

Short-term Intraocular Pressure Changes Immediately After Intravitreal Injections of Anti-Vascular Endothelial Growth Factor Agents

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- **PURPOSE:** To assess short-term trends and the need to monitor intraocular pressure (IOP) changes immediately after intravitreal injections of ranibizumab, bevacizumab, pegaptanib, and triamcinolone acetonide.

- **DESIGN:** Retrospective, interventional case series.

- **METHODS:** Charts of 213 consecutive injections to 120 eyes of 112 patients were reviewed. Pressures were measured before injection, immediately after injection (T0), and at five-minute intervals until IOP was less than 30 mm Hg. Optic nerve perfusion was assessed by testing for hand movement vision and by indirect ophthalmoscopic examination. Kaplan-Meier and Chi-square analyses of IOP after injections and correlation of IOP spikes to drug, needle bore size, injection volume, and history of glaucoma were performed.

- **RESULTS:** Mean preinjection IOP was 14 mm Hg (range, 7 to 22 mm Hg). Mean IOP at T0 was 44 mm Hg (range, 4 to 87 mm Hg). All but one eye had at least hand movement vision and a perfused optic nerve at T0. IOP was reduced to less than 30 mm Hg in 96% of injections by 15 minutes and in 100% by 30 minutes. Eyes with a history of glaucoma took longer to normalize the IOP ($P = .002$). Statistically significant IOP spikes were observed with a smaller needle bore size ($P < .0001$) and in eyes with a history of glaucoma ($P = .001$).

- **CONCLUSIONS:** Elevations in IOP immediately after intravitreal injections are common, but are transient. Prolonged monitoring of IOP may not be necessary on the day of injection in most cases if hand movement vision, optic nerve perfusion, and lack of intraocular complications have been verified. However, cautious monitoring should be considered in select cases. (*Am J Ophthalmol* 2008;146:930-934. © 2008 by Elsevier Inc. All rights reserved.)

INTRAVITREAL INJECTIONS HAVE EMERGED AS AN increasingly common method for treatment of various vitreoretinal diseases. Agents such as triamcinolone acetonide, pegaptanib, ranibizumab, and bevacizumab currently are being used for treatment of exudative age-related macular degeneration (AMD) and macular edema resulting from diabetic retinopathy, vein occlusions, and uveitis.

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Despite the therapeutic benefits of these agents, repeat injections often are required, with agents such as ranibizumab injected as often as every four weeks.¹ As a result, there has been a substantial increase in number of patients treated with this method in the office.

According to the Center for Medicare and Medicaid Services, intravitreal injections were the fastest growing ophthalmic procedure in 2006. Therefore, it is important to investigate ways to ensure patient safety while improving overall patient experience and efficiency of patient flow in the office with these treatments.

One of the ways is to determine the necessity of postinjection intraocular pressure (IOP) monitoring and then to identify patients at high risk for delayed normalization of IOP immediately after injection. Recent guidelines for intravitreal injections recommend "monitoring of IOP after injection and provid[ing] therapy when elevated IOP warrants intervention."^{2,3} However, when to best monitor IOP is debatable. In clinical trials with ranibizumab and pegaptanib, IOP was measured up to one hour after injection.^{1,4} A series on pegaptanib injections has demonstrated short-term safety from an IOP standpoint when patients were evaluated at 30 minutes and five to seven days later and questioned the need for an IOP check 30 minutes after injection.⁵ Although some studies of IOP trends immediately after intravitreal injections of bevacizumab, triamcinolone, or pegaptanib concluded that monitoring of postinjection IOP may not be necessary, others suggest checking once at five to 10 minutes after injection, whereas others recommend IOP checking after injection but do not give guidance as to when or for how long.⁵⁻⁸ Some studies recommend performing paracentesis, whereas others do not.^{5,8-11} Furthermore, the course of IOP spikes after intravitreal injections in patients with glaucoma has not been well characterized in the literature.

In current practices, intravitreal injections of ranibizumab, bevacizumab, pegaptanib, and triamcinolone acetonide consist of different volumes and may be administered with different needle bore sizes. We sought to investigate the short-term IOP trends immediately after these commonly used intravitreal agents and to explore factors that affect IOP changes after intravitreal injections to assess the need for postinjection IOP measurement until normalization. If observed IOP elevation after intravitreal injections is transient in all patient encounters or if

patients at risk for complications because of short-term IOP elevation can be identified, then systematic measurement of IOP after intravitreal injections until normalization may not be mandatory for all patients on the day of injection and perhaps could be targeted toward the identified at-risk groups. This may enhance patient experience by avoiding repeated IOP measurements, shortening clinic visit times, and streamlining clinic flow while ensuring the safety of our patients after intravitreal injections.

