High definition tomography to evaluate filtering bleb with biodegradable collagen implant in patients with high myopia

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PURPOSE: The aim of this study was to identify, by means of computed tomography, the height of the filtering bleb and Ologen® implant in patients with high myopia, in whom the use of mitotic inhibitors in filtering surgery could cause complications.

SETTING: Barraquer Ophthalmology Centre, Barcelona, Spain.

METHODS: A retrospective descriptive study of 10 patients (10 eyes) diagnosed with chronic open-angle glaucoma and high myopia. Patients underwent trabeculectomy with Ologen® implant, without mitomycin, with follow-up at one, three, six and nine months. Follow-up assessment included refraction, intraocular pressure (IOP), presence of complications, and examination of the bleb and implant using high-resolution tomography.

RESULTS: Ten eyes with a mean spherical equivalent of −13.61 ± 5.22 D from ten patients (men: women, 3:7) were studied. Preoperative IOP fell significantly from 27.11 ± 7.51 mmHg to 11.21 ± 3.43, 12.16 ± 3.16, 13.91 ± 2.18, and 13.67 ± 0.81 mmHg at one, three, six and nine months, respectively. Mean bleb height was 1.78 ± 0.26, 1.57 ± 0.25, 1.54 ± 0.38 and 1.42 ± 0.29 mm, and that of the implant was 1.46 ± 0.13 mm, 1.23 ± 0.21, 0.87 ± 0.17 and 0.47 ± 0.22 mm at one, three, six and nine months, respectively. No severe complications were observed.

CONCLUSION: The combination of filtering surgery and Ologen® in patients with scleral thinning and high myopia significantly reduces IOP. In some cases, high-resolution tomography can be a useful tool for measuring bleb height and thickness of the implant.

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The primary objective of glaucoma therapy is to maintain intraocular pressure (IOP) below risk levels for visual function. Trabeculectomy is one of the procedures most commonly performed to achieve this end. Since it was first described in 19681, both the technique and the materials used to maintain and maximise the hypotensive effect of the procedure have been modified2. One of the main developments has been the use of anti-metabolites such as mitomycin C and 5-fluorouracil, which have been shown to improve outcomes in filtering surgery3-9. These drugs reduce the physiological wound-healing response that occurs during the postoperative period by acting on the DNA to inhibit fibroblast proliferation10,11 of the filtering bleb (FB), a process that starts three days after surgery. Excessive scarring of the conjunctiva, Tenon’s membrane and episclera is one of the primary causes of filtering failure because it leads to closure of the fistula, which in turn increases IOP12,13. However, the effect of antimitotics is variable, and there is no general consensus in the literature on dosage and application time14-16. The sequelae of these drugs are also variable, ranging from mild complications such as keratitis to others that can be potentially sight-threatening, such as hypotony, choroidal effusion, avascular blebs, blebitis, persistent leakage (Seidel test) and endophthalmitis17-21.

The use of biodegradable collagen implants such as Ologen® (Aeon Astron, Leiden, The Netherlands)

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has recently been described as a way of preventing or reducing the potential risk of complications from antimitotics. Ologen® is a collagen-glycosaminoglycan matrix made up of millions of micropores, with implants available in different sizes (in the present study, we used the 6 × 2 mm diameter matrix). After trabeculectomy, the implant is placed on the scleral flap and covered with the conjunctiva. These devices are intended to improve FB formation and prevent early failure. According to the manufacturer, the implants have a half-life of six months and two phases of action. In the first phase, they act as an aqueous reservoir to preserve the subconjunctival space of the bleb. Over the following days or weeks, the device acts on the wound-healing process. Unlike antimitotics, the implant does not inhibit fibroblast formation; instead, the matrix acts as a scaffold on which fibroblasts are arranged in an orderly fashion, thereby controlling the wound-healing process to inhibit wound contraction and form a tissue that resembles physiological stroma.

