Autologous ear cartilage as a carrier for the Boston Type I Keratoprosthesis in a rabbit model

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Abstract: Purpose: To evaluate complications and anatomical retention when using autologous ear cartilage as a carrier in type 1 Boston keratoprosthesis (Kpro) surgery. Methods: In New Zealand White rabbits, the Kpro was surgically implanted using autologous cartilage (n = 5) or ipsilateral autologous cornea (n = 1, control) as carrier. Eyes were followed up using slit-lamp photography, anterior segment optical coherence tomography, and histological analysis for 19 days to 24 months. Results: Kpros were retained in all eyes. One eye in the cartilage group had an uncomplicated course; 3 developed granulation tissue over the Kpros optic, 1 developed a retroprosthetic membrane, and 3 developed glaucoma. Two eyes had lacunae. The gap between the Kpros flange and cartilage carrier filled with fibrovascular tissue over time. The control eye developed corneal tissue thinning and an enlarged gap. Conclusion: Auricular cartilage carriers may encourage Kpro-graft adhesion in a rabbit model and may be useful in Kpro recipients who cannot use bandage contact lenses.

Subjects: Medical Technology & Engineering; Ophthalmology; Surgery; Transplant Surgery

Keywords: autologous cartilage; Boston keratoprosthesis; corneal melt; carrier; Kpro-graft gap

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PUBLIC INTEREST STATEMENT

The disease and lesion of the cornea is the fourth leading cause of blindness in the world. The success rate of keratoplasty for some corneal disease is greater than 90%. However, almost all authors believe that the success rate for vascularized cornea and recurrent rejected cornea is dismal. Keratoprosthesis is the last resort reserved for these patients in whom keratoplasty is not feasible. Boston keratoprosthesis is the most widely used keratoprosthesis. The device has a collar button configuration and is composed of a polymethylmethacrylate front plate and stem with a backplate. Although polymethylmethacrylate is well tolerated by the cornea, the incidence of corneal carrier melt around stem varies from 10% to 18%. This experimental study attempted to evaluate the use of auricular cartilage as the carrier to fix the Boston keratoprosthesis and prevent carrier melt, a devastating postoperative complication which leading to aqueous leaks or extrusion of the device.
Corneal melt is an important complication of Boston keratoprosthesis (Kpro) surgery. The occurrence of corneal melt in a recently published Kpro series ranged from 10% to 18%. (Aldave et al., 2012; Shihadeh & Mohidat, 2012) Despite improvements in the design of the device and postoperative management, patients who have ocular chemical burn injuries may have increased risk of developing keratolysis, if they cannot wear a bandage contact lens due to eyelid abnormalities or symblepharon. (Gu, Zhai, Zhou, & Chen, 2016). A retroprosthetic membrane (RPM) and persistent ocular inflammation in autoimmune disease like Stevens-Johnson syndrome are also risk factors for sterile keratolysis. (Sivaraman, Hou, Allemann, de la Cruz, & Cortina, 2013)

The management of corneal melt involves the reconstruction of the eyelid and ocular surface to retain the bandage contact lens, use of topical drugs to inhibit collagenase activity (Fitton, Ziegelaar, & Hicks et al., 1998) and introduction of a titanium backplate to reduce the formation of a RPM (Todani, Ciolino, Ament, & Hicks, 2011). However, despite the recent advances in the Kpro, some of these keratoprostheses patients develop sterile ulcerations and thinning of the corneal tissue, which acts as a carrier for the Kpro, especially those with autoimmune disease. Keratolysis of the donor cornea remains a rare, yet devastating, postoperative complication that leads to exposure of the eye to pathogens, perforation, leakage of the aqueous humor, and extrusion of the Kpro. (Robert & Dohlman, 2014)

Autologous cartilage grafts are considered as a reliable and readily available graft material, and because they do not stimulate the immune response, they are widely used for surgical reconstruction and in cosmetic surgery (Cárdenas-Camarena & Guerrero, 1999; Parker Porter, 2000). Auricular cartilage is resistant to infection and permits mucosal regeneration (Min, Kim, & Kim, 1996). Autologous auricular cartilage grafts are also reported to provide efficient support to the optical cylinder in keratoprosthesis surgery (Hoffart & Guyot, 2017). Therefore, in this preliminary study, we report the results of using autologous ear cartilage as a carrier for the Kpro in an animal model.

