Clinical and Biological Evaluations of Biodegradable Collagen Matrices for Glaucoma Drainage Device Implantation

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PURPOSE. To characterize the clinical and biological properties of biodegradable collagen matrices (BCMs) for possible glaucoma drainage device implantation.

METHODS. A total of 68 refractory glaucoma eyes, followed up postoperatively for at least 6 months, were consecutively enrolled after retrospective chart review. The BCM-augmented Ahmed valve implantations (BAAVI) using our Ologen-6 and Ologen-7 valves were performed and compared with a conventional method. Complete surgical success was defined as an IOP of ≤21 mm Hg (IOP 1) or ≤17 mm Hg (IOP 2) without antiglaucoma medications. Qualified success was defined as an IOP ≤21 mm Hg with or without antiglaucoma medications. The biological properties of each BCM were assessed by enzymatic degradation rates via collagenase under ocular physiological conditions.

RESULTS. The mean ages and preoperative IOPs were similar for the groups. In the conventional, BAAVI with Ologen-6, and BAAVI with Ologen-7 groups, complete success rates with target IOP 1 were 29.2%, 40.0%, and 66.7%; those with target IOP 2 were 12.5%, 30.0%, and 45.8%; qualified success rates were 45.8%, 55.0%, and 75.0%, respectively. The enzymatic degradation rate of Ologen-7 was significantly slower than that of Ologen-6 (12.5 × 10⁻³ vs. 28.8 × 10⁻³).

CONCLUSIONS. The surgical success rate was highest in the Ologen-7 BAAVI group, with the lowest dependency on postoperative antiglaucoma medication use compared with the conventional and Ologen-6 BAAVI groups. The clinical results correlated with the different biological and physicochemical properties based on the degree of enzymatic degradation and on the structural morphology.

Keywords: glaucoma, Ahmed glaucoma valve, biodegradable collagen matrix, degradation time, pore size

Subconjunctival fibrosis is a key phenomenon of the postsurgical healing process that can be induced by several factors, especially in the implantation of glaucoma drainage devices (GDDs).1,2 GDD implantation inevitably causes the pooling of aqueous humor in the subconjunctival and/or sub-Tenon’s space, which contains inflammatory cytokines related to fibrovascular proliferation inside the bleb wall. Insufficient bleb volume can lead to surgical failure after GDD implantation and could be related to the bleb wall property and the timing of aqueous humor inflow into the intraocular space. Therefore, modulation of the bleb wall could be crucial to overcome the fibrosis-related surgical failure.3 Antifibrotic agents, such as mitomycin-C (MMC) and 5-fluorouracil (5-FU), were considered as adjunctives to improve the surgical outcome in spite of the bleb-related problems. Recently, a biodegradable collagen matrix (BCM) has been used for filtration surgery to replace anti-fibrotic agents. The BCM, known as Ologen (Aeon Atron Corporation, Taipei, Taiwan) modulated wound-healing processes during the early stages4 and showed the possibility of use as an adjunctive option for Ahmed valve (AGV; New World Medical, Inc., Rancho Cucamonga, CA, USA) implantation as well as for trabeculectomy.3,5

Collagen is a structural protein that consists of the extracellular matrix, and is one of the most abundant proteins in the body. Due to their excellent biocompatibility and biodegradability,6,7 collagen-based biomaterials have been used in a variety of medical devices for tissue regeneration and reconstructive surgical purposes. Collagen has a triple-helix structure and its characteristics have been analyzed by a variety of biological and physicochemical methods.8 The enzymatic degradation rate via physiological proteases is one indicator used to understand the biological properties in physiological environments of collagen-based biomaterials, because they are influenced by structure, composition, cross-linking degree, or the collagen preparation method.9,10 Various types of proteases, including collagenases, are present at the implantation site and can alter the hydrolysis and degradation patterns of collagen-based biomaterials after BCM-augmented Ahmed valve implantation (BAAVI) surgery.11 Analyses of structural morphol-
ogy and pore size also can provide useful information for interpreting the differences between clinical and biological outcomes.

