

Short-term intraocular pressure changes after intravitreal injection of bevacizumab

Hussein Hollands,* MD, MSc (Epid); Jonathan Wong,* MD; Robin Bruen,[†] BSc;
Robert J. Campbell,* MD, MSc, FRCSC; Sanjay Sharma,*[‡] MD, MSc (Epid), MBA, FRCSC;
Jeffery Gale,* MD, FRCSC

ABSTRACT • RÉSUMÉ

Background: This study examines the changes in short-term intraocular pressure (IOP) in patients receiving intravitreally administered bevacizumab. A prospective series of consecutive patients undergoing injection of intravitreal bevacizumab was investigated.

Methods: All patients received bevacizumab (0.05 cc) injected intravitreally in a standard fashion. IOP was measured at baseline, 2, 5, and 30 minutes after injection by 1 of 2 observers using Goldman applanation tonometry. An intraobserver study was done to assess agreement in IOP measurements.

Results: We accrued 104 patients with a mean age of 76 years: 58% were female, and 42% were male. Most patients (85%) were being treated for neovascular age-related macular degeneration. The mean IOP values at baseline, 2, 5, and 30 minutes after injection were 14.0 (95% confidence interval [CI] 13.4–14.7) mm Hg, 36.1 (95% CI 33.5–38.6) mm Hg, 25.7 (95% CI 23.8–27.5) mm Hg, and 15.5 (95% CI 12.4–16.51) mm Hg, respectively. Three patients (2.9%) had an IOP of 25 mm Hg or higher at 30 minutes. IOP normalized within 2 hours without medical therapy in 2 of these patients, and 1 patient required a 1-week course of glaucoma medication. Regression analysis showed a trend towards phakic patients having higher IOP at 30 minutes (odds ratio = 3.2; $p = 0.089$).

Interpretation: Intravitreal injection of bevacizumab is safe with respect to short-term IOP changes, as almost all patients' IOP returned to a safe range (<25 mm Hg) within 30 minutes. Elevated IOP at 30 minutes after injection does occur, rarely, thus clinicians should consider checking IOP after injection as a precaution. Transient extreme IOP elevations occur in a significant percentage of patients, but the consequences of these events are unknown.

Contexte : Étude prospective de l'évolution à court terme de la pression intraoculaire (PIO) chez des patients à qui l'on a administré du bevacizumab par voie intravitréenne. L'investigation a porté sur une série de patients consécutifs.

Méthodes : Les patients ont tous reçu une injection de 0,05 cc de bevacizumab par voie intravitréenne. La PIO a été mesurée au départ puis 2, 5 et 30 minutes après l'injection par 1 des 2 observateurs à l'aide de la tonométrie par applanation de Goldman. Une étude intraobservateurs a permis d'évaluer la concordance des mesures de la PIO.

Résultats : Nous avons passé en revue 104 patients de 76 ans en moyenne : 58 % féminins et 42 % masculins. La plupart des patients (85 %) ont été traités pour dégénérescence maculaire liée à l'âge néovasculaire. Les données moyennes de la PIO au départ puis 2, 5 et 30 minutes après l'injection étaient respectivement de 14,0 mm Hg (intervalle de confiance [IC] de 95 %, 13,4–14,7), 36,1 mm Hg (IC de 95 %, 33,5–38,6), 25,7 mm Hg (IC de 95 %, 23,8–27,5) et 15,5 mm Hg (IC de 95 %, 12,4–16,51). Trois patients (2,9 %) avaient une PIO de 25 mm Hg ou plus après 30 minutes : 2 ont vu leur PIO redevenir normale en moins de 2 heures sans thérapie médicale et 1 a eu besoin d'une semaine de médicaments pour le glaucome. L'analyse de la régression a indiqué que les patients phakes avaient tendance à avoir une PIO supérieure après 30 minutes (rapport de cotes, 3,2; $p = 0,089$).

Interprétation : L'injection de bevacizumab par voie vitrée est sûre en regard de l'évolution à court terme de la PIO, puisque la PIO de presque tous les patients est revenue à une norme sécuritaire (<25 mm Hg) en deçà de 30 minutes. La PIO peut demeurer élevée 30 minutes après l'injection, mais c'est rare; les cliniciens devraient penser à vérifier la PIO après l'injection par mesure de précaution. Des hausses extrêmes et passagères de PIO peuvent survenir chez une proportion significative de patients, mais on n'en connaît pas encore les séquelles.