1. Materials and methods

1.1. Animals
Six New Zealand White rabbits were used as the experimental model. The pretreatment weight of each rabbit was between 2.5 and 3.0 kg. Ethical approval for the study was given by the Animal Experiments Committee of the Zhongshan Ophthalmic Center (Guangzhou, China), and all animals were treated according to the ARVO statement for use of animals in ophthalmic and vision research. The rabbits were acclimatized for 2 weeks and were housed in a temperature-controlled environment, maintained on a 12-h artificial day/night rhythm.

1.2. Keratoprosthesis design and materials
The Kpro devices were manufactured by the Massachusetts Eye and Ear Infirmary. Five eyes underwent implantation with a Kpro with a titanium backplate, and 1 with a polymethyl methacrylate (PMMA) backplate.

1.3. Surgical technique

1.3.1. Cartilage and autologous cornea harvesting
Rabbits were anaesthetized by intramuscular injection of a mixture of 35 mg/kg ketamine hydrochloride and 5 mg/kg xylazine hydrochloride. To prepare the donor site, an ear was shaved and cleaned with povidone-iodine solution. After 1% lidocaine was infiltrated into the subcutaneous tissue of the ear, 4-cm incisions were made along the longitudinal axis on the dorsal surface of the ear. Using blunt subcutaneous dissection, an area of cartilage 15 × 15 mm in size was harvested
with the perichondrium preserved. The mean thickness of the cartilage was 516.2 ± 20.2 μm (range: 495–545 μm; median, 513 μm).

1.3.2. Kpro implantation in rabbits

A 9.0-mm cartilage graft was punched out from the autologous cartilage; into this tissue, a 3.0-mm hole was punched. The front part of the Kpro was positioned, stem-up, and the cartilage graft was slid over the stem. The backplate was placed on the stem, after which the titanium locking ring was placed on the stem. The locking ring was firmly pushed down until it audibly snapped into the groove.

The rabbit cornea was trephined (8.5 mm diameter) and excised, and the lens was removed using an open-sky extracapsular extraction, after which the surgical field was irrigated with a heparin solution. The combined Kpro and the cartilage graft was then sutured with 16 sutures of 10–0 nylon (Figure 1). One rabbit was implanted with a Kpro using the ipsilateral autologous cornea as the carrier, as described by Salvador-Culla (Salvador-Culla et al., 2014) as a control (Figure 2).

Postoperatively, topical tobramycin dexamethasone eye drops were instilled into the operated eyes 4 times a day during the initial postoperative period (2 weeks); this was tapered until discontinuation (1 month post-implantation).

Slit-lamp examination was performed daily on the first 5 days and weekly thereafter, and slit-lamp photography was performed during each examination. Spectralis high-resolution Fourier-domain anterior-segment optical coherence tomography (AS-OCT, Heidelberg Engineering GmbH, Heidelberg, Germany) was used to obtain cross-sectional images of the implanted device and the donor tissue. All eyes were scanned in the horizontal and vertical meridian. ImageJ software (NIH, USA) was used to measure the Kpro-graft interface gap. The follow-up period ranged from 19 days to 24 months.

1.4. Histological examination

Rabbit 3 died in the cage 19 days after surgery. The rabbit’s operated eye was enucleated and fixed in a 10% formaldehyde solution overnight. The carrier graft was cut into 10-μm-thick sections and stained with hematoxylin–eosin (HE). Three rabbits developed an overgrowth of granulation...
membrane, which covered the optic of the Kpro; these membranes were dissected, and sections were stained with HE, alcian blue and Masson trichrome.

2. Results
The postoperative complications and follow-up for the six rabbits are summarized in Table 1. No carrier cartilage tearing occurred during the surgical process. Surgery was uneventfully completed in all rabbits. Postoperatively, none of the operated eyes showed evidence of leakage of aqueous or infection.