In the present study, we assessed the clinical outcome of BAAVI surgery by using two different BCMs and characterized the biological and physicochemical properties of the BCMs to determine their impact on surgical success percentages.

**MATERIALS AND METHODS**

**Subject Enrollment**

A total of 68 refractory glaucoma eyes were postoperatively followed for more than 6 months and were consecutively enrolled after retrospective chart review. This study was approved by the Institutional Review Board of CHA Bundang Medical Center (Seongnam, Republic of Korea) and the design followed the tenets of the Declaration of Helsinki. The surgical outcomes of AGV using two different BCM types, Ologen #862051 and Ologen #870051 (termed Ologen-6 and Ologen-7, respectively), were compared. Because Ologen-7 and Ologen-6 had no longer been commercially available in the Republic of Korea since late 2015 and late 2016 for approximately 1 year, respectively, the subjects from each group were enrolled consecutively. Refractory glaucoma was defined as an IOP >20 mm Hg despite maximally tolerated medical treatment. Patients who were younger than 18 years, had a previous history of glaucoma surgery, and/or severe postoperative complications (such as tube obstruction due to severe hyphema) were excluded. All eyes were operated on by a single surgeon (SR) from 2014 to 2016. All eyes underwent a full ophthalmic examination, including corrected distance visual acuity (CDVA) determination, Goldmann applanation tonometry by a glaucoma specialist (SR), axial length measurement using an Echotom (US-4000; Nidek, Fremont, CA, USA), and fundus examination. Fundus photography and retinal nerve fiber layer photography were performed with a fundus camera (VX-10i; Kowa, Nagoya, Japan). Anterior segment spectral domain optical coherence tomography (AS-SD-OCT) images were obtained using a Spectralis OCT (Heidelberg Engineering GmbH, Heidelberg, Germany) as described.3

**Surgical Procedure and Postoperative Management**

All surgical procedures were performed according to the previously described protocol. Briefly, after creation of a fornix-based conjunctival incision, a right-angled triangular scleral flap and a bridge-shaped scleral flap in the superotemporal quadrant, a tube-tied and priming-checked Ahmed valve plate was inserted into the sub-Tenon space then fixed at the sclera with 8-0 polypropylene sutures. In the BAAVI group, the valve plate was inserted into the sub-Tenon space then fixed at the sclera with 8-0 polypropylene sutures before the insertion. The cut tube with the proper length was inserted through a scleral tract made by a 23-gauge needle. The scleral flap and conjunctiva were sutured using 8-0 polyglactin sutures. Vigamox (0.5% moxifloxacin hydrochloride; Alcon Pharmaceuticals Ltd., Fribourg, Switzerland) and Pred Forte (1% prednisolone acetate; Allergan, Irvine, CA, USA) were used on the day after surgery and continued four times per day for 1 month. Chamber formation was accomplished using sodium hyaluronate (Unimed, Seoul, Republic of Korea) injection if the IOP within postoperative 2 weeks was lower than 6 mm Hg and the peripheral anterior chamber depth was less than half of the peripheral cornea thickness. If a hypertensive phase was noted, antiglaucoma eye drops were prescribed and added to keep the IOP lower than 20 mm Hg, using preservative-free timolol/dorzolamide fixed combination drops (Cosopt-s; Santen Pharmaceutical Co., Ltd., Osaka, Japan) twice per day, alpha agonist brimonidine drops (Alphagan; Allergan) twice per day, and latanoprost drops at night (Xalatan; Pfizer, New York, NY, USA).

**Surgical Outcome Measures**

Complete surgical success was defined as an IOP ≤21 mm Hg (target IOP 1) and IOP ≤17 mm Hg (target IOP 2) without antiglaucoma medications during the postoperative 6 months. Qualified success was defined as an IOP ≤21 mm Hg with or without antiglaucoma medication use. A hypertensive phase was defined as an IOP increase during two consecutive visits with 2-week intervals of higher than 21 mm Hg.

