

Analysis of intraocular pressure variation after intravitreal injection of ranibizumab

Análise da variação da pressão intraocular após injeção intravítrea de ranibizumabe

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ABSTRACT

Objective: Treatment with anti-angiogenic drugs is one of the most widely used modalities of treatment of macular edema related conditions. Intravitreal injection of a VEGF-A inhibitor is highly effective, but is related to adverse effects such as increased intraocular pressure. The objective of this study was to evaluate intraocular pressure (IOP) variation in patients who underwent intravitreal injections of ranibizumab, variation according to phakic/aphakic and history of previous injections. **Methods:** This was a cross-sectional observational study. All patients submitted to intravitreal injections with diagnosis of exudative age-related macular degeneration, retinal central vein occlusion with macular edema, or diabetic macular edema were included. The IOP was measured before the injection, immediately after and 30 minutes after the injection with a portable tonometer. **Results:** 143 intravitreal injections were performed, with 96 injections performed in 55 participants. The comparison between IOP before and 30 minutes after intravitreal injection showed to be statistically significant with higher than initial IOP ($p < 0.0001$) in patients with diabetic macular edema. Phakic and aphakic patients did not show significant differences regarding IOP variation. When only those participants who had received previous injections were analyzed, no significant variation was found. **Conclusion:** We conclude in this study that there is a significant difference between intraocular pressure before and 30 minutes after intravitreal injection of ranibizumab in patients with diabetic macular edema, showing that this period of time was not sufficient for regression of IOP at the pre-injection value. We did not find significant differences between other groups, comparing phakic and aphakic patients, nor in patients who had received previous injections.

Keywords: Intraocular pressure; Intravitreal injections; Posterior eye segment; Ranibizumab

RESUMO

Objetivo: O tratamento com anti-angiogênicos é uma das modalidades mais utilizadas em patologias relacionadas ao edema macular. A injeção intravítrea de um inibidor do VEGF-A tem alta efetividade, porém está relacionada com efeitos adversos, como o aumento da pressão intraocular. O objetivo deste estudo foi avaliar a variação da pressão intraocular (PIO) em pacientes que se submetem a injeções intravítreas de ranibizumabe, a variação de acordo com facia e com história de injeções prévias. **Métodos:** Este foi um estudo um estudo observacional transversal. Foram incluídos todos os pacientes submetidos a injeções intravítreas com diagnóstico de degeneração macular relacionada à idade exsudativa, oclusão de veia central da retina com edema macular, ou edema macular diabético. A pressão intraocular foi aferida antes da injeção, imediatamente após e 30 minutos após a injeção com tonômetro portátil. **Resultados:** Foram realizadas 143 injeções intravítreas, restando para a análise 96 injeções realizadas em 55 participantes. A comparação entre a PIO antes e 30 minutos após a injeção intravítrea mostrou-se estatisticamente significativa com PIO final maior que a inicial ($p < 0,0001$) em pacientes com edema macular diabético. Pacientes fáticos e afáticos não mostraram diferenças significativas com relação a variação da PIO. Quando analisados apenas os participantes que haviam recebido injeções prévias, não foi encontrado uma variação significativa. **Conclusão:** Concluímos neste estudo que existe uma diferença significativa entre a pressão intraocular antes e 30 minutos após a injeção intravítrea de ranibizumabe em pacientes com edema macular diabético, mostrando que esse período de tempo não foi suficiente para a regressão da PIO ao valor pré-injeção. Não encontramos diferenças significativas entre outros grupos, comparação entre fáticos e afáticos, nem em pacientes que haviam recebido injeções prévias.

Descritores: Pressão intraocular; Injeções intravítreas; Segmento posterior do olho; Saúde ocular; Ranibizumabe

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The authors declare no conflict of interests.

Received for publication 03/10/2017 - Accepted for publication 23/11/2017.

INTRODUCTION

Treatment with anti-angiogenic is one of the most widely used modalities in pathologies related to macular edema, and one of the factors leading to the onset of edema is the increased release of vascular endothelial growth factor A (VEGF-A).⁽¹⁾ Intravitreal injection of a VEGF-A inhibitor is highly effective but is related to adverse effects such as increased intraocular pressure.⁽²⁾ This increase is considered transitory, although new evidence shows that it can continue in a sustainable way.^(3,4)

The objective of the present study was to evaluate the intraocular pressure (IOP) variation in patients who underwent intravitreal injections of ranibizumab, varying according to facial and history of previous injections.

