

Lenticule Reimplantation as a Method of Reversible Refractive Surgery After ReLEx

This procedure restored preoperative keratometry and refraction in experimental settings.

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Excimer-laser-based refractive surgery procedures have been performed in millions of people worldwide to improve vision and quality of life. In combination with more sensitive preoperative screening and wavefront-driven treatment profiles, the current generation of excimer laser platforms is safer, more precise, and more predictable than ever before. LASIK, the most common excimer refractive procedure, is typically performed in two stages and with two laser platforms: flap creation with a femtosecond laser followed by stromal refractive ablation with the excimer laser. Recently, Carl Zeiss Meditec has introduced a single-step, all-femtosecond alternative to the conventional LASIK paradigm.

ALL-FEMTO REFRACTIVE SURGERY

The VisuMax femtosecond laser can be used to create a flap for conventional LASIK or for a single-step, all-femtosecond procedure called refractive lenticule extraction (ReLEx). During ReLEx, the laser dissects an aspheric lenticule of predetermined power within the stroma to perform a refractive correction. The posterior face of the lenticule is created first, followed by the anterior surface, which extends beyond the limit of the posterior cut and is opened to the epithelial surface through a circumferential ring cut at its periphery (Figure 1). The resultant anterior flap is then lifted, similar to a LASIK flap, and the lenticule is removed (Figure 2). The flap is then replaced.

In a variation of this technique, ReLEx small-incision

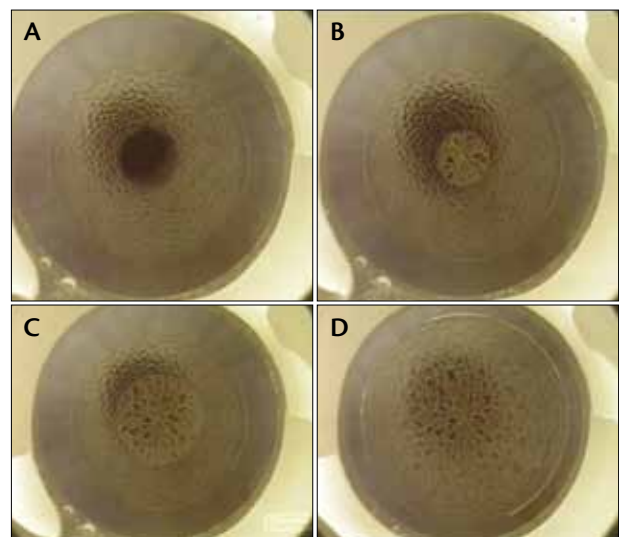


Figure 1. Sequence of ReLEx dissection by the VisuMax laser. (A) The posterior face of the lenticule is dissected centripetally. (B) The anterior face is dissected, beginning in the center and (C) extending outward centrifugally. (D) A ring sidecut with hinge (inferior in this image) completes the laser sequence.

lenticule extraction (smile), the lenticule is removed through a sub-3-mm incision without the need for flap creation or lifting. ReLEx smile has the potential advantage of minimizing damage to the subbasal epithelial nerve plexus, possibly significantly reducing postop-