**Structural Morphology and Pore Size Analyses of Ologen-6 and Ologen-7**

The surface and cross-sectional morphologies of Ologen-6 and Ologen-7 were observed by field emission scanning electron microscope (FESEM) (JSM-7100F; JEOL, Tokyo, Japan) operating at 5 kV. Each sample was coated with platinum, and scanning was performed at room temperature. Pore size was analyzed using ImageJ (http://imagej.nih.gov/ij/; provided in the public domain by the National Institutes of Health, Bethesda, MD, USA) and characterized using the maximum Feret Diameter.

**Enzymatic Degradation Rate Analyses of Ologen-6 and Ologen-7**

The degradation rates of Ologen-6 and Ologen-7 were evaluated using collagenase from *Clostridium histolyticum* (CO130; Sigma-Aldrich Corp., St. Louis, MO, USA). Ologen-6 and Ologen-7 were initially prepared using the same amount (1 mg). Samples were then immersed in 20 μL optical solution (pH 7.2; Rayon Pharmaceutical Company, Seoul, Republic of Korea) containing 20 μg/mL collagenase at 34°C to mimic the ocular physiological conditions. To compare the enzymatic degradation rates of Ologen-6 and Ologen-7, mass changes were measured at specific incubation time points (0, 3, 6, 9, 12, 24, and 48 hours). The initial swollen masses (W0) of Ologen-6 and Ologen-7 were weighed and they were spread over a table until no water dripped from them. The swollen mass after enzymatic degradation (Wi) at each time point was determined. The enzymatic degradation was calculated by the following formula:

\[
(W_i/W_0)^{1/2} = 1 - k t,
\]

where W0 is the weight of the initial swollen samples of Ologen-6 or Ologen-7, Wi is the weight of the swollen samples after enzymatic degradation at each time i, and k is the rate constant.10

**Statistical Analyses**

All data were expressed as the mean ± SD. Based on a previous study,1 a minimal number of 18 subjects for each group was deemed necessary to detect a 4-mm Hg change in IOP values with a 90% statistical power in the setting of a 4-mm Hg SD. All statistical analyses were performed using the SPSS software (version 21.0; SPSS, Inc., Chicago, IL, USA). The $\chi^2$ (or...
### Table 1. Patient Demographics of the Total Population

<table>
<thead>
<tr>
<th></th>
<th>Conventional, n = 24</th>
<th>BAAVI-6, n = 20</th>
<th>BAAVI-7, n = 24</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, y</td>
<td>59.54 ± 12.25</td>
<td>59.50 ± 12.90</td>
<td>63.75 ± 13.52</td>
<td>0.99</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>91.70</td>
<td>65.00</td>
<td>66.30</td>
<td>0.06</td>
</tr>
<tr>
<td>Preop CDVA, Snellen</td>
<td>0.20 ± 0.26</td>
<td>0.25 ± 0.25</td>
<td>0.26 ± 0.30</td>
<td>0.48</td>
</tr>
<tr>
<td>Postop CDVA, Snellen</td>
<td>0.28 ± 0.33</td>
<td>0.39 ± 0.34</td>
<td>0.36 ± 0.35</td>
<td>0.3</td>
</tr>
<tr>
<td>Preop IOP, mm Hg</td>
<td>32.00 ± 8.51</td>
<td>31.95 ± 7.56</td>
<td>31.87 ± 8.70</td>
<td>0.98</td>
</tr>
<tr>
<td>Preop ECC, cells/mm²</td>
<td>23.51 ± 515</td>
<td>2301 ± 483</td>
<td>2274 ± 438</td>
<td>0.79</td>
</tr>
<tr>
<td>Postop ECC, cells/mm²</td>
<td>2142 ± 528</td>
<td>2424 ± 440</td>
<td>2371 ± 434</td>
<td>0.07</td>
</tr>
<tr>
<td>Cause, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NVG</td>
<td>22 (91.7)</td>
<td>10 (50.0)</td>
<td>8 (33.3)</td>
<td></td>
</tr>
<tr>
<td>Other glaucoma</td>
<td>2 (8.3)</td>
<td>10 (50.0)</td>
<td>16 (66.7)</td>
<td></td>
</tr>
<tr>
<td>Preop antiglaucoma medications, n</td>
<td>3.12 ± 0.80</td>
<td>3.55 ± 0.61</td>
<td>3.54 ± 0.98</td>
<td>0.57</td>
</tr>
<tr>
<td>Hypertensive phase, %</td>
<td>58.30</td>
<td>55.00</td>
<td>33.30</td>
<td>0.82</td>
</tr>
<tr>
<td>Hypotony, %</td>
<td>16.70</td>
<td>5.00</td>
<td>12.50</td>
<td>0.36</td>
</tr>
<tr>
<td>Hyphema, %</td>
<td>8.30</td>
<td>0.00</td>
<td>4.20</td>
<td>0.49</td>
</tr>
<tr>
<td>Choroidal effusion, %</td>
<td>4.20</td>
<td>0.00</td>
<td>0.00</td>
<td>1</td>
</tr>
</tbody>
</table>

