



Intravitreal Injections of Bevacizumab: The Impact of Needle Size in Intraocular Pressure and Pain

¹Mónica Loureiro, ²Rita Matos, ³Paula Sepulveda, ⁴Dália Meira

ABSTRACT

Aim: To compare the effect of 30-gauge vs 27-gauge needle size on intraocular pressure (IOP) rise and patients' pain experience after intravitreal injection (IVI) of bevacizumab.

Materials and methods: Cross-sectional, randomized, double-armed study. Patients were randomized to IVI with 30-gauge or 27-gauge needle. The IOP was measured pre and post IVI. Patients' pain was graded using the visual analog scale (VAS).

Results: A total of 54 eyes were included. The IVI caused a significant IOP rise in both groups ($p < 0.001$). In the 30-gauge group, the mean pre- and postinjection IOP was 16.3 ± 3.6 mmHg and 24.1 ± 9.0 mmHg. The corresponding figures in the 27-gauge group were 18.0 ± 2.54 ($p = 0.26$) and 23.1 ± 7.5 mmHg ($p = 0.66$). In the 30-gauge group, the mean VAS pain score was 3.2 ± 2.6 compared to 3.0 ± 2.5 in the 27-gauge group ($p = 0.78$).

Conclusion: The IVI caused a significant rise in IOP after the injection, independently of the needle size used. The 27-gauge needle coursed with lower postinjection IOP without prejudice of the patient comfort.

Clinical significance: The IVI with 27-gauge may be considered for glaucomatous eyes (higher risk eyes), for which IOP spikes are not recommended.

Keywords: Bevacizumab, Intravitreal injections, Intraocular pressure, Pain, Visual analog scale.

How to cite this article: Loureiro M, Matos R, Sepulveda P, Meira D. Intravitreal Injections of Bevacizumab: The Impact of Needle Size in Intraocular Pressure and Pain. *J Curr Glaucoma Pract* 2017;11(2):38-41.

INTRODUCTION

The intravitreal injection (IVI) of anti-vascular endothelial growth factor (anti-VEGF) has become one of the most common intraocular procedures over the past decade.¹ The efficacy and safety profile of anti-VEGF therapy have revolutionized the treatment of several retinal diseases, such as neovascular age-related macular degeneration, retinal vein occlusion, and diabetic macular edema.²⁻⁴ Bevacizumab, an off label anti-VEGF drug used worldwide in the clinical practice for the last decade, is an

humanized monoclonal antibody that binds all VEGF isoforms and interferes with receptor binding to inhibit its signal.³ Its efficacy and safety profile are similar to ranibizumab, but much less expensive, and for this reason is usually the first treatment choice.⁵

The majority of patients, over the course of their diseases, require multiple anti-VEGF IVI. The intraocular pressure (IOP) rise occurring after this procedure revealed to be transient and usually normalizes spontaneously within 30 minutes;⁶⁻⁸ however, repeated IOP spikes may be a contributing factor for sustained IOP elevation in susceptible eyes, related to the trabecular meshwork damage.^{8,9} The presence of vitreous reflux has been associated with lower postinjection IOP¹⁰ and Pang et al¹¹ reported that the incidence of vitreous reflux was higher with larger bore size needles. Hence, we hypothesize that larger 27-gauge needles are less associated with IOP spikes, as they may cause higher vitreous reflux.

Despite this, there is a tendency to favor smaller bore size needles owing to the requirement for less force to penetrate the sclera and the belief that it induces less pain.¹² The patient's pain experience during the injection may hinder his collaboration with sudden movements of the eye that can potentially cause complications and may also affect the decision to keep the treatments. Therefore, patients' comfort has to be taken into account, as IVI treatments are rising exponentially. The visual analog scale (VAS) is a common and easy tool for assessing pain and it has been shown to be a valid and reliable research method in previous ophthalmology studies.¹³⁻¹⁵

The main purpose of the study was to compare the effect of size on immediate postinjection IOP and on patients' pain experienced after the IVI of bevacizumab.