The Ologen® implant can be an alternative to intraoperative antimitotics in patients at greater risk of postoperative complications, such as those with high myopia. In epidemiological terms, these are usually young patients with a rapid healing rate, a factor that can increase the risk of surgery failure due to closure of the drainage fistula. Eyes with high myopia are also characterised by an axial length of over 26 mm and a spherical equivalent of over −6 D. Histologically, the tissue of the myopic eye shows changes in collagen structure, synthesis, and degradation, which in turn leads to progressive thinning and weakening of the sclera. This facilitates abnormal growth of the eye and heightens the risk of postoperative hypotony following intraoperative application of antimitotics.

The presence of myopia is considered to be a risk factor for the onset of diagnosis and follow-up of glaucoma, since the fundus of patients with myopia can have variations in papilla morphology, posterior staphyloma and pathological findings such as retinochoroidal atrophy that can hamper optic nerve assessment and campimetry.

Following glaucoma surgery, FB follow-up can be performed using normalisation scales, and several studies have correlated bleb morphology with functional outcome. However, technologies such as ultrasound biomicroscopy (UBM) and optical coherence tomography (OCT) can provide objective, quantifiable bleb measurements. High definition tomography (Casia OCT, Tomey, Nagoya, Japan), a non-contact high-resolution imaging technique that allows clinicians to examine the anterior segment, was used in this study to evaluate the characteristics of the Ologen® and the FB. OCT is now an accepted means of evaluating the cornea, corneal morphology and thickness, and for pre-refractive surgery assessment and analysis of FBs.

Few studies have been conducted in patients with high myopia undergoing filtering surgery, and no references can be found in the literature that correlate the use of a biodegradable collagen implant with this patient group. The aim of this study was to retrospectively analyse the effectiveness of this approach in lowering IOP, and to conduct a descriptive study in patients with high myopia and uncontrolled glaucoma undergoing trabeculectomy with Ologen® implant. During the postoperative period, the type and frequency of complications, induced astigmatism, and characteristics of the FB and Ologen® implant, based on clinical and OCT examination, were analysed. This enabled us to evaluate the effectiveness of OCT in the study and follow-up of FB. Based on our findings, we also examined the possibility of conducting further prospective studies using a control group.

**METHODS**

A retrospective descriptive study was conducted in the glaucoma department of the Barraquer Ophthalmology Centre, Spain, to evaluate the effectiveness of the Ologen® implant in reducing IOP following filtering surgery. Using OCT, changes in IOP were correlated with changes in the bleb and implant.

The study included 10 patients (10 eyes) diagnosed with advanced chronic open-angle glaucoma and high myopia. All patients underwent trabeculectomy with Ologen® implant, without mitomycin. Inclusion criteria were: presence of advanced glaucomatous damage in the visual field and optical disc assessment under progression criteria, or IOP greater than 21 mmHg despite maximum medical therapy; presence of high myopia with a spherical equivalent of >−6 D and anterior-posterior axis > 26 mm. Prior cataract surgery was not an exclusion criterion. The pre-surgery data taken from all patients were: age at the time of surgery, gender, baseline refraction and axial length of the eye. Exclusion criteria were: glaucoma in patients under 18 years of age, presence of secondary glaucomatous damage (uveitic, pseudoexfoliation, pigmentary, traumatic, neovascular) and presence of other diseases that could alter the study results (non-myopic-related retinopathies, severe corneal alterations or other ophthalmological or systemic diseases that could mask the diagnosis and follow-up).

All patients underwent trabeculectomy without mitomycin C, and biodegradable collagen implant. Follow-up tests were carried out at one, three, six and nine months post-surgery. During follow-up, IOP with tonometry (Goldmann), refraction (particularly the evolution of postoperative astigmatism) and the clinical characteristics of the FB (height, area and vascularisation) were assessed. The characteristics of the
Ologen® implant and the FB were recorded using Casia OCT (Tomey), and any correlations with IOP values were evaluated. Finally, postoperative complications and the need for hypotensive therapy to maintain IOP (topical, postoperative injections of 5-fluorouracil or further surgery) were also recorded. A successful postoperative outcome was considered to be IOP below 18 mmHg without the need for hypotensive therapy, and a relatively successful outcome was IOP maintained at 18 mmHg with hypotensive drugs.