2.1. Rabbit 1 (PMMA backplate)
In rabbit 1, who had received the Kpro with a PMMA backplate, neovascular tissue was found over the carrier cartilage at 8 days post-implantation. The anterior plate was covered by a translucent fibrovascular membrane 30 days after implantation, and AS-OCT revealed the presence of a gap between the posterior surface of the anterior plate and the cartilage (Figure 3(a)). The thickness of the membrane had increased and more vascular tissue was observed in the membrane at 4 months post-implantation. The membrane became translucent and the tissue was vascularized by 8 months post-implantation (Figure 3(b)). The membrane was dissected 22 months after implantation. Slit-lamp photography showed that no RPM had formed and AS-OCT demonstrated that the gap had been filled with regenerative tissue (Figure 3(c,d)). The thickness of the dissected membrane reached a maximum of 0.8 mm.

The dissected membrane was divided into three layers for histological examination. The anterior layer of the membrane showed fibrovascular tissue covered with stratified squamous epithelium, and eosinophils scattered throughout the fibrovascular tissue. The middle layer comprised a homogeneous interstitial matrix. The inner layer, adjacent to the anterior plate, showed the presence of lacunae (Figure 4).

2.2. Rabbit 2
In Rabbit 2, 3 days post-implantation, slit-lamp photography demonstrated the remains of a residual lens cortex in the anterior chamber. Neovascular tissue reached the optic stem by 27 days post-implantation, and gel-like tissue was observed over the anterior plate at 38 days post-implantation. AS-OCT showed that there was no gap between the flange and cartilage. The tissue over the anterior plate became opaque and vascularized by 4 months post-implantation. Twenty months after implantation, the membrane over the anterior plate was dissected; slit lamp photography demonstrated the presence of a vascularized RPM. The histology of the dissected membrane revealed loose attachment of the squamous epithelium to the fibrous matrix. The interstitial matrix was homogenous in structure, with lacunae scattered beneath the epithelium and adjacent to the anterior plate (Figure 5).

| Rabbit No. | Type of backplate | Carrier | Follow-up (months) | Complication |
|------------|-------------------|---------|--------------------|--------------|
| 1          | PMMA              | Cartilage | 24                | OGT,G        |
| 2          | Titanium           | Cartilage | 24                | OGT,RPM,G    |
| 3          | Titanium           | Cartilage | 19 days           |              |
| 4          | Titanium           | Cartilage | 18                | OGT          |
| 5          | Titanium           | Cartilage | 12                | G            |
| 6          | Titanium           | Cornea   | 12                | Corneal thinning |

PMMA, polymethylmethacrylate; RPM, retroprosthetic membrane; OGT, overgrowth granular tissue, G; glaucoma
2.3. Rabbit 3

Fifteen days after implantation, the peripheral surface of the cartilage in Rabbit 3 demonstrated vascularization. AS-OCT revealed a gap between the flange and cartilage. Rabbit 3 was found dead in its cage 19 days after implantation. The operated eye was enucleated within 1 day postmortem; the cartilage specimen showed fibrotic change, and up to 3 layers...
of epithelium were found above the cartilage. Islands of chondrocytes were seen in the deep layer of the donor cartilage. Chondrocytes were seen to be undergoing cell division within their individual lacuna; this type of cartilaginous growth process is called internal growth (Figure 6).

Figure 5. Light micrograph of the membrane over the anterior plate. Squamous epithelia adhere loosely to the fibrovascular tissue. Lacunae are demonstrated adjacent to the epithelial layer and over the optic (arrow, HE).

Figure 6. Internal growth of chondrocytes. The chondrocytes appear in groups and undergo cell division within their individual lacuna (arrow, HE).

Figure 7. Implanted chondro-Kpro in rabbit 4. A. Light micrograph of the membrane over the anterior plate, eosinophils were demonstrated diffusely in the tissue (HE); B. Light micrograph of the membrane over the anterior plate, both collagen and keratin were demonstrated (Masson's trichrome stain).
2.4. Rabbit 4
In Rabbit 4, the anterior plate was covered by a translucent, vascularized membrane at 2 months after implantation. After dissection of the membrane over the anterior plate at 11 months post-implantation, no obvious RPM was observed. Histological examination of the membrane revealed lymphocytes and multiple eosinophils disseminated in the extracellular matrix. Masson’s trichrome staining showed that both collagen and keratin were present in the membrane (Figure 7).