MATERIALS AND METHODS

The study was approved by the local ethics committee and informed consent (according to the tenets of the Declaration of Helsinki) was obtained from participating patients. All patients, referred for IVI of bevacizumab by an ophthalmologist from our institution, older than 18 years of age and mentally able to score the pain, were selected to participate in the study. The exclusion criteria were:

- Previous ocular surgery other than cataract extraction with posterior chamber intraocular lens
- Use of lowering IOP drugs

^{1,2}Resident, ^{3,4}Consultant

¹⁻⁴Department of Ophthalmology, Centro Hospitalar de Vila Nova de Gaia/Espinho, Porto, Portugal

Corresponding Author: Mónica Loureiro, Resident, Department of Ophthalmology, Centro Hospitalar de Vila Nova de Gaia/Espinho, Porto, Portugal, Phone: +00351919281855, e-mail: monicamloureiro@gmail.com

- Corneal diseases that might interfere with the tonometry and
- Ocular pain prior to the procedure.

The patients were randomly selected to be injected with a 30-gauge (0.40 × 12 mm, Braun®) or a 27-gauge (0.30 × 12 mm, Braun®) needle. The periocular skin, eyelid margins, and eye lashes were cleaned with 10% povidone iodine before the IVI. After topical anesthetic oxibuprocaine 0.4% and topical 5% povidone-iodine solution application to the conjunctiva, an eyelid speculum was positioned to stabilize the eyelids. No sedation was administered to any patient. Bevacizumab (1.25 mg/0.05 mL) was dispensed into single-use 27-gauge and 30-gauge needle syringes using an aseptic technique. The anti-VEGF was injected into the vitreous cavity using a straight scleral technique through the pars plana, 3.5 to 4.0 mm posterior to the limbus at the superotemporal quadrant, with the patient in supine position and under sterile conditions.

All patients had immediate pre- and postinjection IOP measurements, using Goldmann applanation tonometry, by the same ophthalmologist who was masked to the needle caliber. The measurements were performed three times and the mean value was used for the analysis. The postinjection IOP was consistently measured within the first 5 minutes after the IVI. After the injection, patients were also asked to rate their pain experience during the procedure on a VAS, which is a psychometric response scale for subjective characteristics that cannot be directly measured, indicating a position along a continuous line between two end points 0 and 10. All VAS measurements were collected by a single ophthalmologist after explaining this method to the patients.

Demographic and patients' characteristics were compared using descriptive statistics and univariate analysis as appropriate. Immediate postinjection IOP and acute IOP variation between groups were compared by

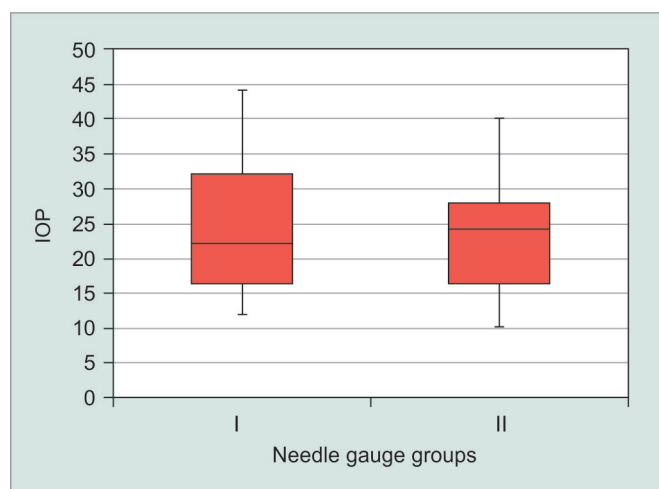
a 2-tailed t test. Considering the VAS scores, categorical parameters were analyzed using Mann-Whitney test and continuous parameters were analyzed by Spearman's rank correlations. A value of $P < 0.05$ was considered to indicate statistical significance.

RESULTS

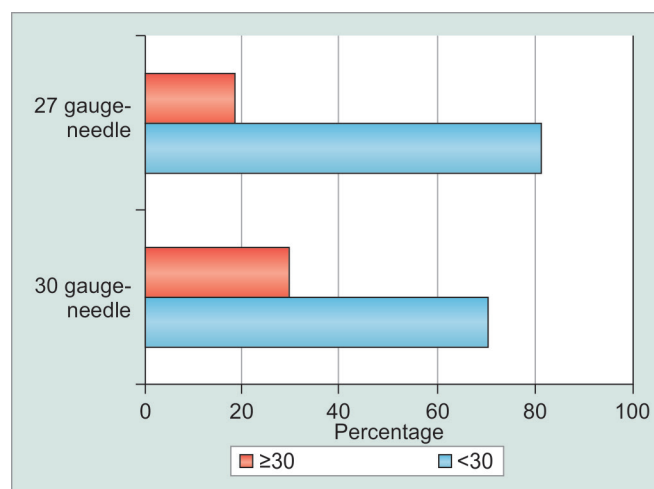
Fifty-four eyes of 48 patients received the bevacizumab IVI for the treatment of diabetic macular edema (63%), neovascular age-related macular degeneration (26%), and retinal vein occlusion (11%). Half of them were injected with 27-gauge needles whereas the other half with 30-gauge needles.