**Surgical technique**

All procedures were carried out by the same surgeon (MICJ) under peribulbar anaesthesia. Traditional penetrating surgery was performed and the scleral flap was closed with four 10-0 nylon sutures. In our experience, both filtering surgeries have similar success rates. We decided to perform a traditional penetrating surgery instead of a deep sclerectomy in order to avoid adding more variables to the study. The Ologen® implant was positioned over the outer third of the sclera, and the conjunctiva was replaced over it with 7-0 vicryl sutures. Intra-operative (1 cc subconjunctival cortisone) anti-inflammatory drugs were administered; postoperative anti-inflammatory therapy consisted of topical tobramycin - dexamethasone 4 times a day (tapered after 15 days) and diclofenac 4 times a day for one month. All patients were followed-up at one, three, six and nine months, according to the protocol described above.

**Statistical analysis**

Data was analysed using SPSS Statistics v 17.0. Given the small sample size, non-parametric paired data tests were used. Mean and standard deviation (± SD) for IOP and baseline FB height (HFB) and implant height (HOLO) are shown, together with the changes in these values at one, three, six and nine months of follow-up, calculated using the Wilcoxon test. Correlation between variables was analysed using Spearman’s correlation coefficient (rho). A significance level of 0.05 was established for all results.

**RESULTS**

Ten eyes from ten patients (men: women, 3:7) with open-angle glaucoma and high myopia were studied. Mean spherical equivalent was –13.61 ± 5.22 D, and mean axial length was 27.82 ± 2.14 mm. Pre-surgery IOP was 27.11 ± 7.51 mmHg despite maximum medical therapy with beta-blocker eye drops, α2- adrenergics and carbonic anhydrase inhibitors. Mean age at surgery was 48.24 ± 16.16 years. All cases were followed-up over nine months.

Post-surgery, mean pressure was 11.21 ± 3.43 in the first month, 12.16 ± 3.16 and 13.91 ± 2.18 in the third and sixth month, respectively, and 13.67 ± 0.81 in the ninth month. Post-surgery pressure was significantly lower than pre-operative pressure in all patients (p < 0.001) (Figure 1), and remained under 18 mmHg over the nine-month follow-up period. None of the patients required hypotensive therapy, and there were no cases of postoperative hypotony.

Clinically, the FBs looked healthy (diffuse, elevated and well-vascularised) (Figure 2). None of the patients presented avascular or cystic blebs. During follow-up, clinical and OCT data on HFB and HOLO were obtained. Mean HFB measured by OCT (Figure 3) fell over the first three months (from 1.78 ± 0.26 mm to 1.57 ± 0.25 mm) and remained practically unchanged from the third to the sixth month (1.57 ± 0.25 and 1.54 ± 0.38 mm, respectively) despite progressive degradation of the implant. At nine months, mean HFB was 1.42 ± 0.29 mm (Table 1). The Wilcoxon

**Figure 1. Evolution of IOP.** Preoperative IOP fell significantly from 27.11 ± 7.51 mmHg to 11.21 ± 3.43, 12.16 ± 3.16, 13.91 ± 2.18 and 13.67 ± 0.81 mmHg at 1, 3, 6 and 9 months, respectively (Wilcoxon test, p < 0.005). In all cases, IOP remained below 18 mmHg over follow-up. Values are mean and standard deviation (± SD), (n=10).
A non-parametric test showed a statistically significant difference in HFB between the first and ninth month ($p < 0.01$).

In all cases, implant degradation was progressive, losing approximately 15% in height every three months. However, after six months none of the patients showed full degradation of the implant, and after nine months it had completely disappeared in only one patient (in this follow-up, the OCT images of two patients did not allow evaluation of HOLO). Mean HOLO was 1.46 ± 0.13 mm after the first month, and 1.23 ± 0.21, 0.87 ± 0.17 and 0.47 ± 0.22 mm after the third, sixth and ninth month, respectively. A non-parametric (Wilcoxon) test showed a statistically significant difference in HOLO in all compared data ($p < 0.01$) (Table 2).