2.5. Rabbit 5
Three days after Kpro implantation in Rabbit 5, vascularization was noted in the peripheral cornea. There were air bubbles underneath the flange of the anterior plate (Figure 8(a)). Fibrovascular tissue overgrew the cartilage by 24 days postoperatively, but a small gap remained visible on slit-lamp photography (Figure 8(b)). The gap beneath the flange was filled with fibrovascular tissue by 3 months after Kpro implantation (Figure 8(c)). Eight months after implantation, part of the donor cartilage became translucent and the holes of the backplate were visible. Three-quarters of the peripheral anterior plate was covered by a whitish membrane (Figure 8(d)). AS-OCT showed a gap between the cartilage and posterior surface of the anterior plate of Kpro at 1 month postoperatively (Figure 8(e)). In AS-OCT scans of the junction between Kpro and the cartilage at 8 months postoperatively, epithelial tissue was observed to extend onto the front plate in 3 quadrants, corresponding to the findings of slit-lamp examination (Figure 8(f)).

2.6. Rabbit 6
In Rabbit 6, which had received the Kpro with a corneal carrier, the central thickness of the cornea as measured by AS-OCT preoperatively was 420 μm. One month post-Kpro implantation, slit-lamp photography revealed neovascularization from 2 o’clock to 3 o’clock in the corneal carrier, and debris beneath the flange of the anterior plate (Figure 9(a)). Two months after implantation, more blood vessels were visible in the corneal carrier. There were multiple air bubbles and debris under the flange (Figure 9(b)). Three months after surgery, slit-lamp photography showed fibrovascular tissue regeneration beneath the flap and the disappearance of the previous air bubbles beneath the flap (Figure 9(c)). Eight months after implantation, air bubbles and debris reappeared underneath the flap (Figure 9(d)). AS-OCT revealed the presence of a thin cleft between the flap and corneal carrier at 1 month after implantation (Figure 9(e)); this may be because the
rabbit cornea is thinner than that of humans. The first segment of the stem of the Kpro, which accommodated the human corneal graft, maybe too wide for the rabbit corneal carrier. Three months after surgery, AS-OCT demonstrated the regeneration of opaque fibrovascular tissue filling the gap in the vertical orientation (Figure 9(f)). Eight months after surgery, AS-OCT in the horizontal orientation showed corneal melt, with thinning of the tissue surrounding the stem. In the vertical orientation, corneal melt with tissue retraction, away from the device stem, was seen in the 12 o’clock position (Figure 9(g)). The mean height of the Kpro-graft gap in four meridians of Rabbit 6 was 342.5 ± 79.8 μm (range: 254–446 μm; median, 335 μm) 12 months postoperatively.

3. Discussion

Corneal transplants are now commonly performed in Guangdong province, China, given the increase in donor corneas provided by the local eye bank. However, corneal transplantation is not always appropriate for patients in whom other surface reconstruction efforts for visual rehabilitation have failed, or in whom standard corneal grafting is not possible. Although the Boston Kpro has been the device most widely used in such cases, tissue melt around the Kpro stem, due to the action of collagenases, remains an important complication, which may lead to leakage, hypotony, and retinal detachment. Previous studies have suggested that corneal melt could be reduced by using collagen cross-linked cornea as the carrier (Arafat et al., 2014) or by using TNF-α inhibitors. (Zhou et al., 2017). The costs of these therapies are currently too expensive for the Chinese population, which, despite rapid advances, still has a wide economic gap.

The rabbit was chosen as the experimental model for this study for several reasons. Primates might have been a better choice in terms of corneal similarity, but primate models are costly to
maintain. The rabbit eye is generally more sensitive than the human eye and readily extrudes foreign material. The central thickness of the rabbit cornea is 407 ± 20 μm (Chan, Payor, & Holden, 1983) which is slightly thinner than that of the human cornea. The preoperative thickness of the carrier cornea in this study evaluated by AS-OCT was 420 μm. The rabbit cornea is also easily hurt, due to the slow blink of the eyelid and lagophthalmos. Therefore, we used this animal model to perform our Kpro carrier melt evaluation. Additionally, postoperative topical drugs were maintained only for 1 month to observe whether infection occurred.

