Amniotic membrane-assisted trabeculectomy for refractory glaucoma with corneal disorders

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Purpose: To report the cases of six consecutive patients who underwent amniotic membrane (AM)-assisted trabeculectomy (TLE) to treat refractory glaucoma with severe corneal disorders.

Methods: This study involved six patients (three males and three females, mean age: 69.5±15.8 years) with refractory glaucoma and severe corneal disorders. The surgical procedure for each patient involved trabecular tissue being excised, and human AM then being placed epithelial side up on the corneal surface, sutured at the limbal sclera, and flipped over onto the sclera to cover the TLE area. The remaining edge of the AM was then inserted into the subconjunctival space and sutured. Medical records of all cases were reviewed with regard to intraocular pressure (IOP), visual acuity, and condition of the filtering bleb and ocular surface.

Results: The mean observation period was 69.5±15.8 months, and mean IOP at presurgery and at 1, 3, and 7 years postoperative was 40.3±6.9, 23.0±12.1, 25.6±12.8, and 28.5±19.1 mmHg, respectively. Glaucoma medications decreased from 3.0±1.1 drugs (presurgery) to 0.8±1.0 drugs (7 years postoperative). However, in some cases, ocular surface conditions or visual acuity worsened during the follow-up period.

Conclusion: Using AM as an internal patch for TLE, moderately good IOP control was obtained initially for the refractory glaucoma with severe corneal disorders; however, ocular surface conditions required special care, and the long-term IOP control was limited in some cases.

Keywords: amniotic membrane, refractory glaucoma, trabeculectomy

Introduction

Glaucoma with corneal disorders including ocular surface diseases is one of the most refractory types of glaucoma. Filtering surgery often fails due to severe inflammation, recurrent conjunctival scarring, proliferation of subconjunctival fibrous tissue, and the high risk of infection in patients taking immunosuppressive drugs. Other surgical procedures such as tube-shunt surgery are not always effective for severe ocular surface disorders because they may result in many problems such as cicatricial reaction of the conjunctivae, exposure of the tube or plate, and corneal endothelial damage.

Recently, the use of human amniotic membrane (AM) in ocular surface reconstruction has reportedly yielded good outcomes. In 1910, Davis first described the use of AM in skin transplantation procedures. In the field of ophthalmology, AM was reportedly used to repair conjunctival defects after chemical burns in the 1940s; however, the results were not promising. Successful AM transplantation for ocular surface reconstruction was reported 50 years later, and AM is now the focus of attention as a
biomaterial for the treatment of severe ocular surface diseases, such as ocular pemphigoid, Stevens–Johnson syndrome, and chemical burns. Koizumi et al and Nakamura et al reported very good prognoses when using AM as a transporter of cultured corneal epithelium to treat patients with severe ocular surface diseases. In ocular surface reconstruction, AM offers several benefits, as it can be easily obtained and preserved for several months, is not rejected immunologically, suppresses fibroblast proliferation, and accelerates cell migration and growth. Therefore, we theorized that AM might be suitable for glaucoma filtering surgery.

To date, there have been few reports on the use of AM in glaucoma surgery. Fujishima et al reported the effectiveness of AM for reducing intraocular pressure (IOP) in high-risk patients when it was placed under the scleral flap, yet Budenz et al found that AM transplantation was not an effective alternative to conjunctival advancement in patients undergoing the repair of leaking glaucoma filtering blebs; however, it should be noted that their total replacement of the leaking bleb with AM exposed it to constant pressure without supportive structures above or beneath the filtering bleb. In the presence of such structures, AM might be able to resist that pressure and function as part of the bleb wall. Based on these considerations, we theorized that an AM patch could be introduced below the filtering bleb. The purpose of this present study was to report six patients with refractory glaucoma having corneal severe disorders who were treated with AM-assisted trabeculectomy (TLE).

**Patients and methods**

This study involved six consecutive patients (three males and three females, mean age: 69.5 ± 15.8 years) with refractory glaucoma and corneal disorders who were treated with AM-assisted TLE between March 2000 and April 2002. Written informed consent was obtained from all patients for the use of AM, and the procedure was approved by the Human Studies Committee of Kyoto Prefectural University of Medicine. All experimental procedures were conducted in accordance with the tenets set forth in the Declaration of Helsinki. IOP measurements of each patient were obtained by use of a Goldmann applanation tonometer, and the surgical procedure for each patient was as follows. First, under local anesthesia, a limbal-based conjunctival flap was produced by careful detachment of the scarred conjunctiva, and an adequate amount of sclera was exposed. A limbal-based scleral flap was then produced and inoculated with a 0.4 mg/mL treatment of mitomycin C for 3 minutes, conventional TLE was performed, and the scleral flap was closed with 10-0 nylon sutures (Figure 1A). Next, deep-frozen human AM obtained at the time of cesarean section was thawed, trimmed to the proper size, placed epithelial side up on the corneal surface, and sutured at the limbal sclera beside the scleral flap using 10-0 nylon sutures. The other edge of the AM was then flipped over to cover the scleral flap (Figure 1B). Finally, continuous conjunctival suturing with 10-0 polypropylene was performed (Figure 1D). A cross-sectional view of the filtering bleb with the AM patch is shown in Figure 1E.

