

Therapeutical evaluation of bevacizumab application in relapsed pterygium

Avaliação terapêutica da aplicação de bevacizumabe em pterígio recidivado

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ABSTRACT

Objective: Therapeutic evaluation of Bevacizumab application in relapsed pterygium concerning visual acuity, keratometry, refraction, symptomatology. **Methods:** Group 1 (4 patients) received 0.1 ml of Bevacizumab (avastin), being evaluated posteriorly on the tenth and thirtieth days after the application, seeking to compare with the exam previously made, being it realized with the other two groups, in which Group 2 (4 patients) received 0.2 ml of Bevacizumab and the Group 3 (3 patients) received 1 ml of the placebo injection. **Results:** In this study, eleven eyes of eleven patients were evaluated. Among these patients, 7 were women (63.6%) and 4 men (36.4%). There was a variation in the cylindrical diopter after the treatment with a dose of 0.1 ml of bevacizumab during the evaluation on the thirtieth day. Whereas the cylindrical shaft had a significantly larger modification after the application of 0.2 ml. Regarding the spherical diopter variation, there were modifications in the 3 groups. The keratometry varied in the 3 groups, mostly after the thirtieth day of evaluation. In relation to symptomatology, it was observed a reduction in the subjective evaluation of the eye burning sensation, the prurience mentioned by the patient and a reduction of the hyperemia biomicroscopy evaluation. **Conclusion:** In bevacizumab application in the recurrent pterygium treatment, there is modification of the spherical and cylindrical parameters of refraction, besides the changes in keratometry and the reduction of the symptomatology.

Keywords: Pterygium/drug therapy; Bevacizumab/therapeutic use; Visual acuity; Refraction

RESUMO

Objetivo: Avaliação terapêutica da aplicação de bevacizumabe em pterígio recidivado com relação a acuidade visual, ceratometria, refração, sintomatologia. **Métodos:** O Grupo 1 (4 pacientes) recebeu 0,1ml de bevacizumabe (avastin) sendo avaliado posteriormente, nos dias 10 e 30 após a aplicação, buscando-se comparar com o exame previamente realizado, sendo o mesmo realizado com os outros dois grupos, em que o Grupo 2 (04 pacientes) recebeu 0,2ml de bevacizumabe e o grupo 3 (3 pacientes) recebeu 0,1 de injeção placebo. **Resultados:** Neste estudo foram avaliados 11 olhos de 11 pacientes. Dentre esses pacientes, 7 (63,6%) eram mulheres e 4 (36,4%) homens. Houve a variação na dioptria cilíndrica após o tratamento com dose de 0,1ml de bevacizumabe, durante a avaliação no trigésimo dia. Já o eixo cilíndrico teve uma modificação significativamente maior após a aplicação de 0,2ml. Em relação a variação dióptrica esférica, houve modificações nos três grupos. A ceratometria variou nos três grupos, principalmente no trigésimo dia de avaliação. Em relação a sintomatologia, observou-se uma redução na avaliação subjetiva da ardência, do prurido referida pelo paciente, e uma redução na avaliação biomicroscópica da hiperemia. **Conclusão:** Na aplicação do bevacizumabe no tratamento de pterígio recorrente, há modificação dos parâmetros esféricos e cilíndricos da refração, além da mudança ceratométrica e redução da sintomatologia.

Descritores: Pterígio/tratamento farmacológico; Bevacizumabe/uso terapêutico; Acuidade visual; Refração.

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INTRODUCTION

Pterygium is a growth in the cornea, usually nasal, of continuous fibrovascular tissue to the conjunctiva. It occurs in the area of palpebral fissure, more frequently in the nasal quadrant than in the temporal quadrant, although either one or the other, or both ("double" Pterygium) occur. High whitish opacities ("Vogt Islands") and an iron deposit line ("Stocker") can delineate the pterygium's head in the cornea. ⁽¹⁾

Pterygium consists of degenerative collagenous changes in the vascularized subepithelial stroma. ⁽²⁾ It is associated with ultraviolet exposure. It is more prevalent and more severe in tropical areas near the equator and less frequent and milder in cooler climates. Outdoor work and situations with high light reflectivity, including from sand and water, intensify the pterygium development, and using sunglasses and hats is a protective measure. ⁽¹⁻¹¹⁾

Although pterygium is classified as a degenerative disease, nowadays there are different scientific thinking strands that consider it a proliferative disease. ⁽³⁾ These differences have been appearing due to recent discoveries of several factors related to its pathogenesis, such as: cornea invasion and invasion of the subconjunctival tissue by fibroblast, conjunctival expression of tumor suppressor gene p53 and presence of angiogenic factors and immunosuppression. Thus, its exact etiopathology remains uncertain.