In our rabbits, postoperative complications included RPM, glaucoma, and granulation tissue overgrowth. RPMs are the most common complication after Kpro surgery in humans (Rudnisky et al., 2012). RPMs are thought to originate from host stromal cornea cells that migrate through gaps in the posterior graft–host junction (Stacy, Jakobiec, Michaud, Dohlman, & Colby, 2011). Histological examination reveals that the RPM is composed of 3 layers: a fibrovascular layer, a stromal iris layer, and a metaplastic layer of lens epithelium. Interestingly, only 1 rabbit in this study developed severe RPM. Residual lens cortex was observed in the anterior chamber of this rabbit, and the RPM developed rapidly. We considered that the development of RPM may be related to the inflammation invoked by the residual lens cortex in the anterior chamber. This emphasizes the need for comprehensive removal of the entire lens cortex during the surgical procedure. It has been suggested that RPM is related to the melting of the corneal carrier and extrusion of the Kpro, and that the thicker the RPM, the more likely is carrier corneal melt. (Sivaraman et al., 2013) This may be because the presence of an RPM impedes nutrient diffusion into the carrier cornea, by occluding backholes (Bourges, Trong, Ellies, Briat, & Renard, 2003). In the present study, Rabbit 2 retained the Kpro for more than 2 years, despite the development of a thick RPM. We speculate that the autologous cartilage may have obtained sufficient nutrients from the implant bed and may have provided sufficient mechanical fixation of the Kpro. Moreover, the overgrowth of granular tissue covering the anterior plate also provided a protective layer against device extrusion.

AS-OCT is useful to evaluate the implanted Kpro and its relationship to the eye. Although the spectral-domain OCT in this study could not provide information about the RPM, due to a shallow scan-depth, it could give structural details of the Kpro–donor interface. Because the thickness of the autologous cartilage is thinner than the width of the first segment of the stem, it leaves a gap between the posterior surface of the anterior plate and donor graft after implantation, which could be observed by AS-OCT. After implantation, neovascular granular tissues were observed over the cartilage and the gap became filled with granular tissue, as corroborated by AS-OCT. The ability to seal this gap is important because it may prevent microorganisms from accessing the anterior chamber as well as extrusion of the device. However, the regenerative ability of the donor cartilage may be excessive. Three rabbits developed granular tissue over the optic surface. The mechanism may involve an overzealous foreign-body reaction because two tissue specimens revealed the presence of eosinophils.

The regenerative ability of the perichondrium may also play an important role. Two specimens of granular tissue revealed the presence of lacunae. It has been reported by Ohlsén that free perichondrium transplanted to subcutaneous tissues, the muscles, and areolar tissue of rabbits could produce new cartilage (Ohlsén, 1976). As reported by Connon and Meek (Connon & Meek, 2003) the rabbit corneal stroma also manifests regenerative properties during corneal wound healing. However, in this study, with longer follow-up, the width of the gap between the flanges and carrier cornea enlarged. The gap was also connected to the ocular surface by 8 months post-implantation, as seen by AS-OCT scan. Given the absence of obvious inflammation in the operated eye, we speculate that the large lid fissure and lagophthalmos of the rabbit caused more evaporative damage to the carrier corneal tissue than could be compensated for by the regenerative properties of the corneal stroma of the rabbit. A device-graft gap not only leads to instability of the Kpro due to collision with the eyelid during blinking but may also allow access to pathogens and collagenases in the tear film.
Our results must be interpreted cautiously due to their preliminary nature. The limitations in our study included the following: Rabbits are poor models since their clinical results have poor correlations with human clinical outcomes. Implantation of Kpro was performed in healthy eyes of rabbits. Because inflammation in severe ocular surface disease also plays an important role in corneal thinning, our results might not be entirely comparable with Kpro implanted in chemically-burned rabbit eyes, a more realistic condition. The rigidity and shape of auricular cartilage do not conform perfectly to the same shape as the corneal tissue, which may transmit an uneven pressure to the surrounding corneal tissue and encroach upon the anterior chamber angle.

4. Conclusion

Our pilot study showed that autologous auricular cartilage, including perichondrium, may encourage Kpro-graft adhesion in a rabbit model. The proliferative potential of autologous auricular cartilage may help to reduce the occurrence of carrier melt or Kpro extrusion in cases where bandage contact lenses cannot be used. Further studies should focus on the prevention and management of post-operative complications, such as tissue overgrowth over the optic and glaucoma, and studies with a large sample are required to evaluate the retention rate of such chondro-Kpro implants.

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