Original article

Comparison study on the efficacy and safety of bevacizumab versus mitomycin C as adjuvants in trabeculectomy

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ABSTRACT

Objective: The objective of this study is to compare the efficacy and safety of bevacizumab versus mitomycin C as an adjuvant anti-scarring agent in trabeculectomy.

Methods: A prospective, comparative, non-randomized, interventional study was conducted on a case series. A total of 49 eyes of 45 patients with uncontrolled glaucoma were recruited: 22 eyes in the bevacizumab (BVZ) group, and 27 eyes in the mitomycin C (MMC) group. Complete success was defined as intraocular pressure (IOP) less than 18 mmHg without any antiglaucoma medications. Follow-up visits were made on 1, 7, 30, 90 and 180 days after the surgery. Visual acuity, mean IOP, number of antiglaucoma medications and additional procedures to control IOP were recorded at each follow up visit. Local and systemic complications were also noted.

Results: At the end of the follow-up there were no significant differences in mean IOP between groups: mean IOP was 13.4 ± 3.5 mmHg (range 8–20) in the BVZ group and 11.6 ± 2.6 mmHg (range 7–17) in the MMC group (p = .08). Complete success was achieved in 77.2% (17 out of 22) in the BVZ group and 96.2% (26 out of 27) in the MMC group, which was a statistically significant difference (p = .024). More patients required antiglaucoma medications to control IOP in the BVZ group at the end of the study: 0.36 ± 0.72 medications versus 0.03 ± 0.19 medications in the MMC group (p = .018). Three patients developed avascular cystic blebs in the BVZ group. None of the patients suffered any ocular or systemic complications related to the use of these agents.

Conclusion: Bevacizumab could be a safe and effective anti-scarring agent; however IOP reduction appears to be greater with MMC, and also less antiglaucoma medications are needed with this anti-scarring agent. Bevacizumab could favor the formation of avascular cystic blebs.

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Estudio comparativo sobre eficacia y seguridad de bevacizumab frente a mitomicina C como adyuvantes a trabeculectomía

Resumen

Objetivo: Comparar la eficacia y seguridad de bevacizumab como adyuvante a la trabeculectomía frente a mitomicina C.

Método: Se diseñó un estudio comparativo prospectivo no aleatorizado de 180 días de duración con 49 ojos de 45 pacientes: 22 ojos en el grupo de bevacizumab (BVZ) y 27 ojos en el grupo de mitomicina C (MMC). Se estableció como éxito completo: presión intraocular (PIO) menor de 18 mmHg sin fármacos adyuvantes. Se realizaron controles en los días 1, 7, 30, 90 y 180 poscirugía. Se evaluaron: agudeza visual, PIO media en cada una de las visitas, procedimientos adicionales y número de fármacos necesarios para el control de la PIO poscirugía, así como posibles complicaciones posquirúrgicas tanto locales como sistémicas.

Resultados: Al final del estudio en la PIO media postoperatoria fue $13.4 \pm 3.5$ mmHg (rango 8–20) en el grupo del BVZ y de $11.6 \pm 2.6$ mmHg (rango 7–17) en el grupo de la MMC sin encontrar diferencias estadísticamente significativas ($p = 0.08$). Se alcanzó el éxito completo al final del seguimiento en un $77.2\%$ (17 de 22) de los pacientes en el grupo de BVZ y en un $96.2\%$ (26 de 27) en el grupo de MMC, siendo esta diferencia estadísticamente significativa ($p = 0.024$). Un mayor número de pacientes requirió fármacos adicionales para el control de la presión en el BVZ al final del seguimiento: $0.36 \pm 0.72$ fármacos frente a $0.03 \pm 0.19$ fármacos en el de la MMC ($p = 0.018$). Se encontraron 3 casos de ampollas avasculares en el grupo del BVZ y ninguno en el grupo de MMC. Ningún paciente desarrolló complicaciones derivadas del uso de los medicamentos.

Conclusiones: Bevacizumab parece ser un fármaco eficaz y seguro como adyuvante a trabeculectomía, sin embargo la reducción de la presión es algo mayor con la MMC con una menor necesidad de medicación hipotensora. Existe la posibilidad de formación de ampollas avasculares con el uso de bevacizumab intraoperatorio.