Data are shown as the mean ± SD except where otherwise indicated. ECC, endothelial cell count; NVG, neovascular glaucoma; Other glaucoma, open angle glaucoma, angle closure glaucoma, or secondary glaucoma.

* Mann-Whitney test and χ² test with Fisher’s exact test (between conventional and BAAVI groups). P values sequentially represent conventional method versus BAAVI-6, conventional method versus BAAVI-7, and BAAVI-6 versus BAAVI-7.

### Results

#### Clinical Data Comparisons

Valve implantation used the conventional method, the BCM-augmented Ahmed Ologen-6 (BAAVI-6), and the BAAVI Ologen-7 (BAAVI-7) method in 24, 20, and 24 eyes, respectively. The demographic characteristics of the population are summarized in Table 1. There was no significant difference between each group with regard to age, IOP, number of preoperative antiglaucoma eye drops, or endothelial cell count. The frequency of a hypertensive phase was significantly lower in the BAAVI-7 group compared with the other groups.

As shown in Table 2, the success rate was generally higher in the BAAVI-7 group than in the conventional group or the BAAVI-6 group (although the difference between BAAVI-6 and BAAVI-7 was not statistically significant). The percentages for qualified success were 45.8%, 55.0%, and 75.0%; complete successes with target IOP 1 were 29.2%, 40.0%, and 66.7%; and complete successes with target IOP 2 were 12.5%, 30.0%, and 45.8% in the conventional, BAAVI-6 group, and BAAVI-7 group, respectively.

The mean IOP changes using the three methods are shown in Figure 1. The IOP at 1 month postoperative was relatively lower in the BAAVI-7 group (15.00 ± 3.68 mm Hg) than in the conventional (18.25 ± 7.69 mm Hg) and BAAVI-6 (18.70 ± 6.68 mm Hg) group (P = 0.06 and 0.07, respectively). The differences among the groups decreased as the number of antiglaucoma eye drops increased after 1 month postoperative (Fig. 2).

Although the bleb morphology assessment using AS-SD-OCT varied widely, most showed some differences between the two BAAVI groups. No difference was noted during the first 2 weeks; however, the bleb wall appeared more heterogeneous in the BAAVI-7 group than in the BAAVI-6 group after 1 month postoperative. As shown in Figure 3, an AS-SD-OCT image of the inner bleb wall (Tenon’s capsule layer) in the BAAVI-7 group after 3 months postoperative appeared to be through the transition period, as previously described. However, the BAAVI-6 group showed an indistinct change in the inner bleb wall properties (Figs. 3A, 3B).