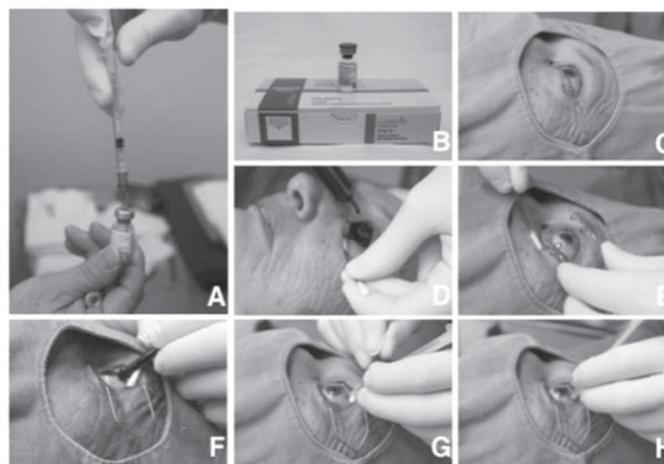
METHODS

This was a cross-sectional study with measurements carried out on the same day. We included all patients submitted to intravitreal injections diagnosed with exudative age-related macular degeneration (AMD), central retinal vein occlusion (CRVO) with macular edema, or diabetic macular edema (DME) from January to May 2017 at the Ophthalmology Department of Hospital Governador Celso Ramos. Patients who had incomplete medical records or other ocular pathologies, such as neovascular glaucoma, neovascular membranes related to angioid streaks or high myopia, proliferative diabetic retinopathy were excluded from the analysis. All patients underwent ophthalmologic evaluation, including slit-lamp biomicroscopy and history of intravitreal injections, and received an informed consent form approved by the institution's Research Ethics Committee (1.861.123/2016).

The medication used was ranibizumab (Lucentis® Genentech Inc.) used by a single ophthalmologist. The protocol for application starts with local analgesia with anesthetic eyedrops based on tetracaine hydrochloride 1%, asepsis and antisepsis of the palpebral skin, surgical field positioning, application of topical iodine-polyvidone in the conjunctiva 5%, placement of blepharostat Bar-raquer and marking a distance of 3.5mm in pseudophakic and 4mm in phakic between conjunctival limb and sclera in the upper temporal quadrant of the eyeball. Aspiration of 0.05 ml of the drug with 18G needle with filter, and preparation of the application with 30G needle. A cotton swab was used to laterally draw the conjunctiva at the site of application, then the needle was positioned at 90° and inserted to infuse the medication. Repositioning of the conjunctiva with the swab after withdrawal of the needle. After the procedure, a drop of eyedrops dexamethasone 0.1% was applied with neomycin sulfate 0.5% and polymyxin sulfate B 600,000 IU% (Figure 1).

Intraocular pressure was measured prior to injection, immediately after and 30 minutes after the injection with portable tonometer Tono-Pen AVIA® (Reichert Technologies). Patients were advised of complications of the procedure and were instructed to return in case of worsening of visual acuity, pain, discomfort, or any other symptom in the eye that received the injection.

The data were entered into a spreadsheet of software Numbers 3 OS X® (Apple inc.) and presented as average + standard deviation (SD). The tests t and Spearman test were used to analyze the associations between the variables of interest considering values of $p < 0.05\%$ as significant.



A. aspiration of medication B. medication vial C. surgical field placement D. application of iodine polisher 5% E. blepharostat positioning F. limbal-scleral distance marking G. lateral traction of the conjunctiva H. intravitreal injection of medication perpendicular to the sclera

Figure 1: Descriptive photos of the steps of the intravitreal injection protocol

RESULTS

We carried out 143 intravitreal injections between January and May 2017. We excluded 17 patients because they had incomplete records, 10 patients had pathologies described in the exclusion criteria (2 neovascular glaucoma, 3 neovascular membrane related to angioid streaks, 1 neovascular membrane of the high myopic, 4 proliferative diabetic retinopathy), with 96 injections remaining for the analysis performed in 55 patients. The results of measurements of the intraocular pressure were described in table 1.

