Original article

Intracameral bevacizumab (Avastin®) in the management of neovascular glaucoma surgery∗,††

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ABSTRACT

Purpose: To describe a case series of neovascular glaucoma treated with intracameral bevacizumab prior to filtering surgery.

Design: Descriptive, retrospective case series.

Methods: Five eyes of 5 patients with neovascular glaucoma due to any cause candidates to filtering surgery who had previously received an injection of intracameral bevacizumab (1.25 mg/0.05 ml) as treatment for neovascularization of anterior chamber. Results observed one week and 4 weeks post-surgery are reported.

Results: Bevacizumab produced regression of the angle neovascularization and the intraocular pressure. Only one case of postoperative bleeding was detected.

Conclusions: Intracameral bevacizumab prior to filtering surgery of neovascular glaucoma diminished the neovascularization and intraocular pressure after 4 weeks of its administration and was effective in preventing intraoperative and postoperative bleeding. It also constitutes a promising way of investigation to prevent surgical complications.

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Bevacizumab (Avastin®) intracameral en el manejo quirúrgico del glaucoma neovascular

RESUMEN

Propósito: Describir una serie de casos con glaucoma neovascular que fueron tratados con bevacizumab intracameral previo a la cirugía filtrante.

Diseño: Descriptivo, retrospectivo, tipo serie de casos.

Métodos: Cinco ojos de cinco pacientes con glaucoma neovascular de cualquier causa candidatos a cirugía filtrante recibieron previamente una inyección de bevacizumab (1,25 mg/0.05 ml) intracameral como tratamiento de la neovascularización angular. Se describieron los resultados observados a la semana y a las 4 semanas poscirugía.

Resultados: Bevacizumab produjo una regresión importante de los neovasos y de la presión intraocular. Se detectó un único caso de sangrado postoperatorio.


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Introduction

Bevacizumab ([BVI]: Avastin®, Genentech, Inc., South San Francisco, CA) is a recombinant monoclonal antibody with specificity for all the active isoforms of the endothelial vascular growth factor A (VEGF-A). It was designed for intravenous use and approved in 2004 for metastatic colorectal cancer in combination with chemotherapy. To date, intraocular administration of bevacizumab is not approved. However, numerous papers suggest it has a beneficial role in ophthalmic use.

In 1998, Tripathi et al. documented the increase of VEGF-A in the aqueous humor of patients with neovascular glaucoma (NVG). Mason et al. proposed intravitreous BVI for patients with NVG, recurring hemorrhage of iridic neovessels and those with neovessels despite panphotocoagulation (PFC). Jonas et al. documented in 2 cases the normalization of intraocular pressure (IOP) with the use of intravitreous BVI together with filtration surgery in NVG. Andreoli and Miller proposed the use of intravitreal BVI in patients who underwent panphotocoagulation to avoid the complete closure of the angle while it takes effect.

The administration of BVI in posterior segment neovascularization processes is broadly documented. However, intra-chamber administration can also be beneficial in anterior segment neovascularization processes. Wakabayashi et al. observed adequate control of IOP in patients with NVG without the closure of the angle if administered in early stages. Recently, a series of 6 cases with neovascular glaucoma and BVI injection prior to panphotocoagulation or filtrating surgery was published. The publication suggested the adjuvant effect of this technique when applied prior to surgery. It seems that IOP can be poorly controlled in advanced stages even though surgical results improved when applying BVI as an adjuvant.

The only comparative study that the authors have found is a retrospective series of cases in which Chen et al. found improved visual acuity in a six-month follow-up. In patients with NVG treated with intravitreous BVI or plus trabeculectomy compared with trabeculectomy on its own.

The objective of this study is to describe a series of cases with neovascular glaucoma treated with BVI intrachamber prior to glaucoma filtrating surgery.

Subjects, materials and methods

The database of the Fuenlabrada University Hospital was searched to select the clinical records with the following inclusion criteria:

- NVG due to any cause. NVG was taken to be a sustained IOP ≥21 mmHg as a consequence of an ocular ischemia process and the presence of neovascularization in the anterior segment or irido-corneal angle.
- Candidate for NVG surgical treatment with filtrating surgery and administration of BVI (single dose of 1.25 mg/0.05 ml) intrachamber 24 h prior to surgery.