METHODS

A RETROSPECTIVE CHART REVIEW OF CONSECUTIVE INJECTIONS given by a single retina specialist (J.E.K.) in an outpatient office setting between May 1, 2006 and November 30, 2006 was performed. Using either a 30- or 32-gauge needle (TSK3213; Air-Tite, Virginia Beach, Virginia, USA), 0.05 ml bevacizumab (Avastin; Genentech, San Francisco, California, USA) or ranibizumab (Lucentis; Genentech) were administered. Because of larger particle size, 0.1 ml triamcinolone acetonide (Bristol-Myers Squibb Co, New York, New York, USA) was injected using a 27-gauge needle. Pegaptanib (Macugen; OSI/Eyetech and Pfizer, New York, New York, USA) was administered with the prefilled syringe containing 0.09 ml of the drug with the attached 27-gauge needle from the manufacturer.

Patients were uniformly sterilely prepped, which included instillation of topical antibiotic and anesthetic drops, insertion of a lid speculum, and a 5% povidone iodine flush, followed by a rinse with balanced salt solution. Using a cotton-tipped applicator soaked with a topical anesthetic, the inferotemporal area of sclera to be injected was anesthetized. After marking the injection site on the sclera with a caliper measuring 3 to 3.5 mm from the limbus, additional 10% povidone iodine on a stick was placed on the injection site. The conjunctiva was displaced slightly with a sterile cotton-tipped applicator just before entering the eye with a needle. After injection, the injection site was occluded temporarily and was massaged with a sterile cotton-tipped applicator as the needle was withdrawn from the eye. Anterior chamber (AC) paracentesis was not performed in any of the injections.

As soon as the needle was withdrawn, a drop of anesthetic was placed on the cornea and IOP was measured by Tono-Pen (Medtronic Xomed Ophthalmics Inc, Minneapolis, Minnesota, USA) tonometry.^{12,13} As soon as the IOP was measured, postinjection vision assessment was performed by occluding the patient's fellow eye and the examiner performing hand movements at 6 inches from treated eye. Positive detection of hand movement was tested in all cases, and in many cases, vision was tested further to ascertain the ability to count fingers at 6 inches. Immediately after this vision check, the eye was inspected with an indirect ophthalmoscope for perfusion of optic nerve, which was defined as obvious filling of vessels with

blood or at least pulsation of central retinal artery. The eye was examined for any immediate intraocular complications, such as vitreous hemorrhage or retinal tears. The lid speculum was removed and interval IOP monitoring was continued until IOP measured less than 30 mm Hg.

All pressures were measured using the Tono-Pen XL applanation tonometry system. IOPs were measured before sterile preparation (baseline IOP) and immediately after injection (T0) and were reassessed at five-minute intervals until IOP declined to less than 30 mm Hg.

Statistical tests were performed using SPSS software version 14.0 (SPSS Inc, Chicago, Illinois, USA).

RESULTS

DATA FROM 213 CONSECUTIVE INTRAVITREAL INJECTIONS to 120 eyes of 112 patients were analyzed. The mean age of patients was 76 years (range, 29 to 92 years), with 48 men and 64 women. Fifty-three eyes were phakic and 67 eyes were pseudophakic. Patients received intravitreal injections for a range of vitreoretinal diseases. The most common reason for injection of ranibizumab, bevacizumab, and pegaptanib was exudative macular degeneration with choroidal neovascular membrane (84%). Other vitreoretinal diseases for which bevacizumab and triamcinolone acetonide were administered included neovascularization resulting from proliferative diabetic retinopathy or vascular occlusion (7%), macular edema resulting from diabetes or central retinal vein occlusion (5%), and pseudophakic cystoid macular edema (3%).