The correlation study between IOP and HFB and HOLO at one, three, six and nine months showed no statistically significant differences (Spearman’s rho), possibly due to the small sample size.

### Table 1. Evolution of filtering bleb height

<table>
<thead>
<tr>
<th>Bleb</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height (mm)</td>
<td>1.78 ± 0.26</td>
<td>1.57 ± 0.25</td>
<td>1.54 ± 0.38</td>
<td>1.42 ± 0.29</td>
</tr>
</tbody>
</table>

The mean height of the FB fell progressively over 3 months ($p < 0.01$) and remained practically unchanged from the third to the ninth month ($p > 0.9$).

There were significant differences in height over the 1-9 month follow-up ($p < 0.01$, Wilcoxon test).

### Table 2. Evolution of implant height

<table>
<thead>
<tr>
<th>Implant</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean height (mm)</td>
<td>1.46 ± 0.13</td>
<td>1.23 ± 0.21</td>
<td>0.87 ± 0.17</td>
<td>0.47 ± 0.22</td>
</tr>
<tr>
<td>Degradation (mm)</td>
<td>0.23 ± 0.13</td>
<td>0.34 ± 0.14</td>
<td>0.35 ± 0.15</td>
<td></td>
</tr>
</tbody>
</table>

Mean height of the implant and degradation (mm) between comparisons. The Wilcoxon test shows statistically significant differences between all comparisons ($p < 0.01$). At six months the implant remained intact in all patients. At 9 months, it had only degraded completely in 1 of 7 patients.

Figure 2. Evolution of Ologen® implant using biomicroscopy. It can be observed that the implant remains intact (un-degraded) after 9 months. Clinically, the filtering blebs appeared healthy (diffuse, elevated and well-vascularised).
In terms of postoperative evolution of refraction, a high rate of induced astigmatism was observed in the first week (−3.6 ± 2.2 D), which was significantly reduced after conjunctiva suture removal at the end of the week (−1.5 ± 0.5 D). Astigmatism remained practically unchanged over the remaining follow-up visits: −1.4 ± 0.5 D in the third month, and −1.5 ± 0.5 D in the sixth and ninth month.

Complications

One patient had persistent postoperative leakage (Seidel test) that required an additional suture. No cases of hypotony-induced anterior chamber narrowing were observed. The implant remained in position in all patients. One patient showed signs of increased vascularisation of the FB with no IOP increase. In this case, two subconjunctival injections of 5-fluorouracil (0.5 mg/ml) were administered. Finally, postoperative diplopia due to decompensation of an existing phoria was observed in one patient, which was corrected with prisms, while another patient presented a small postoperative hyphema that was fully resolved with medical therapy, with no further complications.

DISCUSSION

Several studies associate glaucoma, myopia and postoperative complications such as hypotony with the use of adjuvant mitomycin C. In these cases, intraoperative 5-fluorouracil can be a good alternative. However, although this is also true of low risk glaucoma, use of 5-fluorouracil is not entirely free of complications. A biodegradable collagen implant (Ologen) has recently been described as a possible alternative to antimitotics or as coadjuvant to low-dose antimitotics. There are few references in the literature to filtering surgery in high myopia, and no mention of the use and safety of the Ologen implant in such a high myopia patient group. On this basis, this pioneering descriptive study was conducted based on a retrospective analysis of our experience in treating these patients for whom high doses of antimitotics or lengthy exposure times are not recommended due to the high risk of complications. Patients with greater risk of hypotony and a high rate of scarring that could compromise surgical outcomes due to closure of the aqueous humour drainage fistula were also included. Despite the limitations of the study, which did not include a control group, it is important to focus on this low prevalence patient population with such a high incidence of postoperative complications, in order to conduct new prospective studies in the future with a control group. High myopic patients are excellent candidates for new technologies developed as an alternative to mitomycin, such as the Ologen implant, which reduces hyperfiltration in the early stages and later inhibits scarring. During scarring, a series of physiological events takes place to heal the wound.
Preliminary stages are characterised by increased cytokine production that can be controlled with topical corticosteroids and non-steroidal anti-inflammatory drugs (COX-2 inhibitors). A period of several weeks of increased fibroblast proliferation then follows. During this stage, antimetotics such as mitomycin C and 5-fluorouracil are used to inhibit the cell cycle and halt fibroblast proliferation. During the third stage the scar contracts, and at this time the fibroblasts are activated into myofibroblasts and arranged in order. The Ologen® implant acts during the initial healing stages to preserve the subconjunctival space and aqueous reservoir. It presses on the scleral flap, reduces the risk of early hypotony and prevents direct contact between the conjunctiva and the surface of the sclera, thereby reducing the risk of bleb fibrosis. It also acts at the tissue remodelling stage, evenly arranging the fibroblasts through its porous matrix to form a scar tissue that resembles physiological stroma.