In the 30-gauge group, the mean age was 68.7 ± 9.8 years (54–87) and the mean pre-IVI IOP was 16.3 ± 3.6 mm Hg. In the 27-gauge group, the mean age was 70.1 ± 10.4 years (47–86) and the mean pre-IVI IOP was 18.0 ± 2.5 mm Hg. The groups were compared using independent sample t-test and were matched for age ($p = 0.44$) and pre-IVI IOP ($p = 0.26$). The mean number of IVI previously performed in each patient was 5.3 ± 2.9 in the 30-gauge group compared to 4.3 ± 3.6 in the 27-gauge group ($p = 0.32$).

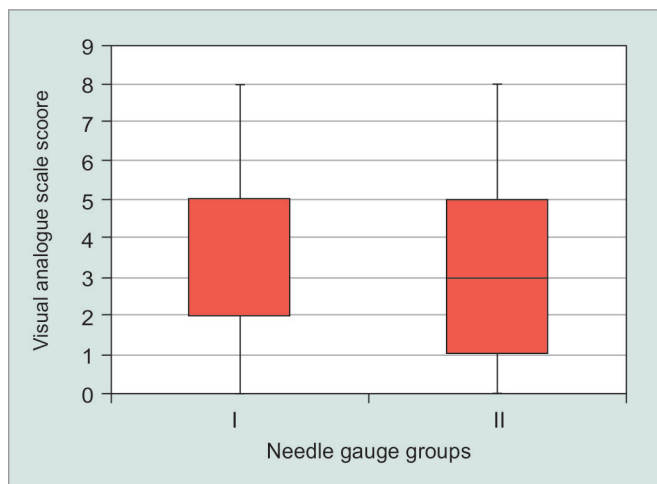
After IVI, a significant rise of the IOP occurred within the first 5 minutes in both groups ($p < 0.001$) and the mean increase was of 6.9 ± 8.2 mm Hg. Eyes injected with 30-gauge needles presented a mean post-IVI IOP of 24.1 ± 9.0 mm Hg, whereas the corresponding figure in the 27-gauge group was lower: 23.1 ± 7.5 mm Hg ($p = 0.66$) (Graph 1). The incidence of a post-IVI IOP of 30 mm Hg or higher was 29.6% ($n = 8$) using 30-gauge needles compared to 18.5% ($n = 5$) using 27-gauge needles ($p = 0.34$) (Graph 2). The acute IOP variation, representing the difference between the pre- and postinjection IOP, was 7.9 ± 9.1 mm Hg in eyes injected with 30-gauge needles, compared to 5.9 ± 7.2 mm Hg in the 27-gauge needles group ($p = 0.38$, 2-tailed t-test).



Graph 1: The postinjection IOP (within the 1st minutes) using 30-gauge needle (group I) and 27-gauge needle (group II)



Graph 2: The percentage of eyes with postinjection IOP of 30 mm Hg or higher after injection using 30-gauge and 27-gauge needles



Graph 3: The distribution of VAS scores using 30-gauge needle (group I) and 27-gauge needle (group II)

The mean VAS pain score in the 30 gauge needle and 27 gauge needle groups was 3.2 ± 2.6 (median 2, mode 2) and 3.0 ± 2.2 (median 3, mode 1) respectively. No significant difference was demonstrated between the two groups regarding pain during the injection ($p = 0.78$) (Graph 3). No significant correlation was found between pain scores and patient's age ($R = 0.31$) or previous IVI number ($R = -0.12$).

DISCUSSION

The IVI of anti-VEGF is a widespread accepted procedure; however, there is no clear consensus in terms of needle gauge used.^{9,16} The arguments surrounding the appropriate needle size choice have been related to the patients' pain experience during the injection and the immediate post-IVI IOP. Therefore, this study might contribute to clarify the significance of needle choice, taking into account these two parameters, and thus helping to establish a standardized protocol.