#### Structural Morphology and Pore Size Assessments of Ologen-6 and Ologen-7

To investigate the morphologic differences, the superficial and cross-sectional structure and pore size of the two Ologen-treated samples were assessed by using SEM and ImageJ analyses (Fig. 4). Both samples contained three-dimensional interconnected and porous structures that are normally seen in collagen-based biomaterials. Although surface pore sizes of the surface of Ologen-6 were significantly different (P < 0.001), no difference between cross-sectional morphology and pore size

### Table 2. Comparison of Success Percent (%) During Postoperative 6 Months

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>BAAVI-6</th>
<th>BAAVI-7</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target IOP 1</td>
<td>29.2</td>
<td>40</td>
<td>66.7</td>
<td>0.45</td>
</tr>
<tr>
<td>Target IOP 2</td>
<td>12.5</td>
<td>30</td>
<td>45.8</td>
<td>0.26</td>
</tr>
<tr>
<td>Qualified</td>
<td>45.8</td>
<td>55</td>
<td>75</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Target IOP 1, IOP of ≤21 mm Hg; Target IOP 2, IOP of ≤17 mm Hg

* χ² test (between conventional and BAAVI groups) with Fisher’s exact test. P values sequentially represent conventional method versus BAAVI-6, conventional method versus BAAVI-7, and BAAVI-6 versus BAAVI-7.
of the Ologen-6 and Ologen-7 was observed \((P = 0.105)\) (Fig. 4B).

### Enzymatic Degradation Rates of Ologen-6 and Ologen-7

To quantify the enzymatic degradation rates, mass changes of Ologen-6 and Ologen-7 due to the hydrolysis of polypeptides by collagenase were measured after incubation at each time point (Fig. 5). The in vitro degradation rate of weight loss of Ologen-6 and Ologen-7 showed dramatically different tendencies. For comparative analyses, the rate constants \((k)\) of the collagenase hydrolysis of Ologen-6 and Ologen-7 were obtained from the initial weight loss slope of the plots in Figure 5A. The rate constant of hydrolysis of Ologen-6 and Ologen-7 were 28.8 \(\times 10^{-3}\) and 12.5 \(\times 10^{-3}\) \((\text{h}^{-1})\), respectively, indicating a slower degradation rate for Ologen-7 compared with Ologen-6 \((P < 0.001)\). The enzymatic degradation tendency also correlated with the other ocular physiological characteristics, including the differences observed at 32°C and the varied enzyme concentration differences (data not shown).

### DISCUSSION

#### Clinical Outcome Assessments

Despite extensive surgical knowledge, the goal to achieve targeted pressure without the need for antiglaucoma eye drops has not been achieved in a considerable number of patients. Recently, Ologen, a commercialized BCM for ophthalmologic use, has been increasingly used for glaucoma surgery. Ologen implants have demonstrated efficacy in terms of IOP reduction with a success percentage similar to MMC-augmented trabeculectomy even after 5-year follow-up. Because intrableb fibrotic change after GDD implantation surgery is known to be more intensive than after MMC-augmented trabeculectomy, the need for novel options for handling fibrosis has increased as the proportion of GDD implantations has increased.

This study demonstrated that the success percentage for BAAVI-7 was significantly higher than that of the conventional group, but the percentage for the BAAVI-6 group did not show a statistical difference. The difference of the success percentages between the BAAVI-7 and the conventional group in this study was similar to that of our previous report that included only the BAAVI-7 group. This tendency was noted until a 1-year follow-up (data not shown). The cause of the poor efficacy of Ologen-6 in terms of IOP reduction with AGV implantation requires further study, and could provide new insight concerning bleb modulation.

#### Biological and Physicochemical Characterizations of Ologen-6 and Ologen-7

Until recently, wound-healing modulation and fibrosis management using anti-inflammatory or antimetabolite strategies via certain cytokines were the primary goals for improving the outcome of filtering surgery. However, mechanical cues also have a considerable impact on scar formation. Cell surface signaling receptors, including integrins and cadherins, couple the actin cytoskeleton to the extracellular matrix (ECM), and are controlled by sensing mechanical stimuli, thus possibly resulting in the modulation of myofibroblast transdifferentiation. Low levels of interstitial flow induce fibroblast-to-myofibroblast differentiation as well as ECM alignment and fibroblast proliferation, even in the absence of exogenous mediators. Therefore, controlling the entire biophysical environment in the subconjunctival/sub-Tenon's space could play an important role in fibrogenesis after glaucoma-filtering surgery.