The medical records of all six cases were reviewed in regard to each patient’s IOP, visual acuity (VA), and the condition of the filtering bleb and ocular surface.

**Results**

The summary of all six cases is shown in Table 1, and the mean observation period was 69.5 ± 15.8 months. All cases
The IOP time course of each case is shown in Figure 2A–C. None of the patients experienced any increase in IOP during the follow-up period, the IOP decreased compared with that before surgery (7 years postoperative). During the 7-year postoperative period, the IOP decreased from 28.5±11.8 mmHg to 12.1±6.2 mmHg, and the mean IOP at preoperative and at 1, 3, and 7 years postoperative was 40.3±6.9, 23.0±12.1, 25.6±12.8, and 13.2±6.7 mmHg, respectively.

In all cases, filtering blebs, comprising an additional layer of AM with its epithelial side down, were established. The blebs functioned well without any leakage or wall thinning (Figure 2A–C). None of the patients experienced any ocular surface inflammation, and no patients with glaucoma and ocular surface diseases noted in the failure of a conventional TLE in which results in the failure of a conventional TLE in 3 cases. The blebs functioned well without any leakage or wall thinning (Figure 2A–C). None of the patients experienced any ocular surface inflammation, and no patients noted the failure of a conventional TLE in which results in the failure of a conventional TLE in 3 cases.

Table 1 Summary of the six cases of patients with refractory glaucoma and severe corneal disorders

<table>
<thead>
<tr>
<th>Case</th>
<th>Age at op, years</th>
<th>Sex</th>
<th>Glaucoma type</th>
<th>Reason of corneal disorder</th>
<th>Previous op</th>
<th>BCVA preop (logMAR)</th>
<th>Gla med pre op (drugs)</th>
<th>IOP preop (mmHg)</th>
<th>BCVA last visit (logMAR)</th>
<th>Gla med last visit (drugs)</th>
<th>IOP last visit (mmHg)</th>
<th>Follow-up period (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>50</td>
<td>M</td>
<td>SG</td>
<td>Chem injury</td>
<td>PKP + PEA + IOL lensctomy</td>
<td>1.5</td>
<td>4</td>
<td>37</td>
<td>2.8</td>
<td>0</td>
<td>20</td>
<td>33</td>
</tr>
<tr>
<td>2</td>
<td>58</td>
<td>M</td>
<td>SG</td>
<td>Injury</td>
<td>TLE, PKP 2 bleb revision</td>
<td>2.7</td>
<td>4</td>
<td>34</td>
<td>2.9</td>
<td>0</td>
<td>8</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>F</td>
<td>SG</td>
<td>Injury infection</td>
<td>PKP TLE</td>
<td>2.4</td>
<td>4</td>
<td>34</td>
<td>2.7</td>
<td>2</td>
<td>38</td>
<td>96</td>
</tr>
<tr>
<td>4</td>
<td>82</td>
<td>F</td>
<td>PACG</td>
<td>APAC several op infection</td>
<td>ECCE + IOL IOL extraction PKP</td>
<td>2.8</td>
<td>3</td>
<td>34</td>
<td>2.9</td>
<td>0</td>
<td>6</td>
<td>68</td>
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<tr>
<td>5</td>
<td>85</td>
<td>M</td>
<td>PEG</td>
<td>Drug-induced OCP</td>
<td>TLE</td>
<td>2.7</td>
<td>3</td>
<td>47</td>
<td>2.8</td>
<td>2</td>
<td>13</td>
<td>76</td>
</tr>
<tr>
<td>6</td>
<td>84</td>
<td>F</td>
<td>SG PEG</td>
<td>PKP + PEA + IOL</td>
<td>TLE</td>
<td>0.5</td>
<td>3</td>
<td>32</td>
<td>2.7</td>
<td>1</td>
<td>13</td>
<td>76</td>
</tr>
</tbody>
</table>

Notes: logMAR visual acuity; hand motion: 2.7, light perception (+): 2.8, and light perception (-): 2.9.