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Introduction

The main cause of filtering surgery failure is the scarring at the subconjunctival and tenon level in the trabeculectomy area. This process comprises: vaculogenesis, necessary for supplying oxygen and important nutrients for the scar, and the migration and proliferation of tenon fibroblasts which synthesize collagen material, finally giving rise to a contradiction in this scar tissue.¹ The use of antimicrotics such as mitomycin C (MMC) and 5-fluoracil (5-flu)²,³ reduce fibrosis and enhance the possibility of filtering surgery success. However, said substances are not free of adverse effects such as corneal toxicity, hypotony, formation of avascular cystic blebs, leaks, blebitis, endophthalmitis, etc.⁴,⁵

The endothelium derived vascular growth factor (VEGF) plays a crucial role in scarring as it stimulates angiogenesis and increases vascular permeability⁶ in addition to enhancing fibroblast proliferation and activity. Bevacizumab (BVZ) (Avastin, Genentech, Inc., San Francisco, CA, USA) is a humanized recombinant monoclonal antibody of the immunoglobulin G1 type which joins VEGF, thus blocking its action. Recent studies have found increased VEGF levels in the aqueous humor of patients with neovascular glaucoma after trabeculectomy.⁷ This finding was also tested in filtering surgery animal models and in patients with open angle primary glaucoma who underwent trabeculectomy.⁹ In addition, BVZ has demonstrated its ability for reducing in vitro fibroblast numbers and activity.⁸ This would make it a serious candidate in the search for new immunomodulating agents adjuvant to surgery.

Material and methods

A nonrandomized, prospective and comparative study was designed comprised by 2 groups: patients who were intervened for trabeculectomy + subconjunctival BVZ in bleb area, and patients intervened for trabeculectomy + adjuvant MMC. The inclusion criteria were: non-controlled intraocular pressure (IOP) with high risk of progression, functional defect worsening despite adequate medical treatment or changes in the cup/disk quotient which indicated disease progression. Patients with previous intraocular surgery and normotensive, inflammatory and neovascular glaucoma were excluded, together with those with noncontrolled diabetes or other systemic diseases which could increase the risk of complications. Finally, patients under 18 years of age, pregnant and lactating women were also excluded. The patients who met the inclusion criteria were consecutively allocated first to the BVZ group followed by the MMC group. All the patients were given complete and truthful information about the objectives and
alternatives of the treatment and signed a fully informed consent on the off-label use of BVZ. The study was carried out at all times in accordance with the Helsinki Declaration.

Trabeculectomy operations were always carried out by the same surgeon under subtenon anesthesia with 0.2% lidocaine infiltrated through the inferior nasal quadrant. A fornix-based conjunctival dissection was performed, 4 mm superficial scleral flap dissection and ×2 mm internal block excision. The superficial flap was sutured with 10/0 nylon. The conjunctiva was closed with vicryl 8/0. At the end of the procedure, a 30 g needle was used to inject 1.25 mg of BVZ in 0.1 ml of saline in the upper subconjunctival space adjacent to the trabeculectomy in the first group, while the second group was administered 0.2 mg/ml MMC during 2 min with a soaked surgical sponge placed above the superficial flap prior to the execution of the deep flap. After instilling atropine, iodine povidone and antibiotic, occlusion was carried out and maintained during 24 h.

The post-surgery treatment was carried out with a fixed combination of tobramycin and dexamethasone every 3 h during the first week, with progressive reduction in the 6 subsequent weeks. One drop of atropine was instilled 4 times a day during the first 4 weeks.

Prior to surgery, information on the presurgery IOP, number of hypotensor drugs and mean deviation in the latest visual field (VF) was obtained. Post-surgery examinations were carried out on day one, 7, 30, 90 and 180. At each visit the ophthalmologist measured visual acuity (VA) and IOP, and carried out a biomicroscopic exploration to detect the presence of flare and inflammatory cells in the anterior chamber as well as carrying out the Seidel test and taking standardized photographs of the blebs. The amount of post-surgery hypotensor medication as well as possible additional procedures for controlling IOP such as examination with bleb needle or suture lysis were determined. In addition, local and systemic adverse effects were registered as well as the need of surgical re-intervention.

The necessary sample size was calculated considering a study power of 80% and accepting an alpha error of 0.05 to detect at least a mean post-surgery IOP difference of 2 mmHg between both groups. On the basis of this estimate, 15 eyes were required in each group. Thus, assuming a possible loss of 5% throughout the follow-up period, the minimum final recruitment was established at 18 eyes per group. Data were analyzed utilizing SPSS v15.0 (SPSS, Inc., Chicago, IL, USA). The normality of data was assessed with the Kolmogorov–Smirnov test. For comparing mean values the t for Student’s test was used and for comparing category variables and percentages the Chi square test was used. Statistical significance was established as a value of p < 0.05.