The Ahmed valve was implanted in all surgeries because our hospital has more experience with it. The indication for surgery was established in the case of failed IOP and symptomatic control despite having received PFC and at least 2 ocular hypotensor drugs.

The cases that previously received any dose of intraocular or systemic antiangiogenic drug (BVI, ranibizumab or pegaptanib) were excluded.

It was considered that intrachamber administration excluded some of the risks involved in intravitreal injection such as iatrogenic cataracts, retinal regmatogenous lesions or subconjunctival drug diffusion. As the purpose was to act upon iris and angle neovascularization, that intrachamber pathway allowed the action of BVI on the NVG vessels, involving lower risk for the eye.

The BVI injection in the anterior chamber was done with a 30g and assisted by surgical microscope.

The patients were informed verbally and in writing that the indication of intrachamber BVI is based on compassionate use due to the current lack of evidence recommending its administration. All patients signed the appropriate informed consent.

All the variables considered to be relevant to describe the effect of intrachamber BVI in filtrating surgery were analyzed.
Table 1 – Characteristics of study cases.

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Previous glaucoma</th>
<th>Cause of neovascularization</th>
<th>Follow-up (weeks)</th>
<th>Previous treatments</th>
<th>Intra-op bleeding</th>
<th>Immediate postop bleeding (&lt;48 h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>F</td>
<td>62</td>
<td>No</td>
<td>PDR</td>
<td>7</td>
<td>PFC, FC</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Case 2</td>
<td>M</td>
<td>83</td>
<td>No</td>
<td>PDR</td>
<td>24</td>
<td>PFC, FC, BCZv</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Case 3</td>
<td>V</td>
<td>33</td>
<td>No</td>
<td>CRVT</td>
<td>5</td>
<td>PFC, B/T, ATR, ACZ</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Case 4</td>
<td>V</td>
<td>58</td>
<td>No</td>
<td>PDR</td>
<td>13</td>
<td>PFC, B/T, ACZ</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Case 5</td>
<td>V</td>
<td>33</td>
<td>OHT postuveitis</td>
<td>Unknown</td>
<td>10</td>
<td>PFC, D/T, DXTc</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>


Table 2 – Intraocular pressure prior to bevacizumab and at weeks 1 and 4.

<table>
<thead>
<tr>
<th>Case</th>
<th>Initial IOP (mmHg)</th>
<th>1 week assessment</th>
<th>4 week assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>35</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>Case 2</td>
<td>30</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Case 3</td>
<td>38</td>
<td>40</td>
<td>28</td>
</tr>
<tr>
<td>Case 4</td>
<td>40</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>Case 5</td>
<td>43</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Medians</td>
<td>37.2 ± 4.9 (CI 95%)</td>
<td>17.2 ± 13.02 (CI 95%)</td>
<td>19.0 ± 6.0 (CI 95%)</td>
</tr>
</tbody>
</table>

(Tables 1 and 2). The main variable was anterior chamber bleeding either during or after surgery. The analyzed data were collected 24–48 h prior to the injection and one week and 4 weeks after it.

SPSS version 11.5 (SPSS Inc., Chicago, IL) statistical software was utilized to analyze the data. After verifying that the distribution of variables did not fit normality by means of the Kolmogorov–Smirnov tests, nonparametric tests were applied. The T for student for paired data was used to compare the IOP results before and after the intervention. The main variable was studied on the basis of percentage and a confidence interval (CI) of 95%.

Results

The samples comprised 5 eyes of 5 patients, 4 of them females (80%) and one male (20%). The mean age was 53.8 ± 21.23 years (CI 95%). The mean follow-up time was of 14.4 ± 6.7 weeks (CI 95%). Vascularization causes were multiple: diabetic retinopathy in the cases, retina central vein thrombosis in one and unknown etiology in the last case, possibly ocular ischemia syndrome. In all cases previous retinal PFC had been performed (Table 1).

The initial IOP was the last one recorded before the BVI injection, taken between 24 and 48 h earlier. The mean IOP value was of 37.2 ± 4.9 (CI 95%). The IOP values were recorded one and 4 weeks after the injection (Table 2). Gonioscopy revealed variable degrees of angular closure due to neovascularization in all cases (Fig. 1 and Table 3).

The comparison of mean values before and 4 weeks after the injection was made applying the T for student for paired data. The results exhibit statistically significant differences (Fig. 2); the initial IOP ranged between 42.1 and 32.3 mmHg and the IOP values 4 weeks after the injection ranged between 26.00 and 13.00 mmHg with a p = 0.043 (Table 2).