From *the Department of Ophthalmology and [†]the Faculty of Medicine, Queen's University, Hotel Dieu Hospital, Kingston, Ont.; and [‡]Unit for Cost-Effective Ocular Health Policy, Hotel Dieu Hospital, Kingston, Ont.

Correspondence to: Hussein Hollands, MD, Department of Ophthalmology, Hotel Dieu Hospital, Johnson 6, 166 Brock St., Kingston, ON K7L 5S9; 8hh1@qlink.queensu.ca

Originally received May 4, 2007. Revised Aug. 6, 2007
Accepted for publication Aug. 14, 2007
Published online Nov. 16, 2007

This article has been peer-reviewed. Cet article a été évalué par les pairs.

Can J Ophthalmol 2007;42:807–11
doi:10.3129/i07-172

With over 15 000 annual intravitreal injections worldwide, bevacizumab (Avastin, Genentech Inc., San Francisco, Calif.) is rapidly becoming one of the leading treatments for neovascular age-related macular degeneration (AMD).¹ Bevacizumab is not approved for intraocular injection by the U.S. Food and Drug Administration or by Health Canada. However, there is growing evidence of the benefits of bevacizumab for treating other ocular diseases associated with neovascularization, such as diabetic retinopathy² and pathologic myopia.³

Previous studies support the use of intravitreal bevacizumab for treating various conditions of ocular pathology.^{4,5} The largest collection of data concerning the safety of bevacizumab was compiled by the International Intravitreal Bevacizumab Safety Survey,¹ which reported on complications such as endophthalmitis, cataract progression, subretinal hemorrhages, and retinal tears. However, as that report relied on voluntary reporting to ascertain complication rates, underestimation of these rates seems quite possible. Furthermore, the role of intraocular hypertension was not studied quantitatively.

Numerous published reports highlight the potential for a significant rise in intraocular pressure (IOP) following intravitreal injections in general.^{6–8} An acute rise in IOP has been shown in animal models to block axonal transport to the optic nerve head; in addition, a higher rise in IOP is associated with more severe damage.⁹ An acute rise in IOP has also been shown to decrease juxtapapillary retinal and optic nerve head blood flow proportionally to the quantitative rise in IOP.¹⁰ However, in our review of the literature we were unable to find any study that investigated the short-term IOP changes associated with intravitreal administration of bevacizumab or other similar antivascular endothelial growth factor agents.

Three recent studies have investigated the short-term change in IOP following intravitreal injection of triamcinolone acetonide (TA).^{6–8} In the study by Benz et al.,⁶ the IOP normalized in most patients 30 minutes after injection, but 10% of patients who did not have vitreous reflux after injection had an IOP greater than 25 mm Hg at 30 minutes. The mechanism for the short-term IOP rise immediately after intravitreal injection of TA was thought to be a result of the increase in volume of the vitreous cavity after injection. As the intravitreal use of bevacizumab is growing exponentially, the safety of this procedure is of fundamental importance. Given the potential for significant IOP elevation in the immediate postinjection period, we investigated the changes in IOP following 0.05 cc intravitreal bevacizumab in order to more clearly outline the safety of this novel treatment modality.

METHODS

This was a prospective case series of consecutive patients undergoing intravitreal injection of bevacizumab at our centre. The patients were asked to participate if they were

over 18 years of age and were able to have IOP measured by applanation. To maximize generalizability, exclusion criteria were kept to a minimum. These included previous ocular surgeries or intravitreal injections of corticosteroid within the previous 3 months. Ethics approval was obtained for this study through the Queen's University Research Ethics Board. Informed consent was obtained orally for each patient in the study.