Of the 213 injections, 142 (67%) were with bevacizumab, 29 (14%) were with pegaptanib, 26 (12%) were with ranibizumab, and 16 (8%) were with triamcinolone acetonide. Injections of bevacizumab and ranibizumab were 0.05 ml with 30- or 32-gauge needles, whereas injections of pegaptanib and triamcinolone acetonide were 0.09 or 0.1 ml with 27-gauge needles. There were 62 injections with 32-gauge needles, 106 injections with 30-gauge needles, and 45 injections with 27-gauge needles. Therefore, nearly 80% of the injections in this study were with smaller-volume and smaller-needle agents.

There were 20 patients with a diagnosis of preexisting glaucoma. This group included 11 eyes with primary open-angle glaucoma, five eyes with history of steroid-induced glaucoma, and four eyes with ocular hypertension. Among these patients, 14 injections were administered with a 27-gauge needle and 30 injections were administered with 30- or 32-gauge needles. Interventions included 21 injections with bevacizumab, nine injections with ranibizumab, eight injections with pegaptanib, and six injections with triamcinolone acetonide.

Mean baseline IOP before injection was 14 mm Hg (range, 7 to 22 mm Hg). Mean IOP immediately after injection (T0) was 44 mm Hg (range, 4 to 87 mm Hg). At T0, the incidence of IOP of 30 mm Hg or higher was 79%

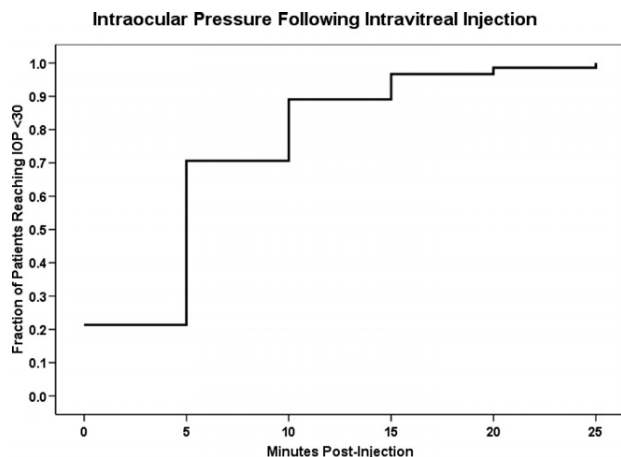


FIGURE 1. Graph showing the cumulative fraction of patients reaching an intraocular pressure (IOP) of less than 30 mm Hg as a function of minutes after injection.

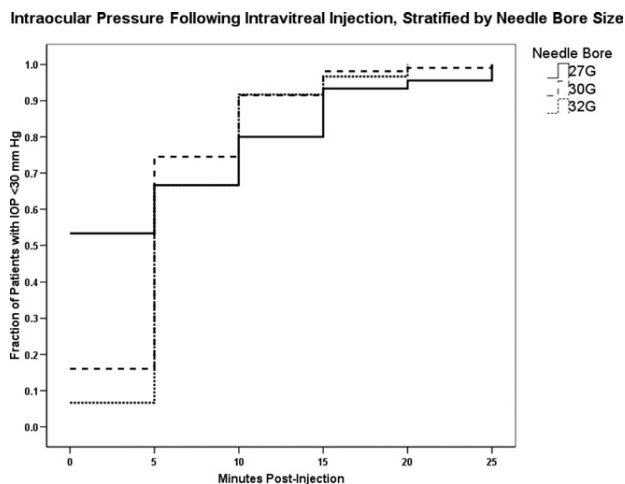


FIGURE 2. Graph showing the cumulative fraction of patients reaching an IOP of less than 30 mm Hg as a function of minutes after injection stratified by needle bore size used for intraocular injection (solid line, 27 gauge; long-dashed line, 30 gauge; short-dashed line, 32 gauge).

(Figure 1). However, the incidence of IOP of 30 mm Hg or higher fell to 30% within five minutes, and this rate continued to decline such that, by 30 minutes, no eye had an IOP of 30 mm Hg or higher.

Distributions of times to normalization for different needle bore sizes used were not statistically different ($P = .49$, log-rank test). However, at T0, the smaller-bore needle resulted in a statistically higher incidence of elevated IOP than the larger-bore needles (Figure 2). The incidence of IOP of 30 mm Hg or higher at T0 was 94% for injections with 32-gauge needles, 84% for injections with 30-gauge needles, and 47% for injections with 27-gauge needles ($P < .0001$, Pearson Chi-square test).