Many studies have shown that VEGF in pterygium pathogenesis is increasing. There is a variety of options for the pterygium treatment. The VEGF expression in the pterygium's tissue lead us to think that antiangiogenic / anti-VEGF therapy could induce the blood vessels regression and, consequently, slow pterygium progression. ⁽⁴⁾

Bevacizumab is a whole humanized monoclonal antibody that binds and inhibits all biologically active forms of VEGF-A. FDA approved bevacizumab in 2004 for the metastatic colorectal cancer systemic treatment (intravenous). Studies showed that intravenous administration could reduce the leakage by the NVC, improve vision significantly and reduce the retina center thickness. ⁽¹⁻¹²⁾

Hence, in this study, the bevacizumab application in relapsed pterygium was realized seeking to observe the signal and symptoms modification, since only surgical treatments have a reduced efficiency. Such study, for being innovator, serves as basis for the achievement of bigger and more complex studies.

METHODS

This study is randomized clinical case, realized in the (Goiania Eye Institute – Instituto de Olhos de Goiânia), between August 2015 and November 2015, in patients with relapsed pterygium, considering these the fibrovascular tissue growing above the limbo in an area where the excision was previously realized.

Initially, patients with relapsed pterygium were randomly selected, they were attended in the Goiania Eye Institute, in which the surgical excision was indicated. Initially, they were collected visual acuity, keratometry, refraction, and subjective symptomatology, looking for lacrimation, eye burning, itching, photophobia, among others. These patients were allocated, posteriorly, into three groups with the same amount of patients, that received random and different medications.

Group 1 (4 patients) received 0.1 ml of bevacizumab (avastin), being evaluated posteriorly on the tenth and thirtieth days after the application, seeking to compare with the exam previously made, being it realized with the other two groups, in which Group 2 (4 patients) received 0.2 ml of Bevacizumab and the Group 3 (3 patients) received 1 ml of the placebo injection.

The injection applications were realized in the prelimbal area, next to the subconjunctival vessels of greater caliber, and all of the patients were treated with tobramycin every four hours.

Data were observed and translated into numbers cataloged in Microsoft Excel 2010 spreadsheets in which the researchers themselves realized the statistical study. For the statistical analysis of the variables in this study, the statistical program Statistical Package for the Social Sciences (SPSS) 18.0 version was used, which has resources to analyze data, create graphics and make fast and reliable predictions. In data obtaining, it was considered statistically significant p less than 0.5 to greater reliability of results.

The research was based on the Terms of Resolution 196/96 of the Brazilian National Health Council and it started only after the by the Research Ethics Committee of the Goiania Eye Institute, to ensure all the involved basic principles of bioethics, ie autonomy, non-maleficence, benevolence and justice.

RESULTS

In this study, eleven eyes of eleven patients diagnosed with recurrent pterygium attended in Goiania Eye Institute were evaluated. Among these patients, 7 (63.6%) were women and 4 (36.4%) were men, with ages ranging 55-72 years, the average age was 64 years, all coming from Goiania (Brazil).

Regarding the observed signs, first we highlight the variation in the cylindrical diopter, in which we can contrast a larger change (0.1875 diopters, after treatment with 0.1 ml bevacizumab dose during the evaluation on the thirtieth day, since neither the dose of 0.2 ml of the anti-VEGF nor the placebo didn't show any diopter change (Figure 1).

The cylindrical axis had a significantly larger modification after the application of 0.2 ml (17.5 degrees) compared with the evaluation after the first 10 days of the groups that received 0.1 ml of bevacizumab and 0.1 ml of placebo (Figure 2).

Regarding spherical diopter change, it was possible to observe that there were changes in the three groups (0.6875, 0.083 and 0.1875 for Groups 1, 2 and 3, respectively), with no variation between the tenth day and the thirtieth day evaluations, highlighting a significantly larger alteration after applying 0.2 ml of anti-VEGF.

Given the many evaluations, it was found that even though the keratometry varied in the three groups, mainly on the thirtieth day of evaluation, with modifications that vary between 0.1875 and 0.296, and the placebo group had a tendency to greater variation (Figure 3).

