RANDOMIZED CLINICAL TRIAL OF OCT-GUIDED LASER-ASSISTED LAMELLAR ANTERIOR KERATOPLASTY IN ADULTS FOR KERATOCONUS

1. INTRODUCTION

The purpose of this protocol is to compare and develop new surgical technique of partial-thickness corneal transplantation for treating keratoconus. The new technique, called LALAK, will be tested and compared with standard full-thickness corneal transplantation. The new technique replace only the anterior portion of the cornea and does not have the risks associated with conventional full-thickness corneal transplant methods. Additionally, optical coherence tomography (OCT) will be used to guide the depth of the graft and donor dissections.

This protocol seeks to answer the following question:

> *Can the OCT-guided partial thickness corneal transplant techniques result in equivalent surgical outcome as the conventional full-thickness corneal transplant for keratoconus?*

This study is part of the NIH/NEI funded grant R01EY018184 entitled “Guiding the treatment of anterior eye disease with optical coherence tomography in which” one section of this grant is aimed at developing OCT-guided laser-assisted lamellar anterior keratoplasty (LALAK).

2. BACKGROUND

Corneal transplantation (keratoplasty) is the most common organ transplant, with 42,606 procedures in the U.S. in 2009. Many surgeons are moving away from full thickness corneal transplantation, also called penetrating keratoplasty (PK), because of risks involving rejection, irregular astigmatism and wound dehiscence. They are moving towards partial thickness (lamellar) transplantations of either the anterior or posterior (endothelial) layers, which can reduce these risks.

The femtosecond laser has been used to create excellent tongue-in-groove junctions between the graft and host in full thickness PK.[1] This technique, called IEK (Intralase-enabled keratoplasty), has now become a standard surgical procedure. The tongue-in-groove junction achieved at the circumferential edge of the graft and host leads to a continuous smooth anterior surface and strong wound healing.

The new technique is called LALAK. In this technique, the anterior lamellar graft is prepared by one of the following two approaches: 1). the femtosecond laser is used to create an anterior lamellar graft with dove tailed side cuts, The cut depth will be proportional to the central stromal thickness of the donor cornea. 2). microkeratome is used to create an anterior lamellar graft of about 300 microns The femtosecond laser is also used to create a shallow anterior lamellar dissection and beveled side cuts on the recipient cornea to match the graft. The excimer laser is then used to create a smooth lamellar bed.

In the new technique, the depth of the graft and donor dissections will be guided by OCT measurements. The proposed trial will test if the new technique can reproducibly achieve good visual outcomes without the risk of rejection. The outcome of the LALAK procedure will be compared to that of IEK.

3. INCLUSION CRITERIA

Eyes with keratoconus that cannot be adequately or safely corrected with spectacles, contact lens or excimer laser surface ablation. The cornea must have healthy endothelium (endothelial cell density > 1,500/mm^2).

4. EXCLUSION CRITERIA

1. Preoperative corneal thickness less than 300 microns.
2. Corneal edema
3. Central guttata
4. Inability to give informed consent.
5. Inability to maintain stable fixation for OCT imaging.
6. Inability to commit to required visits to complete the study.
7. Eyes with concurrent cataract, retinal diseases, glaucoma, or other eye conditions that may limit the visual outcome after surgery.
8. Patients with severe collagen vascular diseases or ocular surface disorders

5. SUBJECT CHARACTERISTICS

The study will include adults 18 years of age or older.

6. STUDY DESIGN

A prospective, randomized interventional trial will be conducted in 64 adult subjects with keratoconus. The study subjects will be selected from the study subjects enrolled in the observational study of keratoconus, corneal opacity and post-keratoplasty eyes in adults (IRB 6612). One eye of each subject will receive a LALAK procedure or IEK. The procedure will be randomly assigned:

- 1/2 of the subjects will receive LALAK
- 11/2 of the subjects will receive IEK

If both eyes are eligible, the eye to be treated will be randomized in addition to the treatment randomization. The eye that is not randomly chosen for treatment will not be included in the study and handled independently of the study eye and as determined by the attending physician.

The OCT systems to be used in this study will be the RTVue-XR (Optovue, Inc., Fremont, CA) or the Visante (Carl Zeiss Meditec, Inc., Dublin, CA). Both are FDA-approved for the mapping of corneal thickness.

The femtosecond laser system to be used in this study for host cornea preparation will be the Intralase FS system (iFS, AMO, Inc., Santa Ana, CA). The iFS is FDA-approved for corneal surgery including full thickness and lamellar keratoplasty. Eye banks use earlier versions of the Intralase system which are also FDA approved for this indication. The iFS has been used by several investigators to successfully perform PK using zigzag,[2] mushroom,[3] and tophat [4, 5] configurations. It has also been used to facilitate big-bubble DALK using the zigzag configuration.[6-8]

