open-angle glaucoma, and one had pseudoexfoliative glaucoma. The IOP in these patients was stable prior to the anti-VEGF injections. Four patients required trabeculectomy, and one patient underwent selective laser trabeculoplasty for IOP management. One patient's IOP was controlled by topical medications alone.

What are the recommendations for patients' care based on the results of these studies?

IOP should be regularly monitored in patients receiving repeated injections of anti-VEGF agents for AMD, even in individuals without a prior history of glaucoma or ocular hypertension. Patients who have received many injections or are receiving more frequent injections may require closer monitoring. Findings from previous studies

suggest that patients with preexisting glaucoma may also need to be closely observed. Laser or surgical therapy is not frequently required for spikes in IOP associated with intravitreal anti-VEGF injections, but it can be used in cases where medical therapy is not sufficient. ■

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