Visual Acuity Continues to Improve After DSEK for Fuchs’ Endothelial Corneal Dystrophy

In a prospective cohort study conducted at Mayo Clinic’s campus in Rochester, Minnesota, researchers found that patients’ visual acuity continued to improve through five years after Descemet stripping endothelial keratoplasty (DSEK) for Fuchs’ endothelial corneal dystrophy (FECD) and was associated with evidence of optical and anatomic repair.

“Prior studies have been retrospective. This study, however, assessed standardized visual function, optical quality and anatomic properties of eyes with FECD through five years after primary DSEK,” says Sanjay V. Patel, M.D., Ophthalmology chair at Mayo Clinic in Rochester, Minnesota.

Study outcomes were published by Katrin Wacker, M.D., and others in *Ophthalmology* in 2016.

In DSEK, abnormal host Descemet membrane and endothelium are removed and replaced by donor Descemet membrane and endothelium with a variable thickness of donor corneal stroma. Because DSEK does not disrupt the anterior corneal surface, visual function and quality of life improve quickly for patients after DSEK.

Many patients also experience better uncorrected distance visual acuity and less astigmatism after the treatment, compared with penetrating keratoplasty. Five-year graft survival also is comparable. As a result, vision (as well as graft survival) is now a primary outcome measure of corneal transplantation.

**Structural change assessment**

The impact and reversibility of structural changes in the host cornea on optical long-term outcomes after endothelial keratoplasty are unknown. Changes may include residual anterior corneal haze, increased anterior surface high order aberrations and subepithelial fibrosis, which begin in the early stages of FECD.

To assess those structural changes, researchers determined associations between visual function (acuity and disability glare) and anatomic changes (corneal and graft thickness, and corneal haze). They hypothesized that the remodeling of anatomic structures was associated with visual rehabilitation. They also evaluated graft survival and endothelial cell loss through five years.

The study included 52 eyes of 45 patients with FECD undergoing primary DSEK between October 2006 and March 2010. Participants were examined before surgery and at fixed intervals through 60 months. At each visit:

- Graft survival was determined by slit-lamp examination.
- Best spectacle-corrected visual acuity was measured using the electronic Early Treatment Diabetic Retinopathy Study protocol.
- Total anterior corneal high order aberrations were derived from corneal topography.
- Corneal backscatter, corneal thickness and endothelial cell density were measured from confocal microscopy images. Corneal thickness was also measured by ultrasonic pachymetry.

“Best spectacle-corrected visual acuity continued to improve between one and five years after DSEK to a mean of 20/25,” says Dr. Patel. “This change was accompanied by improvements in corneal backscatter and optical aberrations, suggesting gradual repair.
K<sub>ATP</sub> Channel Opener Cromakalim Lowers IOP in Human and Mouse Models

Elevated intraocular pressure (IOP) is the most prevalent and the only treatable risk factor for glaucoma. Unfortunately, current therapeutics used to treat elevated IOP have significant and sometimes irreversible side effects.

Michael P. Fautsch, Ph.D., Ophthalmology, and a team at Mayo Clinic’s campus in Rochester, Minnesota, work to develop novel compounds for the treatment of glaucoma. In a study published in *PLOS One* in 2015, the team evaluated the IOP lowering ability of ATP-sensitive potassium (K<sub>ATP</sub>) channel opener cromakalim in human and murine models. Results indicate that cromakalim can significantly lower IOP in human and animal model systems without observable toxic side effects. Combination treatment with latanoprost free acid, a commonly used ocular hypotensive drug, produced a significantly greater reduction in IOP compared with treatment with either drug alone in mice.

“Compatibility with existing glaucoma drugs also is important,” says Dr. Fautsch. “The use of multiple agents working through different pathways to lower IOP will provide better opportunities for IOP reduction in patients with glaucoma to slow disease progression.”

**K<sub>ATP</sub> and IOP**

K<sub>ATP</sub> channels are hetero-octameric proteins that are affected by changes in micromolar concentrations of intracellular ATP. These channels connect the metabolic and energetic state of cells and are involved in the regulation of several vital cellular functions. Previous studies from Dr. Fautsch’s laboratory identified K<sub>ATP</sub> channel openers diazoxide and nicorandil as IOP reducing agents. In contrast, cromakalim, another K<sub>ATP</sub> channel opener, had been reported to increase IOP modestly in rabbits. “Because this was the opposite result the team had found with K<sub>ATP</sub> channel openers diazoxide and nicorandil, we evaluated the effect of cromakalim on IOP in human anterior segment organ cultures and murine experimental model systems,” says Dr. Fautsch.

**Model systems**

In the human anterior segment model, 17 donor eyes — from 12 males and 5 females, ages 40–93 — were bisected at the equator and the front of the eyes were clamped in modified petri dishes and perfused with Dulbecco’s modified Eagle’s
media containing 1 percent antibiotic-antimycotic solution at the normal human aqueous humor flow rate (2.5 µl/min). Pressure inside the anterior chamber was monitored in real time through a secondary access cannula built into the modified petri dishes. Following attainment of stable baseline pressure, different concentrations of cromakalim were added to one eye while the contralateral eye received the vehicle in the same proportion.

Cultured human anterior segments, when treated with 2 µM cromakalim, showed a decrease in pressure (19.3 ± 2.8 mm Hg at 0 hours to 13.2 ± 2.6 mm Hg at 24 hours; P < 0.001) when compared with vehicle-treated controls (15.9 ± 5.3 mm Hg at 0 hours to 15.6 ± 4.9 mm Hg at 24 hours; P = 0.9).