### Results

The sample of the present study included 49 eyes of 45 patients, 22 in the BVZ group and 27 in the MMC group. The demographic characteristics of the sample are shown in Table 1. Complete success involved patients having IOP values of 18 mmHg or less without topical antiglaucoma treatment, while partial success involved IOP of 18 mmHg or less with topical treatment, and surgery failure was interpreted when IOP exceeded 18 mmHg despite topical treatment.

In addition, the percentage IOP reduction prior to surgery and at month one, 3 and 6 after surgery was also measured together with the number of drugs used before and after surgery.

The mean presurgery IOP was 19.68 ± 3.7 (range 15–25) in the BVZ group and of 20.55 ± 6.3 (range 15–44) in the MMC group (p = 0.911) with a mean value of 2.18 ± 1.09 and 2.37 ± 0.88 hypotensor drugs respectively, without finding statistically significant differences between both groups (p = 0.672).

No statistically significant differences were found in mean IOP values between of groups in any of the visits. IOP evolution throughout the study is shown in Fig. 1. At the end of the study, mean post-surgery IOP was 13.4 ± 3.5 mmHg (range 8–20) in the BVZ group and of 11.6 ± 2.6 mmHg (range 7–17) in the MMC group (p = 0.08). However, differences were found in the amount of hypotensor drugs utilized by both groups at month 6 after surgery, where the BVZ group made higher use thereof: 0.36 ± 0.72 drugs against 0.03 ± 0.19 drugs in the MMC group (p = 0.018).

The complete success percentage was 77.2% (1 of 2) in the BVZ group and of 96.2% (2 of 7) in the MMC group, a statistically

### Table 1 – General sample characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab</th>
<th>MMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>22</td>
<td>27</td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>66.94 ± 9.49</td>
<td>68.22 ± 11.53</td>
</tr>
<tr>
<td>Sex (F/M)</td>
<td>12/10</td>
<td>14/13</td>
</tr>
<tr>
<td>Diagnose (OAPG/PSXG/PGG)</td>
<td>20/2/0</td>
<td>22/4/1</td>
</tr>
<tr>
<td>Pre-IOP (mean ± SD)</td>
<td>19.68 ± 3.7</td>
<td>20.55 ± 6.3</td>
</tr>
<tr>
<td>Pre-drugs (mean ± SD)</td>
<td>2.18 ± 1.09</td>
<td>2.37 ± 0.88</td>
</tr>
</tbody>
</table>

SD: standard deviation; OAPG: open angle primary glaucoma; PSXG: pseudoexfoliative glaucoma; M: males; F: females; MMC: mitomycin C; IOP: intraocular pressure.

![Fig. 1 – Mean IOP evolution and p values in both groups at each of the follow-up examinations.](image-url)
significant difference ($p = 0.024$). The mean IOP reduction at month 6 in the BVZ group was 31.91% and in the MMC group was 42.1% ($p = 0.087$).

At the end of the follow-up period, 3 eyes in the BVZ group exhibited avascular and polycystic bleb walls (Fig. 2). None of the patients in the MMC group developed avascular blebs.

In what concerns additional procedures for controlling IOP, 2 patients in each of the groups required revision of a bleb with +5-flu needle due to conjunctival scarring and early bleb failure. All 4 cases achieved adequate IOP control after needling.

None of the patients required re-intervention.

Table 2 summarizes the post-surgery complications in each group.

No adverse systemic effects were recorded in either group.

Discussion

Nowadays, controlling post-surgery scarring is one of the fields of greatest interest in glaucoma research, with angiogenesis being a crucial stage in the scarring process and VEGF one of the mediator molecules involved in the process.

Recent studies\textsuperscript{9,10} in animal models have demonstrated that VEGF levels in aqueous humor rises significantly after trabeculectomy and remain abnormally high up to day 30 post-surgery. In addition, tenon fibroblasts (which are key cells in the scarring process) express 2 VEGF receptors in their membranes so that, in vitro, VEGF joins to said receptors stimulating the proliferation of fibroblasts while anti-VEGF inhibits said cellular proliferation.