Intravitreal injections were given by 2 surgeons (Sanjay Sharma, Jeffery Gale) using similar techniques at an outpatient ophthalmology clinic. Demographic and clinical data were collected through patient interview and chart review. Visual acuity and IOP values were obtained at baseline. Patients were prepared and draped in a standard fashion and positioned supine for the procedure. A solution of 10% povidone-iodine was used for sterilization, a lid speculum for lid control, and either topical or subconjunctival 2% lidocaine for anesthesia. The intravitreal bevacizumab injection was prepared by drawing-up approximately 0.1 cc of bevacizumab (2.50 mg/0.05 cc) into a 1.0 cc tuberculin syringe. The excess was removed, and the remainder (0.05 cc or 1.25 mg) was injected with a 27-gauge needle through the inferotemporal or inferonasal pars plana at 3.0 mm or 3.5 mm posterior to the limbus if the patient was phakic or pseudophakic, respectively. The needle was inserted approximately 1.0 cm into the globe, and the injection was performed. After injection a sterile cotton swab was placed on the injection site to prevent reflux of the medicine.

Patients were elevated to the slit-lamp, and an IOP measurement was performed at 2, 5, and 30 minutes after injection using Goldman applanation tonometry. All IOP measurements were performed by 1 of 2 trained observers. If the IOP was above 24 mm Hg after 30 minutes then patients were observed for another 1.5 hours and then managed medically by the attending physician.

To investigate the reliability of IOP measurements between the 2 observers, an interobserver reliability study was performed on patients from a general ophthalmology clinic. In a random group of patients not involved in the study and without intraocular hypertension, IOP was measured by both of the observers consecutively. A coin toss was used to determine which observer would measure IOP first. Both observers were blind to any previous IOP measurements in the patient chart, and the second observer was blind to the IOP measurement taken by the first observer.

Data were analyzed using the Statistical Package for the Social Sciences v. 12.0 for Windows (SPSS, Chicago, Ill.). Basic demographic and clinical data were analyzed using means and proportions, and appropriate 95% confidence intervals (CIs). The main outcome measure was the proportion of patients with an IOP of above 24 mm Hg at 30 minutes after injection. A secondary outcome measure was the proportion of patients with an IOP ≥ 5 mm Hg above baseline at 30 minutes after injection. A multivariate logistic regression analysis with backward selection

(exclusion of $p \geq 0.10$) was used to simultaneously investigate factors associated with increased IOP after 30 minutes. An intraclass correlation coefficient was used to assess inter-rater reliability of IOP measurements between the 2 observers.

RESULTS

There were 104 consecutive patients accrued in our study. Three patients were not included because of timing difficulties (within the first 5 minutes after injection) or difficulty with positioning during IOP measurement. No other patients were excluded. Fifty-eight percent of our sample were female, 42% were male, and the mean age was 76 (SD 10.33) years. Most patients (85%) were receiving intravitreal injection of bevacizumab for neovascular AMD. Table 1 shows basic demographic and clinical data for the sample.

We sampled 41 patients randomly for our interobserver reliability study. IOP measurements were within 3 mm Hg in 90.2% of cases. The intraclass correlation coefficient between observers was 0.87 (95% CI 0.77–0.93).

Patients with a history of glaucoma ($n = 16$) tended to have higher baseline IOP ($p = 0.041$). For all study patients, the mean IOP values at baseline, 2, 5, and 30 minutes after injection were 14.0 (95% CI 13.4–14.7) mm Hg, 36.1 (95% CI 33.5–38.6) mm Hg, 25.7 (95% CI 23.8–27.5) mm Hg, and 15.5 (95% CI 12.4–16.51) mm Hg, respectively.

Variable	No. (%)
Sex	
Female	60 (57.7)
Male	44 (42.3)
Age, years	
18–59	8 (7.7)
60–69	13 (12.5)
70–79	43 (41.3)
80+	40 (38.5)
Glaucoma	
Present*	16 (15.4)
Diagnosis	
Neovascular AMD	88 (84.6)
Diabetic macular edema	7 (6.7)
Other (including ocular histoplasmosis)	9 (8.7)
Injection number	
One	33 (31.7)
Two	49 (47.1)
Three	21 (20.2)
Four	1 (1.0)
Eye	
OS	59 (56.7)
OD	45 (43.3)
Physician	
Sanjay Sharma	60 (57.7)
Jeffery Gale	44 (42.3)
Lens status	
Phakic	59 (56.7)
Pseudophakic	45 (43.3)

*Glaucoma diagnosed in the eye being injected.
Note: AMD, age-related macular degeneration.