Because the agents used and the volume used were related to the needle bore size, IOP spike at T0 also varied according to the volume and agent injected, with smaller-volume agents paradoxically resulting in higher IOP. At T0, the incidence of IOP of 30 mm Hg or higher was 88% for 0.05 ml of agent given with 30- or 32-gauge needles (ranibizumab and bevacizumab), 48% for 0.09 ml of agent given with a 27-gauge needle (pegaptanib), and 44% for 0.1 ml of agent given with a 27-gauge needle (triamcinolone acetonide).

At 25 minutes after injection, IOP of 30 mm Hg or higher was observed in two of the 213 injections (35 and 31 mm Hg), but reached less than 30 mm Hg by 30 minutes. One of these patients had preexisting glaucoma and was noncompliant with medications. This patient was restarted on the previous regimen of topical ocular hypotensive medications after injection. No other IOP-lowering interventions were performed in other eyes after intravitreal injections.

Among 20 eyes with a prior diagnosis of glaucoma, there was a statistically significant difference in IOP elevation at T0 between eyes with any type of glaucoma as compared with eyes without glaucoma ($P = .001$). Furthermore, eyes with a history of glaucoma took longer to achieve an IOP of less than 30 mm Hg than those without glaucoma ($P = .002$, log-rank test) (Figure 3).

In 76 injections (36%), IOP at T0 was 50 mm Hg or higher. Nevertheless, all but one eye had at least hand movement vision and a perfused optic nerve visualized with indirect ophthalmoscopy. In one patient, light perception was not noted immediately after injection but became apparent within one minute after the injection with careful observation for optic nerve perfusion with indirect ophthalmoscope. After the optic nerve became perfused, the patient saw light. His T0 IOP was the highest of the series at 87 mm Hg, but the IOP normalized to less than 30 mm Hg by 30 minutes. No immediate intraocular complication was noted with indirect ophthalmoscopic examination in any of the eyes.

DISCUSSION

AS INTRAVITREAL INJECTIONS BECOME AN INCREASINGLY common method of treatment, investigating the need for monitoring IOP after injection is important for patient safety, increased patient satisfaction despite need for repeated injections, and enhancement of office flow. In addition, this study aimed to determine factors that affect IOP immediately after injection. We found that elevations in IOP after intravitreal injections were common, can be quite high, and can occur with all currently used intravitreal injections. However, these IOP spikes were transient, and AC paracentesis was not required. This is in agreement with previous studies.^{5-7,10,11} For immediate short-term after injection, intravitreal injections were well

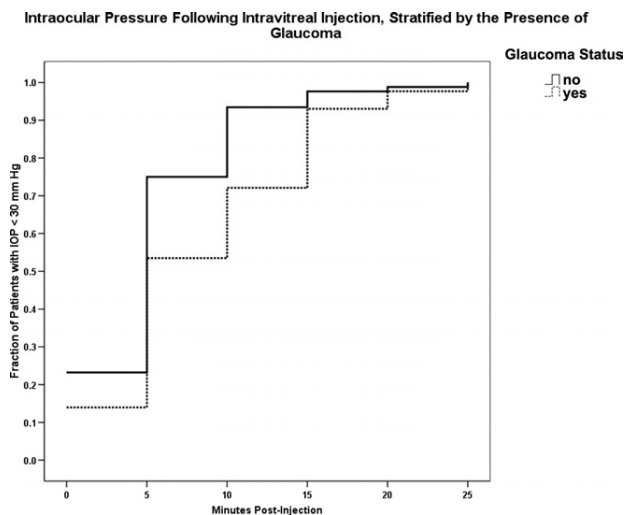


FIGURE 3. Graph showing the cumulative fraction of patients reaching an IOP of less than 30 mm Hg as a function of minutes after injection stratified by the presence of glaucoma (solid line, glaucoma; short-dashed line, no glaucoma).

tolerated by the patients, with normalization of IOP to less than 30 mm Hg in all patients by 30 minutes in our series. In the injection setting with volume and needle bore size as used in this series, factors that affected IOP immediately after injection included small needle bore size because of less reflux and history of glaucoma. Testing for hand movement vision seemed to be a good measure of optic nerve perfusion.

