Surgery May Reverse Glaucoma Damage

Conventional wisdom holds that glaucoma treatment may preserve vision but cannot reverse damage. Now, researchers at the UCLA Stein Eye Institute report that damage may be reversible, at least for some patients, following trabeculectomy.\(^1\) Stein Eye researchers found that filtering surgery not only slowed the rate of perimetric decay from glaucoma but also provided evidence of sustained, long-term improvement of visual function.

The implications for clinical treatment are profound. Rather than simply treating glaucoma patients to maintain stability, doctors should understand that long-term improvement of visual function is possible, says Joseph Caprioli, MD, David May II Chair in Ophthalmology and chief of the Stein Eye Institute’s Glaucoma Division. “Clinicians should begin to evaluate visual fields in a different way, and not always dismiss apparent improvement as an artifact.”

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for good manufacturing practices, so that we can move forward with a Phase I clinical trial for a treatment that could fulfill an unmet medical need in the United States.”

Corneal disease is the fourth-leading cause of blindness globally, according to the World Health Organization, with an estimated 3.2 million people blinded in both eyes from corneal opacity. LSCD is associated with ocular disorders resulting from chemical injuries, genetic conditions, multiple eye surgeries, contact lens wear, and chronic severe conjunctivitis.

LSCs maintain the normal homeostasis of the transparent corneal epithelium. “When these stem cells become deficient or non-functional, the corneal epithelium does not heal,” Dr. Deng explains. “At that point, the adjacent conjunctival epithelial cells migrate over to assist with the wound-healing process. Eventually, the entire cornea surface is covered with these conjunctival epithelial cells, which do not belong in the cornea. This leads to recurrent erosion of the corneal epithelium, and eventually the cornea becomes scarred, opaque, and patients lose functional vision.”

Dr. Deng notes that corneal transplantation is ineffective for patients with LSCD. “The corneal transplant does not treat LSCD,” she says. “To restore the clarity of the optical path of the cornea, the stem cell population needs to be restored so that there is a normal, intact epithelium. Once that occurs, a subsequent corneal transplantation can be performed to treat any residual stromal scar to improve vision.”

The current approach to LSCD treatment in the United States is to replenish the LSC population to a sufficient level by transplanting functional LSCs, either through allogeneic or autologous keratolimbal transplantation, or through an artificial cornea. The long-term success rate for allogeneic keratolimbal transplantation is 27 to 50 percent, even with systemic immunosuppression. Keratolimbal autografts have a higher success rate—ranging from 82 to 100 percent—but they require between one-third and half of the limbus from a donor eye; this puts donor patients at such high risk for iatrogenic LSCD that it is rarely performed.

A new procedure, simple limbal epithelial transplantation (in which only a small limbal biopsy is directly transplanted), has been shown to achieve a higher success rate. Although artificial corneas, Boston type I keratoprosthesis, achieves excellent initial visual recovery, it is also associated with blinding complications, such as endophthalmitis, glaucoma, and retinal detachment. “The best and safest approach for treating someone with LSCD is the one that’s intuitive—replenishing the patient’s own stem cells.” Dr. Deng says. “One major challenge in assessing the true clinical success of all limbal stem cell therapies and comparing the efficacy of each therapy, however, is the lack of a standardized way to diagnose.”

Transplantation of functional autologous LSCs involves taking a small (2x2 mm) limbal biopsy from the healthy eye and expanding the LSC in culture, requiring only a small amount of donor tissue for the LSC expansion. The cultured LSCs are then transplanted to LSCD-affected eyes in order to restore a healthy corneal epithelium. This therapy has been the standard of care in Europe for more than a decade. But, while transplantation of cultivated LSCs has achieved the most successful long-term outcomes among LSCD treatments, it has limitations. For one, the culture system employs mouse 3T3 feeder cells and bovine serum, which has raised concerns about cross-contamination; these safety concerns are among the reasons the treatment remains unavailable in the United States, Dr. Deng notes.

In addition, the reported success rate of 50 to 76 percent over the last decade in Europe remains lower than that of other solid organ transplantations, and because cultivation and transplantation protocols vary widely across studies of the treatment, it is impossible to compare the quality of different cultivation methods and the clinical outcomes of different clinical protocols.

Dr. Deng and her Stein Eye colleagues are addressing these issues with a multi-pronged effort. Beyond the 95 percent success rate of their culture method for manufacturing LSCs, their method is free of any animal product, eliminating the potential risk of cross-contamination. More importantly, Dr. Deng’s group has identified several quantifiable in vitro biomarkers that can be used to characterize the stem cell population and composition of the cultivated LSCs. “A better characterization of the LSC graft enables us to correlate it with the biological function after transplantation, and it can be potentially used as a predictor of clinical outcome,” Dr. Deng says.

The research team has also developed a live imaging technique using in vivo laser scanning confocal microscopy (IVCM) that can be used to quantify LSC function through an evaluation of the corneal epithelial surface before and after LSC transplantation in patients. “This could lead to the first in vivo parameters for objectively measuring clinical outcomes,” Dr. Deng says. IVCM can also be used to identify and localize residual normal limbal epithelial cells for biopsy in eyes with severe bilateral disease—potentially expanding this stem cell therapy to such patients rather than limiting it to patients with unilateral disease. The imaging approach also appears to have diagnostic value—the researchers found that when patients have only a segment of their eye affected, the areas that appear clinically normal can be found to have significant structural damage detected only through this high-resolution in vivo imaging modality.

Dr. Deng’s current study aims to develop in vitro parameters that will help to standardize the limbal stem cell manufacturing process, as well as in vivo parameters for clinical protocols.
Study design. The retrospective, comparative, longitudinal cohort study involved two groups. In the surgery ("Trab") group, 74 eyes of 64 patients underwent trabeculectomy with mitomycin-C. The comparison group included 71 eyes of 65 patients with open-angle glaucoma who did not have surgery. Baseline damage, number of visual field (VF) tests, and follow-up were similar in both groups.

Patients were followed for about five years before and five years after surgery. To mitigate “noise” effects, VF tests were acquired at multiple points before and after surgery.

Key results. “The finding that surprised me the most was that improvement was a fairly common event, if you look for it properly,” says Dr. Caprioli.

Among the findings:
- The magnitude of intraocular pressure (IOP) reduction correlated with the number of VF locations that exhibited long-term improvement postoperatively.
- 80 percent of Trab eyes improved at five or more test locations in the VF.
- More than half of the Trab eyes (57 percent) showed improvement at 10 or more VF test locations.

Possible mechanism. While medical therapy might also yield VF improvement, “a more dramatic effect can be seen with the kind of robust pressure reduction that one can achieve with trabeculectomy,” Dr. Caprioli says. (Mean IOP fell 32 percent, from an average of 15 mm Hg preoperatively.)

Clinical implications. In the meantime, Dr. Caprioli has modified his therapeutic approach. “In patients who are not too elderly, do not have too much visual damage, and who have relatively high pressures, I am becoming more aggressive about lowering eye pressure to a level at which some reversal of visual loss occurs.”

Dr. Caprioli encourages others to be mindful of the study’s findings. “I would like those physicians who care for glaucoma patients to simply have a mindset that allows them to believe that sustained improvement of visual function after treatment can occur.”

To explain their findings, the researchers theorize that retinal ganglion cells that are damaged, but not dead, contribute to decreased perimetric sensitivity. Reduction of IOP-related stress after surgery may restore function in these damaged cells. This insight could lead to an approach called neurorescue—novel treatments to revive dying nerve cells.

The researchers will follow these patients to monitor duration of effect. They are also planning studies to help predict which patients would achieve visual gains from treatment.

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