Table 2 shows the range of IOP values at baseline and at the 3 postinjection intervals; this information is also shown graphically in Fig. 1. IOP increased sharply 2 minutes after injection ($p < 0.0005$), at which time 13 patients (12.5%) had an IOP over 50 mm Hg, and 3 patients had an IOP over 70 mm Hg. Over the next 30 minutes IOP tended to normalize; however, at 5 and 30 minutes after injection, the mean IOP remained statistically significantly above baseline ($p < 0.0005$, $p = 0.02$, respectively). Fourteen patients (13.5%) had 30-minute postinjection IOPs that were at least 5 mm Hg greater than baseline values, but for only 3 patients (2.9%) was the IOP 25 mm Hg or higher at 30 minutes. The IOP for 2 of these patients (with 30-minute values of 27 and 28 mm Hg) returned to under 25 mm Hg within 2 hours and did not require initiation of glaucoma medication. The third patient, whose IOP at 30 minutes was 45 mm Hg, required initiation of glaucoma medication the following day. The patient's IOP was controlled within 1 week, and the glaucoma medication was discontinued at that time.

A multivariate logistic regression analysis was used to investigate factors related to higher IOP at 30 minutes after injection. Since only a small proportion of patients had an IOP of ≥ 25 mm Hg at 30 minutes (primary outcome), we used the secondary outcome measure (IOP ≥ 5 mm Hg above baseline) as our dependent variable in the regression analysis. Regression analysis showed a trend towards phakic patients having higher IOP at 30 minutes (odds ratio = 3.2; $p = 0.089$). Demographic and clinical variables not statistically significant in our model were as follows: sex, age, history of glaucoma, diagnosis requiring intravitreal bevacizumab injection, previous injections, surgeon, and eye (OS or OD).

INTERPRETATION

Intravitreal injection has become an increasingly common intervention in the treatment of retinal disease. With more than 15 000 projected worldwide injections this year, intravitreal bevacizumab is being positioned as a

Table 2—Introcular pressure (IOP) at baseline and at various times after intravitreal injection of bevacizumab

IOP (mm Hg), range	No. (%)			
	Baseline	2 min. after injection	5 min. after injection	30 min. after injection
0–19	99 (95.2)	7 (6.7)	32 (30.8)	83 (79.8)
20–24	4 (3.8)	15 (14.4)	22 (21.2)	18 (17.3)
25–29	1 (1.0)	12 (11.5)	20 (19.2)	2 (1.9)
30–34		17 (16.3)	13 (12.5)	
35–39		14 (13.5)	6 (5.8)	
40–44		14 (13.5)	8 (7.7)	
45–49		12 (11.5)		1 (1.0)
50–59		8 (7.7)	2 (1.9)	
60–69		2 (1.9)	1 (1.0)	
70–79		2 (1.9)		
80+		1 (1.0)		

Note: min., minutes.

major treatment modality for exudative AMD, which is the leading cause of new blindness in North America.¹ However, little is known about its safety.

Our investigation showed that a 0.05 cc intravitreal bevacizumab injection has an excellent safety profile with respect to sustained short-term IOP changes. Although there was a statistically significant higher IOP at 30 minutes after injection when compared with baseline, this difference (1.4 mm Hg) was not clinically significant. The vast majority (97.1%) of patients had an IOP of less than 25 mm Hg after 30 minutes. However, our study did show that IOP rises substantially in some patients immediately after injection but rapidly normalizes. More than 10% of subjects experienced an IOP spike above 50 mm Hg. This likely induces ocular perfusion pressure below the auto-regulatory range of optic nerve head blood flow.¹¹ Moreover, acute deformations in the contour of the lamina cribrosa also occur at these IOPs.¹² The long-term consequences of these transient events are unknown. However, the potential for negative sequelae should be considered, especially in patients with advanced glaucomatous optic neuropathy. A pre-injection anterior chamber tap as prophylaxis could be considered for these patients.