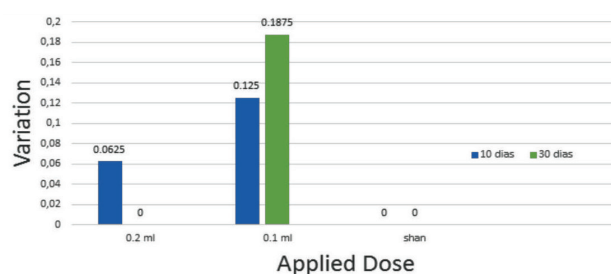


Figure 1: Variation of Cylindrical Diopter After Application of Bevacizumab

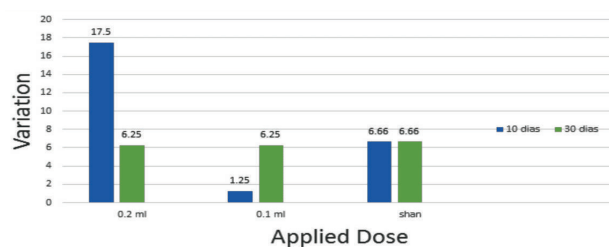


Figure 2: Variation of the Cylindrical Axis After Application of Bevacizumab

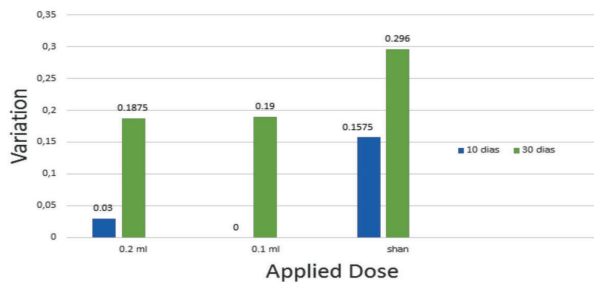


Figure 3: Variation of Keratometry After the Application of Bevacizumab

In relation to symptomatology, among the most mentioned signals, we have eye burning, itching and hyperemia. There were reductions in the subjective eye burning evaluation, itching reported by the patient and in the biomicroscopy evaluation of hyperemia. Since no hyperemia was observed after the first ten days in eight out of the eight patients undergoing anti-VEGF injection, and, on the other hand, all the three patients submitted to placebo continued with hyperemia.

DISCUSSION

This study sought to prospectively demonstrate the effect of the treatment of relapsed pterygium with bevacizumab through a randomized clinical essay. Several references mention discoveries that stood out in the last two decades, with the unveiling of a variety of angiogenic modulators that may be related to the pathogenesis of pterygium, since it is formed predominantly by fibrovascular tissue. Thus, it becomes important to carry out studies demonstrating the anti-VEGF action not only in reducing the size of pterygium, but also in the modification of the signs and symptoms outlined in the ophthalmologic examination.

The most prevalent topographical change is symmetrical with-the-rule astigmatism, caused by the flattening of the cornea towards the lesion^(6,7,8). In figures 1 and 2, we see a change in corneal topography through the diopters and cylinder axis modification, in which after evaluation on the subsequent tenth and thirtieth days after the application, was observed a cylindrical axis alteration of about 17.5 degrees, after ten days of application, with a further reduction of this modification to 6.65 degrees, showing that bevacizumab application leads to a change of this axis. Such fact could be related to the size reduction (grade) of pterygium after applying this medication that showed that there was a reduction of about 2 mm in the pterygium size after two months of anti-VEGF application.⁽⁹⁾ The modifications in those parameters, however, were not able to interfere with visual acuity of patients who proved to be equal in post-implementation evaluations.

Several studies show that pterygium manipulation may be responsible for modifying the refractive power of the cornea with astigmatism induction and modification of topographical regularity of it.⁽¹²⁻¹⁵⁾ Figure 3 shows a marked change in keratometry with placebo application. This change may have occurred due to this manipulation, making it dubious, if keratometric alterations found after the medication application occurred because of the manipulation or if there was the action of anti-VEGF with the reduction of the existing irregularities. This fact opens the door to studies that relate to the size of pterygium reduction with the modification of clinical parameters. However, it does not invalidate our study that was able to demonstrate significant variations in signs and symptoms related to this disease, therefore, leaving it to further correlation.

The application of bevacizumab also proved to be effective in reducing irritative symptoms (72.72%), corroborating with existing data in the literature that show a reduction of over 90% in irritative symptoms after treatment.

CONCLUSION

Given the above, we can state that in the application of bevacizumab in the treatment of recurrent pterygium there is modification in the spherical and cylindrical parameters of refraction, besides keratometry alteration. However, such changes require studies correlating not only changes, but also quantifying the consequent improvement or worsening of this therapy.

Regarding biomicroscopic signs, not with standing visual acuity that showed no changes, there was a reduction of hyperemia, itching and photophobia within thirty days of treatment.

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