In the murine model, IOP was measured in live, conscious wild-type C57BL/6 and K_r6.2(-/-) mice using a hand-held rebound tonometer. IOP was measured daily for three days before treatment to obtain baseline IOP. For treatment, a 5µl drop of cromakalim (5-mM concentration) was added to one eye while the contralateral eye received a vehicle (DMSO and Cremophor EL) in equivalent proportions to the treated eye. Once-daily treatment continued for five consecutive days with IOP measured at one, four and 23 hours after each treatment. Post-treatment IOP was recorded for three consecutive days at similar time points.

In wild-type C57BL/6 mice, cromakalim reduced IOP by 18.8 ± 2.2 percent compared with vehicle-treated contralateral eyes (17.0 ± 0.3 mm Hg at 0 hours to 13.8 ± 0.4 mm Hg at 24 hours; n = 10, P = 0.002). Cessation of treatment resulted in IOP returning to baseline levels within 48 hours.

To examine K_ATP channel subunit specificity, mice lacking one of the functional K_ATP channel subunits (K_r6.2) were treated with cromakalim. In contrast to wild-type mice, no change in IOP was noted.

In the last set of experiments, cromakalim was added separately and in combination with latanoprost to K_r6.2(-/-) mice. Results showed that the combination of cromakalim and latanoprost lowered IOP greater than either drug alone, indicating the drugs have an additive effect on IOP reduction.

“Treatments targeting the underlying physiology of the outflow pathways are beneficial in slowing disease progression in patients with glaucoma and advancing our knowledge and understanding of glaucoma," says Dr. Fautsch. “This study suggests that cromakalim is an excellent candidate for therapeutic development.”

Results confirm:
• Cromakalim is a potent ocular hypotensive agent that lowers IOP via activation of K_r6.2 containing K_ATP channels
• Its effect is additive when used in combination with the commonly used glaucoma drug latanoprost

For more information

Research Identifies Characteristics of Convergence Insufficiency in Adults

Convergence insufficiency (CI) is a common disorder of ocular alignment among both children and adults. It is characterized by an exophoria at near fixation and reports of horizontal diplopia and eye strain with prolonged reading. CI is diagnosed on the findings of a remote near point of convergence and decreased fusional convergence at near fixation.

“There is considerable variability in the reported prevalence of CI, with most estimates ranging from 2.25 to 8.3 percent among pediatric and young adult populations,” says Brian G. Mohney, M.D., Ophthalmology, at Mayo Clinic’s campus in Rochester, Minnesota. “The purpose of this study was to describe the clinical characteristics of CI in a population-based cohort of adults 19 years of age and older, diagnosed over a 20-year period, using a medical record retrieval system.”

Dr. Mohney and a team of researchers studied the onset of CI in patients 19 years and older at the time of diagnosis drawn from a 20-year period in the Rochester Epidemiology Project (Sidebar, page 4). Results of the study were published by Rafif Ghadban, M.D., and others, in Ophthalmology in 2015.

Diagnosis of CI was based on either of the following criteria:
• Symptoms of double vision while reading with an exophoria or exotropia at near fixation test and an absence of double vision at distance
• An exophoria or exotropia of 10 prism diopters or more at near on prism alternate cover test with orthophoria or small (less than 10 prism
diopters) phoria at distance. Each patient’s entire medical record was reviewed for other ocular or medical conditions. Of 118 patients, 32 percent had hyperopia and 38 percent had myopia. Other ocular disorders included age-related macular degeneration in 17 percent and glaucoma in 8 percent of patients. The most prevalent associated systemic conditions included hypertension in 23 percent and coronary artery disease, hyperlipidemia and cancer in approximately 10 percent each. Four patients (3.4 percent) were diagnosed with Parkinson’s disease.

A total of 118 adults (age- and gender-adjusted annual incidence, 8.44 per 100,000 patients) were diagnosed with CI between Jan. 1, 1985, and Dec. 31, 2004, constituting 15.7 percent of all forms of adult-onset strabismus observed in this population. The median age at diagnosis was 68.5 years, and 68 (57.6 percent) patients were female. Women in their 60s were the most prevalent.

The mean initial exodeviation at near was 14.1 prism diopters and 1.7 prism diopters at distance. The Kaplan-Meier survival curve rate of exotropia increasing over time by 7 prism diopters or more at near was 4.2 percent at five years, 13.5 percent at 10 years and 24.4 percent at 20 years.

Conservative management
Patients were followed up for a mean of 9.3 years. Although there was a significant increase in incidence with increasing age and nearly 25 percent of patients had an increase of their near exodeviation of at least 7 prism diopters by 20 years after diagnosis, most patients were managed conservatively:
• 13 (11 percent) of 118 patients’ records did not supply management data
• 92 (88 percent) of the 105 patients were treated with prism spectacles
• 9 (9 percent) were treated with convergence exercises
• 4 (4 percent) underwent eye muscle surgery
• 3 (3 percent) elected to occlude one eye

“Convergence insufficiency is one of few forms of ocular misalignment that is relatively common in both children and adults. However, progression and surgical intervention is more likely in adults compared with children,” says Dr. Mohney. “The results of multiple studies provide conflicting recommendations for managing CI in adults. Although home-based convergence exercises are the most commonly prescribed treatment, three of four patients in this study were managed with prism correction and only 9 percent with convergence exercises. This low rate of exercises in part may be the result of the difficulties elderly adults encountered with exercises and personal preference of treatment by the ophthalmologists.”

For more information