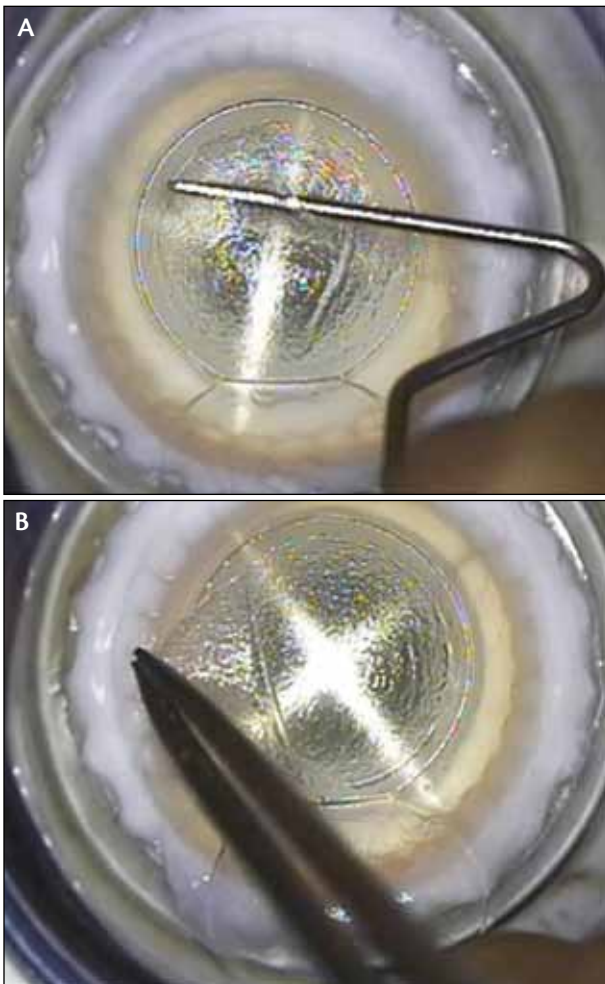


Figure 2. Lenticule dissection and removal in a human cornea. (A) The surgeon dissects below the lenticule with a Siebel spatula; the anterior flap has been reflected. (B) The lenticule is peeled away with fine forceps. At the end the ReLEx procedure, the flap is replaced.

erative dry eye and eliminating the risk of flap-related complications such as striae and early and late flap dislocation. The procedure may also result in a more biomechanically stable cornea than those that require flap creation.

ReLEx can be used to treat spherical myopic refractive errors up to -10.00 D and up to 5.00 D of astigmatism, and software for hyperopic treatments has recently been introduced.¹ In our experience and in other reported studies, ReLEx has demonstrated refractive results comparable to LASIK results.²⁻⁴ At the Singapore National Eye Centre (SNEC), we are currently conducting a randomized contralateral eye study comparing ReLEx and LASIK that will better clarify the outcomes of these two techniques.

CAN LASER REFRACTIVE SURGERY BE REVERSED?

Excimer laser refractive surgery results in a permanent, irreversible loss of stromal tissue. Enhancements and retreatments result in yet more loss of stromal volume, leading to further thinning and biomechanical weakening of the cornea and inherent risk of corneal ectasia. During our experience with ReLEx, we began to wonder whether it might be possible to store the extracted lenticule from the patient and reimplant it at a later date by lifting the flap and replacing the lenticule in an anatomically oriented position. We hypothesized that lenticule reimplantation would restore stromal volume to its original state, thereby restoring near-preoperative refraction. Restoration of stromal volume could open the possibility of further treatment in a number of clinical scenarios, including:

- Refractive surgery in patients who find themselves presbyopic and may benefit from monovision;
- Stromal restoration combined with corneal collagen crosslinking (CXL) in patients with postrefractive surgery ectasia; and
- Use of the stromal lenticule as an intrastromal corneal inlay for presbyopia treatment.

STROMAL REIMPLANTATION FOR REVERSAL OF REFRACTIVE SURGERY

We designed a series of sequential experiments to assess the feasibility and efficacy of lenticule reimplantation. First, in human cadaver eyes, we investigated the feasibility of lenticule storage and the viability of intrastromal keratocytes, leading to the development and optimization of a lenticule storage system. Second, a pilot rabbit study was conducted to assess the effect of lenticule reimplantation after ReLEx on corneal wound healing responses, topography, keratometry, and refraction. Third, a year-long study was conducted in primates.

During the pilot study, rabbits underwent ReLEx in one eye (-6.00 D correction), and the lenticule was stored in an anatomically oriented container at -80° C. After 28 days, the lenticule was reimplanted in the same eye and the rabbits were allowed to recover for 28 days before their tissue was analyzed for wound healing responses. Corneal slit-lamp photography, grading of corneal haze, confocal microscopy, anterior segment optical coherence tomography, corneal topography, and autorefractometry were performed at all time points. Fellow eyes were used as controls. Following positive results in the rabbit pilot study, we conducted a second study in rhesus macaque monkeys. Again, a -6.00 D correction with ReLEx was performed in one eye, and lenticule reimplantation occurred 3 months later. Investigations listed in the rabbit study were conducted at all significant time points.