The morphology of the FB has been associated with its function. Under biomicroscopy, elevated, diffuse, well-vascularised FBs are associated with better function, and therefore better IOP levels. One of the technologies used for evaluating FBs is OCT. In these cases, previous studies have shown that bleb height can be correlated with better pressure levels. This technology has also been used to assess the status of FBs with Ologen®. Studies comparing HFB in trabeculectomy with Ologen® implant vs. trabeculectomy with mitomycin differ in terms of anti-metabolite dosage and application time. Applied at high dosage (0.4 mg/ml for four minutes), HFB is greater in the mitomycin group, whereas at lower dosage (0.2 mg/ml for two minutes), HFB is greater in the implant group.

In this descriptive study, both HFB and HOLO were measured during the nine-month follow-up, finding that HFB remains practically unchanged from the third to the ninth month, despite degradation of the implant. No statistically significant correlation was found between loss of height in FB and Ologen® measured by OCT (Spearman’s rho) over the follow-up period. HFB could initially be determined by HOLO and inflammation, as described by other authors. Biomicroscopy showed greater inflammation and subconjunctival humour during the first month. The high rate of postoperative astigmatism, meanwhile, did not seem to be related to the implant, since it was significantly reduced following suture removal, and remained practically unchanged despite degradation of the device. In any event, these results should be viewed with caution due to the small size of the sample.

Contrary to the information in the implant brochure, it was observed both clinically and with the aid of OCT that it remained intact (no degradation) for six months in all patients. After nine months, it had disappeared completely in only one patient. No evidence of such a long follow-up using OCT was found in the literature. Based on our experience and the literature consulted, OCT is considered to be a useful tool in these cases, since it was able to measure both HFB and the thickness of the implant. Nevertheless, it is less useful in measuring other morphological variables such as the area of the bleb. OCT is a very operator-dependent technology; measurements taken by different operators might not be consistent, and bias or artefacts can prevent correct measurements, as shown by the loss of two patients in the ninth month of follow-up.

In this study, IOP in all patients remained below 18 mmHg over the 9-month follow-up period, without the need for hypotensive therapy. Only one patient needed postoperative 5-fluorouracil due to increased vascularisation of the bleb observed with biomicroscopy. All the studies reported a significant decrease in IOP in the postoperative period, and also in the number of hypotensive drugs needed. The Ologen® implant, however, does not seem to offer any statistically significant improvement compared with trabeculectomy alone, although more studies are needed to substantiate this, while in terms of hypotensive outcome, the benefits of the implant over mitomycin C are open to debate. Although the hypotensive effect is greater in the mitomycin group after application of high-dose mitomycin, in the case of shorter application time or low dosage, IOP reduction is similar in both groups, or greater in the mitomycin group.

It is important to point out, however, that this study used the previous version of the Ologen® implant. In cases of intraoperative low-dose mitomycin combined with Ologen® implant, significant IOP improvement and anatomical and functional FB are obtained. No definitive superiority studies have yet been conducted that show a greater reduction of IOP with the Ologen® implant. Like this study, however, most report a statistically significant reduction in IOP, low rate of complications, and a physiological FB; the approach reported here could be a feasible alternative for patients at risk of postoperative complications, as is the case with high myopia. Despite a promising start, more consistent findings can only be obtained from further studies with a control group and large cohort or longer follow-up.

REFERENCES