Our study evidenced a significant IOP rise within the first minutes after the IVI, independently of the needle bore size. Despite the fact that the 27-gauge group presented a lower acute IOP variation, there was not a significant difference compared to the 30-gauge group. Previously, Kim et al¹⁷ showed greater IOP with 30- and 32-gauge needles in comparison to 27-gauge needles; however, the injections done with 30- and 32-gauge needles consisted of bevacizumab or ranibizumab, while injections done with 27-gauge needles were of pegaptanib or triamcinolone. Differently, in our study, we used the same drug and volume in both groups.

Pang et al¹¹ investigated the effect of needle size on post-IVI IOP and reflux and found that eyes injected with 32-gauge needles had higher IOP and lower incidence of vitreous reflux compared to the eyes injected with larger 30-gauge needles. Therefore, these findings suggest that

a larger bore size needle facilitate the vitreous reflux and thus lower IOP spikes after IVI are expected. In fact, in our study, the 27-gauge group had lower IOP after the injection and, furthermore, the IOP variation was lower than with 30-gauge needles, however, not significantly.

Attending to the technique, the tunneled scleral and the straight scleral IVI were previously compared by Knecht et al¹⁸, in terms of IOP increase after the injection and patient discomfort, without differences between the groups. Therefore, we used a straight scleral IVI technique in all patients and only studied the needle size impact.

With the increasing occurrence of patients receiving injections, often repeated for several times, evaluating the pain associated with this procedure is important to optimize patient's comfort and compliance. The VAS is a convenient tool, easily performed by anyone cognitively capable of understanding the parameters and responding to clinician instruction. After a brief explanation, no patients had difficulty in classifying the degree of their pain. The VAS is frequently used in the Portuguese population to assess the analgesic effect of a therapy and has been widely used in ophthalmic research.¹³⁻¹⁵ In our study, the IVI proved to cause only a mild pain, being well tolerated by the patients, independent of the needle bore size used.

Regarding the caliber of the needle and the pain during IVI, Güler et al¹⁹ and Rodrigues et al²⁰ reported that patients injected with 30-gauge needle experienced less pain compared to those injected with 27-gauge needle. In fact, Pulido et al¹² reported that 27-gauge needles require almost twice the force to penetrate the sclera, which theoretically may have implications for patients' comfort. However, both Rifkin and Schaal²¹ and Haas et al²² found that the 27- and 30-gauge needles did not influence significantly the pain. In a similar way, in our study, there was no difference between the 27- and 30-gauge needles.

A limitation of our study was the sample size which did not allow to analyze the effect of demographic factors on the pain score and postinjection IOP. Although the evaluation of the vitreous reflux could be of interest, the assessment of its absence (no detectable reflux) or presence (any visible reflux) is subjective. Therefore, quantitative studies regarding vitreous reflux and post-IVI IOP are needed. The axial length was not taken into account; however, it was not a predictor of subsequent IOP elevation in a previous study.²³

CONCLUSION

The IVI caused a significant rise in IOP after the injection, independently of the needle size used. Although not significantly, the postinjection IOP and IOP variation

were lower in the 27-gauge group. The 27-gauge might be selected in cases requiring less IOP variation, such as glaucomatous eyes in which IOP spikes can cause visual field deterioration. The use of 27-gauge needles showed no significant effect in the patients' pain level.