With BAAVI-6 and BAAVI-7, we attempted to provide the proper environment in the subconjunctival/sub-Tenon's space with the goal of lowering IOP. As a result, BAAVI-7 showed a significantly higher success percentage (Fig. 2). Biological and physicochemical characterizations of Ologen-6 and Ologen-7 provided a few clues for explaining different clinical outcomes. Ologen-6 and Ologen-7 showed different structural morphology, pore size, porosity; and differing enzymatic degradation rates. Notably, statistically smaller pore sizes and lower porosity in Ologen-7 were observed compared with Ologen-6 (Fig. 4), and the enzymatic degradation rate of Ologen-6 was
FIGURE 3. Comparison of bleb morphology using AS-SD-OCT images and bleb photos on postoperative day 90. (A, B) Two cases of bleb morphology in the BAAVI-6 group. An upper higher reflectance layer (conjunctiva, green arrowhead) and a lower relatively lower reflectance layer (Tenon's capsule) were noted on postoperative day 90. (C) A representative case of bleb morphology in the BAAVI-7 group. Note that the lower layer of the bleb is not prominent (A) or is denser (B) in the BAAVI-6 group than in the BAAVI-7 group (C). However, the lower layer of the bleb in the BAAVI-7 group showed lower intensity with a sparse feature (green arrow).

FIGURE 4. Structural morphology and pore size assessments of Ologen-6 and Ologen-7. (A) The surface and cross-sectional SEM images of Ologen-6 and Ologen-7. (B) Pore size measurements of Ologen-6 and Ologen-7. Scale bars: 100 μm.

FIGURE 5. Enzymatic degradation rate of Ologen-6 and Ologen-7. (A) Percentage weight decrease of Ologen-6 and Ologen-7 plotted as a function of collagenase digestion time. (B) $\left(\frac{W_i}{W_0}\right)^{1/2}$ plotted as a function of collagenase digestion time.
significantly faster than that of Ologen-7 (Fig. 5). All the above results indicated that Ologen-7 provided a more robust system in a clinical environment when compared with Ologen-6.

In an experimental setting, the interstitial flow induced alpha-smooth muscle actin (α-SMA) expression in approximately 97% of the fibroblasts after 5 days, whereas most of the fibroblasts in static conditions remained undifferentiated and only 14% were α-SMA-positive after 5 days. Ologen also plays a role as a primary wall against fluid inflow into the interstitial tissue. Therefore, we expect that if Ologen degrades too fast, the change in bleb will begin early. Because α-SMA expression characterizes the differentiation of fibroblast to contractile myofibroblasts that is a crucial process for wound healing and a key feature of tissue fibrosis and scarring, minimizing the shear stress to fibroblasts may be beneficial. It was suggested that perpendicular fiber alignment of the ECM yields lower shear stress and pressure forces on the fibroblasts leading to decreased permeability. 24 To increase permeability of the bleb, it is appropriate that the ECM architecture needs to be in a parallel or at least in a cubic arrangement (perpendicular + parallel alignment). Therefore, theoretically, a preserved BCM with a proper duration in vivo would ameliorate this surgical scarring issue.

Ologen-6 and Ologen-7 have a similar composition of 90% collagen and 10% glycosaminoglycan (GAG). Their different biological and physicochemical characteristics might result from their different cross-linkable units or drying processes. 24-26 The cross-linkable units also could play a role in allowing more or less access to the cleavage sites along the collagen backbone. Thus, cross-linking gives tensile strength and enzymatic resistance to collagen-based biomaterials. 25 As the reconstituted forms of collagen-like films, or sponges, may disintegrate on handling or collapse under pressure in vivo, the rate of biodegradation should be customized according to its application using different cross-linking processes. Cross-linking on collagen-based biomaterials can be achieved by 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC), glutaraldehyde, dehydrothermal treatment, and exposure to UV or gamma-irradiation. In addition, the freeze-drying process compared with Ologen-6.

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