Van Bergen et al. studied the role played by various VEGF isoforms in scarring after filtrating surgery and found that VEGF165 and VEGF121 predominantly regulate angiogenesis whereas VEGF189 has higher participation in fibrosis.\textsuperscript{11}

BVZ is nonselective in the inhibition of all VEGF isoforms and therefore could be efficient for controlling these processes.

In animal trabeculectomy models, the use of adjuvant intravitreal BVZ produces a reduction of post-surgery scarring associated to a significant reduction in vasculogenesis at day 3 post-surgery and diminished collagen synthesis between days 14 and 30 post-surgery.\textsuperscript{9,12}

BVZ began to be applied as adjuvant in glaucoma surgery for patients with neovascular glaucoma. Jonas et al. were the first to successfully apply BVZ with intravitreal administration as adjuvant for trabeculectomy in neovascular glaucoma.\textsuperscript{13}

In a pilot study\textsuperscript{14} Grewal utilized BVZ in 12 patients, obtaining good results in terms of pressure control and exhibiting the formation of functional blebs without adverse effects and with good tolerance.

Some authors have already carried out comparative studies on the efficiency of the BVZ as adjuvants to trabeculectomy instead of classic mitotics. A small comparative study on trabeculectomy with MMC with and without intravitreous ranibizumab by Kahhok\textsuperscript{15} did not find differences in tension control but did find them between the 2 groups in what concerns bleb morphology: the group that was administered the antiangiogensics exhibited a significantly more diffuse bleb with lower vascularization in the peripheral area. However,
this study does not include sufficient sample size and follow-up time to draw conclusions.

In the present study, the authors found that the BVZ appears to be an efficient and safe adjuvant to filtering surgery, even though its efficacy could be somewhat below that of MMC because, at the end of the study, a higher number of patients in the BVZ group required antiglaucoma medication in order to reach the target IOP. Other authors have reported similar findings: a comparative, prospective and randomized trial by Nilforushan et al. compared trabeculectomy results with MMC (0.02% 3 min) and trabeculectomy with subconjunctival BVZ (2.5 mg/0.1 ml). Similarly to the present results, said author verified that even though BVZ was more efficient and safe, pressure reduction in the MMC group was greater with less hypotensive medication requirements.16

A year-long prospective and randomized study comparing patients intervened with trabeculectomy + subconjunctival BVZ at a dosage higher than that utilized by the authors (2.5 mg/0.1 ml) vis-à-vis MMC (0.2 mg/ml by 3 min) found a higher proportion of patients achieving complete success (IOP under 2 mmHg without medication) at 12 months in the MMC group.17

Other authors have found similar results when comparing BVZ with 5-flu. A study comparing 2 nonrandomized trabeculectomy groups + subconjunctival BVZ (1.25 ml/0.1) with trabeculectomy + 5-flu after 12 months exhibited nonsignificant better results in the 5-flu group.18 However they did find differences in the amount of hypotensive medication required one year later to maintain IOP under control, which was higher in the BVZ group. It must be emphasized that in the said study the subconjunctival BVZ injection was carried out intra-surgery and repeated at day 1 and 7 post-surgery.

In the group of the present study, 3 eyes in the BVZ group (13.6%) developed blebs with avascular cystic walls. This finding was made in the 90-day examination in the 3 patients and remained stable up to the end of the follow-up without associated complications.

To date, the authors have not found in the literature any reported case of avascular blebs with the use of BVZ adjuvants to trabeculectomy.

The above-mentioned studies16,17 do not present significant differences in the morphology and vascularization of blebs between BVZ and MMC. In a prospective study about trabeculectomy with MMC (0.2 mg/ml during 2 min), Anand et al. found a frequency of 56% of avascular blebs at follow-up month 6 and also observed that when blebs appear they do so at a mean value of 106 days after surgery (CI 95%: 69–143).19

The possibility of avascular bleb formation with the use of antiangiogenics merits in-depth research as it is one of the adverse effect ophthalmologists endeavor to avoid in the search for new immunomodulator therapies.

The authors believe that the subject matter of this study is a highly interesting field of research and that the modulator effect of antiangiogenics deserves deeper research. Controlled studies are necessary in order to establish the existence of actual benefits vis-à-vis conventional antimitotics, as well as the possible short and long-term adverse effects, adequate dosages and administration pathways, together with the possibility of developing blebs with avascular and polycystic walls.

Conflict of interests

No conflict of interests has been declared by the authors.

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