Benz and associates investigated immediate IOP changes after intravitreal triamcinolone acetonide injections.¹⁰ They found that the eyes without vitreous reflux when the needle was withdrawn had a short-term risk of IOP elevation, but that IOP normalized rapidly over 30 minutes. They did not find significant elevation of IOP after injection in eyes that had reflux. Their study was limited to cases where 0.1 ml intravitreal triamcinolone acetonide was given with a 27-gauge needle and excluded eyes with a history of glaucoma. Although reflux was not noted in a prospective manner in our study, nor would it be possible to quantify accurately the amount of reflux, their findings support findings in our study. We also found that IOP normalized over 30 minutes. We found that the incidence of IOP elevation immediately after injection was significantly higher with smaller bore needle size, despite the smaller volume injected with these needles. This is most likely because of less reflux through a smaller injection opening, whereas larger-bore needles allowing more reflux.

In the absence of variable of reflux, one would expect physics of volume in a closed system to hold such that a significantly higher IOP spike can be expected with a larger volume injected.⁹ In addition to reflux and volume injected, other factors such as the size of the globe and scleral rigidity also may play a role in IOP spike after

intravitreal injection. For instance, in the absence of variable of reflux, hyperopic eyes may have higher IOP elevation after injection because of the effect of relatively larger volume being injected into a smaller-size eye.⁹ Therefore, if more than 0.05 ml were to be injected with a small-gauge needle, which does not allow for much reflux, or if reflux does not occur when a larger volume is injected with a larger-bore needle, even higher T0 IOP may be expected than that observed in our series, and these eyes should be monitored more closely with further caution.

Information on short-term IOP trends after intravitreal injections in eyes with glaucoma is limited and clinical trials on antivascular endothelial growth factor therapies tend to exclude eyes with glaucoma. We included eyes with glaucoma to simulate our daily clinical practices as well as to obtain information necessary to manage such patients. In two studies that included eyes with glaucoma, one found that glaucoma was not a statistically significant variable, whereas the other found that eyes with glaucoma were less likely to have an IOP of less than 35 mm Hg at 10 minutes after injection, but this difference became less marked with time.^{8,11} In our series, 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 a normalized IOP to less than 30 mm Hg within 30 minutes. This may be because of compromised outflow, but a study with a larger number of patients with glaucoma would be helpful to confirm our findings.

Most previous studies did not examine IOP immediately after injection, but rather initiated IOP measurements two to 30 minutes after injection. We found that IOP spike can be extremely high at T0 with current treatment methods. The long-term effect of repeated IOP spikes, albeit transient, that may occur with repeated intravitreal injections on eyes with already compromised perfusion status is unknown and may need to be investigated further.

Limitations to our study include not having records of refractive error of eyes being injected. Also, we did not analyze our data based on age or gender of the patients. It is possible that these factors may affect intraocular volume and scleral rigidity that might have theoretic bearing on the tendency for IOP spikes.⁹ The reflux of vitreous fluid after withdrawing of the needle was neither controlled actively nor recorded in a systematic manner.^{9,10} Even when reflux occurred, the amount of reflux seemed to vary between small-bore needles and larger-bore needles, and the amount of reflux was believed to be difficult to quantify. Depending on the frequency or volume of reflux, the IOP measured may differ from that of our study. Finally, IOP measured with the TonoPen may underestimate the IOP at the upper extremes of pressure compared with Goldmann tonometry.^{12,13} However, with frequent IOP measurements required in our practice and uniform use of the TonoPen throughout the study, IOP measurements with the TonoPen were considered to be acceptable

and practical for our purposes, and the trends in IOP reduction should remain internally consistent.

In conclusion, all eyes in our series achieved normalization of IOP within 30 minutes without need for any immediate intervention, such as paracentesis. Therefore, in most cases, repeated or prolonged IOP monitoring for normalization after intravitreal injections may not be necessary on the day of injection, and such an absence does not seem to compromise patient safety. However, hand movement or better vision, perfusion of optic nerve, and lack of intraocular complications should be verified

after injection and should be monitored closely if these are not present. We included all types of intravitreal pharmacotherapies in the manner currently used in our practices as well as patients with glaucoma. Therefore, the findings are applicable to many of our current practices. In cases where more than 0.05 ml is injected with a small-bore needle or no reflux is seen after injection with a larger-bore needle or in patients with a prior history of glaucoma, cautious monitoring of postinjection IOP may be needed, because these eyes seem to have a higher incidence of significant pressure spike.

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Biosketch

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