In 2 patients with high pressure after injection, the IOP normalized over 1.5 hours, and one additional patient required a short course of IOP-lowering medication. This 1 patient was male, relatively young (<50 years), had 30-minute IOP of 45 mm Hg, and was being treated for diabetic macular edema. He did not have previous glaucoma but had received an injection of a corticosteroid

within the previous year. It is possible that this patient sustained some damage to the trabecular meshwork as a result of the previous steroid injection and was consequently unable to adequately clear the additional volume of fluid from the injection. Our sample was too small to study this question adequately, but future research into IOP change after intravitreal bevacizumab injection in patients with previous corticosteroid injection may be useful.

Recently, Benz et al.⁶ studied short-term IOP changes after injection of 0.1 mL intravitreal TA. They found that 7.1% of patients had an IOP greater than 25 mm Hg at 30 minutes after injection and postulated that the IOP rise after injection may be mechanical as a result of a 2.5% increase in vitreous volume. In our study comparatively fewer patients (2.9%) had IOP values over 25 mm Hg at 30 minutes. The most obvious reason for this is that we injected less medication (0.05 cc vs. 0.1 cc) into the vitreous cavity. In addition, bevacizumab is not known to cause IOP increases in the long term, whereas corticosteroids have a known long-term risk of ocular hypertension linked to corticosteroid-dependent mechanical and biochemical changes to the trabecular meshwork,^{13,14} resulting in increased outflow obstruction.

To our knowledge, this is the first study investigating short-term IOP changes after intravitreal administration of bevacizumab. It is prospective and has a relatively large sample compared with other similar safety studies.^{6–8} We deliberately used minimal exclusion criteria in order to simulate the safety of this treatment modality in the real world; consequently, this can be considered an effectiveness study.

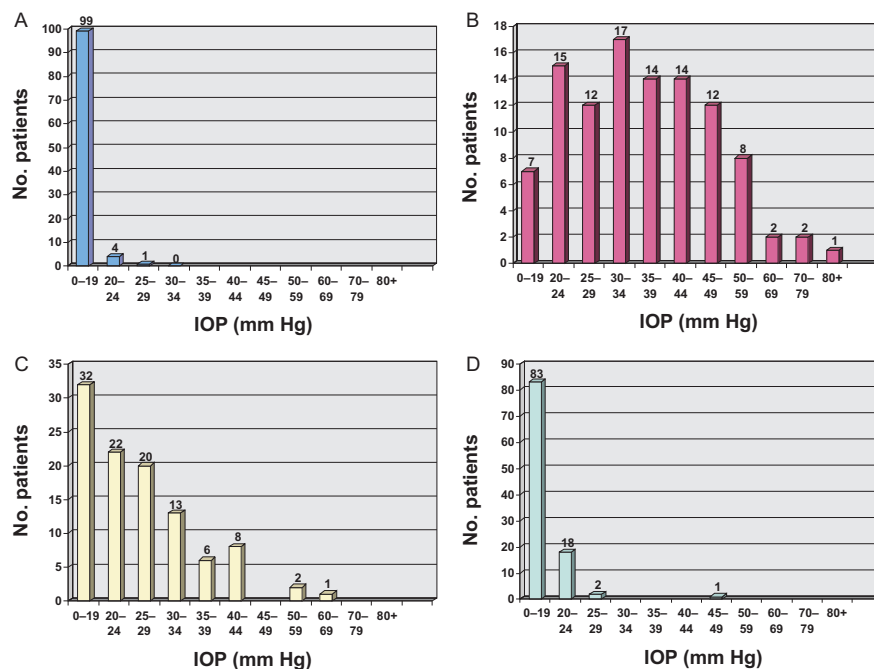


Fig. 1—Distribution of intraocular pressure at (A) baseline, (B) 2 minutes after intravitreal injection of bevacizumab, (C) 5 minutes after injection, and (D) 30 minutes after injection.

In addition, we demonstrated excellent inter-rater reliability with respect to IOP measurement. One weakness of the study was to not quantify medication reflux at the time of injection. This has been done in the past when short-term IOP changes after intravitreal injection of corticosteroids have been studied⁶ and might have enabled better prediction of which patients would have immediate IOP pressure spikes. However, vitreous reflux is a subjective measure and is especially difficult to quantify with intravitreal injection of bevacizumab since the medication is clear. This is different from the reflux of intravitreal TA, which has a milky-white appearance and would be easier to quantify. Therefore, it is uncertain whether attempting to quantify vitreous reflux of the bevacizumab would have added reliable data to our study.