The LALAK for keratoconus:

a. Both fresh corneal tissue and VisionGraft sterile cornea allograft will be considered for use as the graft tissue. VisionGraft is currently approved for use in lamellar keratoplasty. One of the two methods will be use to prepare the graft tissue: 1). a “dovetail” shaped cut will be made on the graft using a femtosecond laser at the eye bank. The cut depth will be proportional to the central stromal thickness of the graft. 2). microkeratome is used to create an anterior lamellar graft of about 300 microns at the eye bank. This graft will be separated from stromal bed by eye bank personnel for examination of the cut surface. High-quality graft will be replaced in preservation medium and shipped to the surgeon prior to surgery.
b. The host cornea will receive femtosecond laser cut consisting of a shallow lamellar cut with angled side cut to match the graft in a tongue-in-groove fashion. The central cornea will then be ablated with the excimer laser to the desired depth using predetermined settings. Both laser treatments will be performed under topical anesthesia. The femtosecond laser is an FDA-approved device for use in this indication (corneal transplantation including lamellar keratoplasty). The excimer laser is FDA-approved for refractive surgery but will be used off-label for the preparation of the host stromal bed. [10, 11] The excimer laser ablations will consist of a combination of hyperopic astigmatism and myopic ablations as is commonly used in phototherapeutic keratectomy off-label treatments. A protective eye shield is placed over the eye.
c. The patient is transported to an operating room in the Casey Eye Institute Outpatient Surgery Center. Retrobulbar block or general anesthesia is given as is customary for corneal transplantation surgery.
d. The graft will be sutured into the host bed.

The IEK technique:

a. A full thickness graft will be prepared at the eye bank with zigzag side cuts prepared with a femtosecond laser. The graft is separated from the rim, replaced in the preservation medium, and shipped to the surgeon prior to the surgery.
b. In the laser suite, the host cornea will be cut with the femtosecond laser with zigzag side cuts leaving a 70-100 micron bridge. A protective eye shield is placed over the eye.
c. The patient is transported to an operating room in the Casey Eye Institute Outpatient Surgery Center. Retrobulbar block or general anesthesia is given as is customary for corneal transplantation surgery.
d. The graft will be sutured into the host bed.

Postoperative medications in the operative eye will include a 4th generation flouroquinolone eye drop to prevent infection (such as gatifloxacin 0.3%) 4 times daily for 1 week or longer, until the surface is re-epithelialized. Prednisolone acetate 1% eye drops will be used 4 times daily for 1 week, 3 times daily for 3 weeks, twice daily for 1 month, and once daily for 1 month to prevent inflammation This drop regimen is standard post-operative treatment for patients receiving PK via the physicians in the Cornea department at Casey Eye Institute.

Clinic staff will confirm with subjects’ insurance companies prior to surgery that the cost of surgery will be covered. The OCT will be charged to the study as well as the use of the femtosecond laser. The surgeons will waive their fee for the laser treatment in order to reduce the amount charged to the study.

7. DATA COLLECTION, MANAGEMENT AND ANALYSIS

a. Informed Consent:

Patients attending Casey Eye Institute clinics will be invited to participate in the study. Informed consent for participation in the study will be discussed and obtained by the time of their initial visit.

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b. Assignment of Study Identification Number

All patients that sign a consent form will be assigned a study identification number (Study ID). This number will be assigned by the study coordinator in chronological order, using the next available number on the AED OCT Coordinating Center subject tracker spreadsheet.

c. Subject Data Collection

OCT and ancillary testing will be performed by trained ophthalmic technicians and photographers. Clinical history will be obtained by the clinical investigators and ophthalmic technicians. Eye examinations will be performed by clinical investigators who are board-certified ophthalmologists. Surgeries will be performed by clinical investigators who are board-certified ophthalmologists and fellowship-trained specialists in corneal and refractive surgery. OCT will be performed specifically for the study.

The following information will be collected:

1. OCT images and derived measurements
2. Corneal topography.
3. Clinical history
4. Record of eye examination
5. Demographic information
6. Results of ancillary testing
7. Details of surgical procedures performed, postoperative management, clinical and visual outcomes.

d. Clinical Procedures

Patients will be examined 1 day, 1 week, 1 month, 3-5, 6-8, 12-14 and 22-24 months.

Slit-lamp photography, OCT scans, confocal microscopy, topography, refraction, and visual acuity will be acquired preoperatively and 3-5, 6-8, 12-14 and 22-24 months after the surgery. The primary outcome measures will be best spectacle-corrected visual acuity (BSCVA) using the Snellen chart and intraoperative perforation rate. Secondary outcome measures will be postoperative refractive error, topographic astigmatism, interface clarity (masked OCT and confocal microscopy grading), endothelial cell count (specular microscopy), and complications (rejection, interface opacification, others).

Table 1 Visit Schedule

	Initial Visit	Visit 1 1 D (± 1d)	Visit 2 1 Wk (± 1d)	Visit 3 1 Mo (±1wk)	Visit 4 4 mo (±1mo)	Visit 5 7 mo (±1mo)	Visit 6 13 mo (±1mo)	Visit 7 23 mo (±1mo)
Informed consent	X							
Initial history	X							
Interval history		X	X	X	X	X	X	X
Slit Lamp Photography	X				X	X	X	X

Specular Microscopy	X					X		X
Topography	X				X	X	X	X
Refraction	X				X	X	X	X
BSCVA	X				X	X	X	X
OCT	X				X	X	X	X
Surgery		X						

e.

e. Data Analysis and Outcomes–

Postoperative refractive error, topographic astigmatism, interface clarity (masked OCT and confocal microscopy grading), endothelial cell count, and complications.

f. Data and Safety Monitoring Plan

A Data and Safety Monitoring Plan (DSMP) has been developed in order to oversee the safety activities of this protocol. This DSMP is included as part of the NIH/NEI grant application 2R01EY018184 which is included with this IRB application.

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