REFERENCES

1. Peyman GA, Lad EM, Moshfeghi DM. Intravitreal injections of therapeutic agents. *Retina* 2009 Jul-Aug;29(7):875-912.
2. Cazet-Supervielle A, Gozlan J, Cabasson S, Boissonnot M, Manic H, Leveziel N. Intravitreal ranibizumab in daily clinical practice for age-related macular degeneration: treatment of exudative age-related macular degeneration in real life. *Ophthalmologica* 2015;234(1):26-32.
3. Avery RL, Pearlman J, Pieramici DJ, Rabena MD, Castellarin AA, Nasir MA, Giust MJ, Wendel R, Patel A. Intravitreal bevacizumab (Avastin) in the treatment of proliferative diabetic retinopathy. *Ophthalmology* 2006 Oct;113(10):1695.e1-e15.
4. Berger AR, Cruess AF, Altomare F, Chaudhary V, Colleaux K, Greve M, Kherani A, Mandelcorn ED, Parsons H, Rhéaume MA, et al. Optimal treatment of retinal vein occlusion: canadian expert consensus. *ophthalmologica* 2015;234(1):6-25.
5. CATT Research Group, Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 2011 May;364(20):1897-1908.
6. Falkenstein IA, Cheng L, Freeman WR: Changes of intraocular pressure after intravitreal injection of bevacizumab (Avastin). *Retina* 2007 Oct;27(8):1044-1047.
7. Bakri SJ, Pulido JS, McCannel CA, Hodge DO, Diehl N, Hillemeier J Immediate intraocular pressure changes following intravitreal injections of triamcinolone, pegaptanib, and bevacizumab. *Eye (Lond)* 2009 Jan;23(1):181-185.
8. Kampougeris G, Spyropoulos D, Mitropoulou A. Intraocular pressure rise after anti-VEGF treatment: prevalence, possible mechanisms and correlations. *J Curr Glaucoma Pract* 2013 Jan-Apr;7(1):19-24.
9. Yannuzzi NA, Patel SN, Bhavsar KV, Sugiguchi F, Freund KB. Predictors of sustained intraocular pressure elevation in eyes receiving intravitreal anti-vascular endothelial growth factor therapy. *Am J Ophthalmol* 2014 Aug;158(2):319-327.
10. Lemos V, Cabugueira A, Noronha M, Abegão Pinto L, Reina M, Branco J, Gomes T. Intraocular pressure in eyes receiving intravitreal anti-vascular endothelial growth factor injections. *Ophthalmologica* 2015;233(3-4):162-168.
11. Pang C, Mrejen S, Hoang Q, Sorenson JA, Freund KB. Association between needle size, postinjection reflux, and intraocular pressure spikes after intravitreal injections. *Retina* 2015 Jul;35(7):1401-1406.
12. Pulido JS, Zobitz ME, An KN. Scleral penetration force requirements for commonly used intravitreal needles. *Eye (Lond)* 2007 Sep;21(9):1210-1211.
13. Salo D, Eget D, Lavery RF, Garner L, Bernstein S, Tandon K. Can patients accurately read a visual analog pain scale? *Am J Emerg Med* 2003 Nov;21(7):515-519.
14. Yau GL, Jackman CS, Hooper PL, Sheidow TG. Intravitreal injection anesthesia-comparison of different topical agents: a prospective randomized controlled trial. *Am J Ophthalmol* 2011 Feb;151(2):333-337.
15. Cintra LP, Lucena LR, Da Silva JA, Costa RA, Scott IU, Jorge R. Comparative study of analgesic effectiveness using three different anesthetic techniques for intravitreal injection of bevacizumab. *Ophthalmic Surg Lasers Imaging* 2009 Jan-Feb;40(1):13-18.
16. Green-Simms AE, Ekdawi NS, Bakri SJ. Survey of intravitreal injection techniques among retinal specialists in the United States. *Am J Ophthalmol* 2011 Feb;151(2):329-332.
17. Kim JE, Mantravadi AV, Hur EY, Covert DJ. Short-term intraocular pressure changes immediately after intravitreal injections of anti-vascular endothelial growth factor agents. *Am J Ophthalmol* 2008 Dec;146(6):930-934.
18. Knecht PB, Michels S, Sturm V, Bosch MM, Menke MN. Tunneled versus straight intravitreal injection: intraocular pressure changes, vitreous reflux, and patient discomfort. *Retina* 2009 Sep;29(8):1175-1181.
19. Güler M, Bilgin B, Çapkin M, im ek A, Bilak . Assessment of patient pain experience during intravitreal 27-gauge bevacizumab and 30-gauge ranibizumab injection. *Korean J Ophthalmol* 2015 Jun;29(3):190-194.
20. Rodrigues EB, Grumann A Jr, Penha FM, Shiroma H, Rossi E, Meyer CH, Stefano V, Maia M, Magalhaes O Jr, Farah ME. Effect of needle type and injection technique on pain level and vitreal reflux in intravitreal injection. *J Ocul Pharmacol Ther* 2011 Apr;27:197-203.
21. Rifkin L, Schaal S. Factors affecting patients' pain intensity during in office intravitreal injection procedure. *Retina* 2012 Apr;32(4):696-700.
22. Haas P, Falkner-Radler C, Wimpfissinger B, Malina M, Binder S. Needle size in intravitreal injections-pain evaluation of a randomized clinical trial. *Acta Ophthalmol* 2016 Mar;94(2):198-202.
23. Hoang QV, Jung JJ, Mrejen S, Freund KB. Influence of axial length and post-injection reflux on sustained intraocular pressure elevation as a result of intravitreal anti-vascular endothelial growth factor therapy. *Retina* 2014 Mar;34(3):519-524.