In conclusion, we have shown that intravitreal injection of bevacizumab has an excellent safety profile with respect to sustained IOP changes. Elevated IOP after 30 minutes of observation may occur in a small number of patients. While transient extreme IOP elevations occur in a significant percentage of patients, the consequences of these events are unknown. Clinicians should consider checking IOP after intravitreal bevacizumab injection as a precaution. In addition, a pre-injection anterior chamber tap could be considered as prophylaxis for patients with advanced glaucoma.

The authors have no proprietary interest in any aspect of this article.

REFERENCES

1. Fung AE, Rosenfeld PJ, Reichel E. The International Intravitreal Bevacizumab Safety Survey: using the internet to assess drug safety worldwide. *Br J Ophthalmol* 2006;90(11):1344–9.
2. Jorge R, Costa RA, Calucci D, Cintra LP, Scott IU. Intravitreal bevacizumab (Avastin) for persistent new vessels in diabetic retinopathy (IBEPE study). *Retina* 2006;26(9):1006–13.
3. Tewari A, Dhalla MS, Apte RS. Intravitreal bevacizumab for treatment of choroidal neovascularization in pathologic myopia. *Retina* 2006;26(9):1093–4.
4. Bashshur ZF, Bazarbachi A, Schakal A, Haddad ZA, El Haibi CP, Nouredin BN. Intravitreal bevacizumab for the management of choroidal neovascularization in age-related macular degeneration. *Am J Ophthalmol* 2006;142(1):1–9.
5. Rich RM, Rosenfeld PJ, Puliafito CA, et al. Short-term safety and efficacy of intravitreal bevacizumab (Avastin) for neovascular age-related macular degeneration. *Retina* 2006;26(5):495–511.
6. Benz MS, Albini TA, Holz ER, et al. Short-term course of intraocular pressure after intravitreal injection of triamcinolone acetonide. *Ophthalmology* 2006;113(7):1174–8.
7. Dwinger MC, Pieper-Bodeewes I, Eter N, Holz FG. Variations in intraocular pressure (IOP) and necessity for paracentesis following intravitreal triamcinolone injection [in German]. *Klin Monatsbl Augenheilkd* 2005;222(8):638–42.
8. Singh IP, Ahmad SI, Yeh D, et al. Early rapid rise in intraocular pressure after intravitreal triamcinolone acetonide injection. *Am J Ophthalmol* 2004;138(2):286–7.
9. Quigley HA, Anderson DR. Distribution of axonal transport blockade by acute intraocular pressure elevation in the primate optic nerve head. *Invest Ophthalmol Vis Sci* 1977;16(7):640–4.
10. Michelson G, Groh MJ, Langhans M. Perfusion of the juxta-papillary retina and optic nerve head in acute ocular hypertension. *Ger J Ophthalmol* 1996;5(6):315–21.
11. Riva CE, Hero M, Titzel P, Petrig B. Autoregulation of human optic nerve head blood flow in response to acute changes in ocular perfusion pressure. *Graefes Arch Clin Exp Ophthalmol* 1997;35(10):618–26.
12. Yan DB, Coloma FM, Metheerairut A, Trope GE, Heathcote JG, Ethier CR. Deformation of the lamina cribrosa by elevated intraocular pressure. *Br J Ophthalmol* 1994;78(8):643–8.
13. Jonas JB, Degenring R, Kreissig I, Akkoyun I, Kamppeier B. Intraocular pressure elevation after intravitreal triamcinolone acetonide injection. *Ophthalmology* 2005;112(4):593–8.
14. Jones R 3rd, Rhee DJ. Corticosteroid-induced ocular hypertension and glaucoma: a brief review and update of the literature. *Curr Opin Ophthalmol* 2006;17(2):163–7.

Key words: intravitreal injection, short-term intraocular pressure, intraocular pressure, Avastin, bevacizumab