In what concerns the main variable, i.e., the intra-and immediate postop (<24 h) bleeding which was taken to be positive if exhibiting hyphema, hemovitreous or choroidal hemorrhage, did not arise in any case during surgery and in one case in the immediate postop (Table 1, Figs. 3 and 4).

Other recorded variables comprised angular neovascularization and maximum corrected visual acuity (MCVA) (Table 3). In what concerns the latter, it was observed that in the first week assessment case 5 was the same and the remaining cases had worsened. At week 4, 2 had worsened vis-à-vis the baseline (cases 1 and 2) and the remainder were the same. Rubesisis iridis improved in 3 patients at week 4 (cases 3, 4 and 5), remaining the same in one case (case 1) and worsening in a further case (case 2) (Table 3). Said data match those observed in the Wakabayashi et al. series for patients with NVG and

Fig. 2 – Comparison of intraocular pressure mean values at baseline, one week and 4 weeks after bevacizumab.
Discussion

In what concerns the main variable of the study, it can be said that no patient suffered intra-surgery bleeding and only one had post-surgery bleeding (case 1: Table 1 and Fig. 3). In our experience, intra- and post-surgery bleeding are considerably more frequent without the use of BVI than in the samples, which was of 0% and 20% respectively.

Published data on this topic refer hyphema frequencies in the area of 11.4% in the first month in a sample of 70 eyes by Montañez et al. and in the area of 5% in a sample of 22 eyes by Luttrull and Avery. It is not possible to analyze a comparison of hypotheses because all patients received the same treatment. Likewise, we cannot compare our data with said studies because they are non-analogous samples.

The effect over IOP is also due to filtrating surgery and therefore we are unable to assess the magnitude of the effect of intrachamber BVI.

With a sample as small as in this study it is not possible to identify risk factors for the improvement or worsening of the visual equity or ruberosis iridis. However, it must be emphasized that the only case that worsened had the differential characteristic of previously receiving intratireal BVI 5 weeks earlier.

The risks of intrachamber BVI administration are endophthalmitis, retina detachment, cataracts and uveitis. None of these effects were observed in our sample. In intravenous administration hypertension, increased thromboembolic risk, gastrointestinal perforation, mio collagen infarct and even death have been observed.

The serum levels of BVI after intravitreal administration are much lower than those reached after intravenous administration. The VISION study which collected pharmacological safety data during a two-year period did not reveal increases in cardiovascular diseases associated to systemic administration. The mean life of intravenous BVI is of 17–21 days although the duration of the antiangiogenic effect after administration and the existence of any type of permanent effect is yet to be determined.

In our sample, intrachamber BVI 24 h prior to the Ahmed valve implant produced a low frequency of bleeding in the anterior chamber and good IOP and symptom control at week 4.

The above data allow us to suspect the beneficial effect of intrachamber BVI to prevent said complications. In addition, we consider that the intrachamber pathway involves some advantages vis-à-vis the intravitreal pathway, including diminished iatrogenic cataract risk because the tip of the needle can be seen at all times as well as the disappearance of the risk of regmatogenous lesion or subconjunctival diffusion of antiangiogenic. In addition, the concentration of BVI in the anterior chamber would probably be higher than in intravitreal administration, above all in phakic patients, which increases the effect of the drug on anterior segment neovessels. Possible toxic effects on the cornea did not seem clinically significant according to other studies carried out with intrachamber BVI injections.

At this time there are several studies which confirm the rapid response of anterior segment neovascularization to BVI...
and its usefulness for controlling IOP, symptoms and prognosis of GNV.\textsuperscript{14,19} As in the posterior pole, the antiangiogenic effect is limited in time and it is known that the BVI per se does not enable controlling the antiangiogenic stimulus, making strict monitoring necessary together with treatment for the underlying cause.\textsuperscript{20,21}

Due to the lack of randomized clinical trials on the intraocular use of BVI, many questions remain unanswered including its absolute and compared efficacy vis-à-vis other antiangiogenics, its posology (dosage, number and intervals between the injections) and secondary intraocular and systemic effects.\textsuperscript{10,13}

Intracameral BVI for treating anterior segment neovascularization and preventing surgical complications constitutes a promising path for research.

\textbf{REFERENCES}