Table 1
Result of IOP measurements before, immediately after and 30 minutes after the intravitreal injection of ranibizumab

	IOP average + SD
IOP before the injection	16.7 mmHg ± 3.14
IOP immediately after the injection	39.98 mmHg ± 8.47
IOP 30 minutes after the injection	18.11 mmHg ± 3.81

IOP = intraocular pressure; SD = standard deviation

The average age ± SD was 70 ± 11 years, with 17 males and 44 females. Exudative AMD was the reason for the application in 30 participants, the DME in 18, and the CRVO with macular edema in 7. The ophthalmologic examination showed 17 pseudophakic and 35 phakic eyes. Regarding previous treatments, 13 patients applied the injection for the first time, whereas 42 received at least one previous injection in the same eye, with an average of 3.27 ± 2.70 injections.

The comparison between IOP before and 30 minutes after intravitreal injection was statistically significant, with higher IOP than the initial IOP. Phakic and aphakic patients did not show significant differences regarding IOP variation. When only participants who had received previous injections were analyzed, no significant variation in the IOP was found (Table 2).

Table 2
Result of the analysis comparing the IOP before and 30 minutes after the intravitreal injection in all patients, comparing phasic and pseudo-phasic ones and patients with history of previous injections.

	T test
Comparison between average IOP before (16.71 mmHg) and 30 minutes after injection (18.11 mm Hg)	$p < 0.0001$
Comparison between IOP variation in phasic (1.54 mmHg) and aphasic patients (1,04 mm Hg) during the first 30 minutes	$p = 0.430$
	Spearman Test
Relation between the number of previous injections and increased IOP	$p = 0.884$

IOP = intraocular pressure

The sub-analysis of the groups showed that IOP before and 30 minutes after injection was statistically higher in the DME group ($p < 0.0001$), but was not significant in the group with AMD ($p = 0.0514$), nor in the group with CRVO ($p = 0.0563$).

After the injection, 5 participants reported irritative symptoms, such as foreign body sensation due to areas of corneal desepithelialization. No other complications were observed.

DISCUSSION

The increase in IOP is an existing concern with the application of intravitreal medications. Several methods have been reported to avoid or prevent this increase and thus prevent damage. We can mention ocular massage as a non-invasive procedure, and anterior chamber paraesthesia as an invasive procedure.⁽⁵⁾ There is no evidence suggesting that such techniques reduce the risk of complications related to increased blood pressure, but patients at higher risk may receive some of those techniques to avoid damage.⁽⁵⁾ The development of the technique with the use of thinner needles or pertuitotunellization reduces the reflux of medication and vitreous, which may be related to an immediate and transient increase in the IOP.⁽⁶⁾

Our study identified an initial peak immediately after intravitreal injection and a reduction at 30 minutes, but the comparison between the IOP before it and the IOP after 30 minutes showed a significant difference, suggesting that this time interval was not enough for the IOP normalization. Subanalysis of the data showed that only the DME group had a significant persistence of the IOP after 30 minutes. Our result contrasts with another study which detected normalization of IOP within 30 minutes after injection in general.⁽⁷⁾ We suggest other studies with measurements in larger time intervals to assess the time required for normalization of IOP.

A meta-analysis evaluating the IOP in patients receiving anti-VEGF applications demonstrated sustained long-term increase of the IOP, mainly in glaucoma patients.⁽⁸⁾ The reason for the sustained increase in IOP is not completely understood and seems to be multifactorial, and may be due to the passage of high molecular weight molecules through the anterior hyaloid or zonule and consequent obturation or damage of the trabecular

mesh with repeated applications.⁽⁹⁻¹¹⁾ Evaluating the patients who had received previous injections, our study did not find a significant relation between the IOP variation and the number of previous injections, a result similar to another study showing that IOP change in patients receiving multiple injections was of little significance.^(12,13) Our analysis considered only the measurements made on the day of the injections, as we did not have access to the patients' data before starting treatment with intravitreal injections. The comparison between phakic and pseudophakic patients did not show significant differences in relation to IOP variation.

Our limitations were the reduced number of patients and the lack of evaluation of the cameral angle and other aspects of the patients, such as diagnosis and treatment of glaucoma. We suggest such evaluation in future studies with the aim of analyzing intraocular pressure variation.

CONCLUSION

In the present study, we concluded that there is a significant difference between intraocular pressure before and 30 minutes after intravitreal injection of ranibizumab in patients with diabetic macular edema, showing that this period of time was not enough for IOP regression at the pre-injection value. We did not find significant differences between patients with age-related macular disease, central retinal vein occlusion, phakic and aphakic comparison, nor in patients who had received previous injections.

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