Abbreviations: op, operation; preop, preoperative; IOP, intraocular pressure; M, male; SG, secondary glaucoma; chem, chemical; PKP, penetrating keratoplasty; TLE, trabeculectomy; F, female; PACG, primary angle closure glaucoma; ECCE, extracapsular cataract extraction; PEG, pseudoxfoliatio glaucoma; OCP, ocular cicatricial pemphigoid; TLE, trabeculectomy; LI, laser iridotomy; PPV, pars plana vitrectomy; logMAR, logarithm of minimal angle of resolution; PEA, phacoemulsification aspiration; IOL, intraocular lens; APAC, acute primary angle closure; Gla med, glaucoma medications; BCVA, best corrected visual acuity.
gradually becoming small and flat. However, in some cases, the ocular surface conditions or VA worsened during the postoperative follow-up period.

We examined the subconjunctival structure of the filtering bleb in the first case using optical coherence tomography (OCT, OCT-3000; Carl Zeiss Meditec AG, Jena, Germany). This is a noncontact, noninvasive method to visualize not only the bleb wall constructed by the AM but also the subconjunctival structure filled with aqueous humor. The OCT image showed a dome-shaped filtering bleb of equal thickness along the entire wall and a uniform subconjunctival lesion representing the aqueous humor posteriorly (Figure 2D).

Figure 2 Images of three representative cases.
Notes: (A–C) Filtering blebs post AM-assisted TLE in all three patients. (D) Optical coherence tomography image (sagittal view) of the filtering bleb in case 1 at 2 years postoperative.
Abbreviations: AM, amniotic membrane; TLE, trabeculectomy.

Figure 3 Time course of IOP changes in all six cases.
Abbreviation: IOP, intraocular pressure.
Discussion
The effects of subconjunctival AM transplantation are twofold, as the transplanted AM functions not only as a mechanical barrier but also as a biological modifier. As a mechanical barrier, it patches the conjunctival hole or tear, strengthens the fragile wall of the bleb, and prevents aqueous humor from overfiltrating and bacteria from entering into the subconjunctival and intraocular space. As a biological modifier, the AM offers a foundation and substrate for the conjunctival basal cells that stimulate epithelialization, traps polymorphonuclear cell infiltration, thereby preventing inflammation, promotes wound healing by inhibiting protease activity, and suppresses transforming growth factor (TGF-β) signaling, thereby exerting antiscarring effects.

TGF-β reportedly plays an important role in conjunctival scarring after glaucoma surgery. Cordeiro et al. investigated the effects of TGF-β1, -β2, and -β3 in vitro on Tenon’s fibroblast contraction, proliferation, and migration. They concluded that TGF-β, which exists in the anterior chamber and subconjunctival space, is implicated in the conjunctival scarring of the filtering bleb. Their group also reported the effects of a new recombinant human antibody to TGF-β2 on in vitro and in vivo conjunctival scarring and after glaucoma surgery. We expect subconjunctival AM transplantation to have effects similar to those elicited by the treatment of the subconjunctival tissue with anti-TGF-β2 antibody.

The twofold effect of AM is derived from its histological structure, ie, the epithelial cellular monolayer and the stromal layer, which have different characteristics. The stromal layer is beneficial like an extracellular matrix that promotes cellular proliferation and migration on the conjunctival epithelium and epithelial cells produce cytokines to prevent severe scarring. Therefore, it may be important to place the AM epithelial side down on the scleral flap.

There are still many open questions regarding the use of AM in glaucoma surgery. For example, a question still exists as to whether or not the transplanted AM wall stays strong enough to maintain the filtering bleb wall for long periods. Also, it remains to be determined whether it is better to introduce the AM with the stromal side up or the epithelial side up on the scleral flap. In practice, the filtering bleb used for our first patient consisted of two layers of AM and lasted for >2 years without dissolving. To determine the long-term prognosis regarding IOP control by AM-assisted TLE, we continue to follow our patients carefully to identify and treat potential wound reopening or infection.

Recently, Nakamura et al. also reported about AM-assisted TLE, comparing the intrableb structures of AM-TLE with those of TLE alone using an ultrasound biomicroscope. The findings of that study revealed that the intrableb structures in AM-assisted TLE contained a wide fluid-filled space with a relatively thin wall, whereas those produced during TLE alone had no or minimal fluid-filled space. When the fluid-filled space extended posteriorly, IOP was reportedly well controlled, whereas if the eyes did not have any fluid-filled space or had a restricted space, the IOP control was poor. Case 1 in this study also showed a large fluid-filled space with good IOP control at 2 years postoperative when examined by OCT (Figure 2D), yet the bleb size gradually decreased and IOP increased as time passed.

Conclusion
Our new surgical technique, which uses AM as an internal patch for TLE, is an alternative treatment for patients with glaucoma and severe corneal disorders because of its initial good IOP control. However, special care and strict attention toward the condition of the ocular surface is required, and the long-term IOP control was limited in some cases.

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Disclosure
The authors report no conflicts of interest in this work.

References