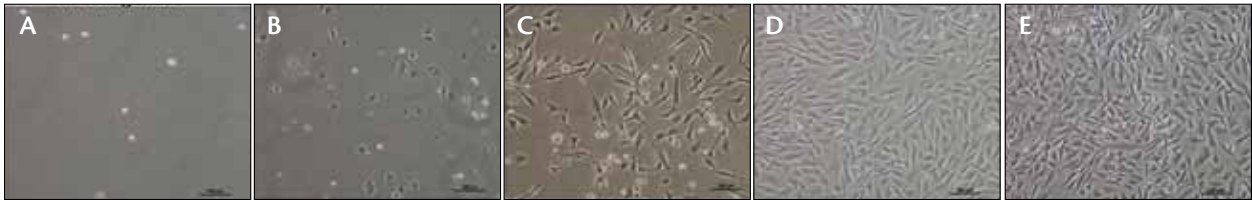


Figure 3. A montage of images showing viable cell cultures from explanted lenticules. (A) Free-floating keratocytes in culture medium after collagenase digestion, (B) cell seeding at day 1, (C) cell proliferation at day 4, (D) the direct cultured fresh control cornea yields confluent cultures of corneal fibroblasts at day 5, and (E) viable confluent fibroblasts are also obtained from lenticules frozen for 1 week and 1 month.

RESULTS

Storage and lenticule viability. ReLEx was performed on human cadaver corneas, and lenticules were submerged in dimethyl sulfoxide and stored at -80°C for 28 days. Lenticules were then thawed to room temperature and placed in a standard cell culture for several days. Explant cultures were observed daily by phase contrast microscopy. Viable and confluent keratocyte cultures developed within a few days, confirming the viability of intralenticular stromal keratocytes following storage (Figure 3). Western blot gel electrophoresis demonstrated an identical protein profile between stored and fresh lenticule cell cultures, suggesting that the storage process does not alter lenticular keratocytes.

Having demonstrated lenticule viability, we adapted a standard contact lens case for lenticule storage, maintaining the 12-o'clock orientation of the lenticule on the eye to allow reimplantation in the same position. These results have recently been published.⁵

Lenticule reimplantation in rabbits and primates.

Lenticules were reimplanted by lifting the previous ReLEx flap in a manner similar to a LASIK flap lift for retreatment. In each case, the anatomically oriented lenticule was placed on the exposed stromal surface, the flap was replaced over the lenticule, and a contact lens was placed over the flap for 3 days. Animals were treated with subconjunctival cefuroxime and dexamethasone at the time of surgery and with topical application of the same drugs for the next 7 days. No complications were seen following reimplantation.⁶

Thirty days after reimplantation, all eyes achieved complete restoration of corneal thickness to preoperative values. Minimal haze was noted immediately after reimplantation but disappeared by day 28. There was no evidence of lenticule rejection, and epithelial surfaces healed within 3 days. Over the duration of the experiment, the rabbit eyes underwent a maturation-related change in refraction that was evident in the control eyes and has been reported before.⁷ Taking this into account, mean keratometry and refraction after reimplantation were not significantly different between the

operated and control eyes 28 days after reimplantation. Importantly, corneal immunohistochemistry revealed only negligible inflammatory cells and wound healing response and no myofibroblasts (which cause haze).

Similar results were observed in the primate studies, with complete restoration of keratometry indices and refraction. The animal study results have been submitted for publication.

DISCUSSION

Our studies of ReLEx lenticule storage and reimplantation in rabbits and primates have, for the first time, shown proof of principle for reversing the effects of laser refractive surgery and restoring the cornea to its preoperative condition in terms of stromal volume and keratometry. This technique may offer patients the novel opportunity to bank autologous tissue in case of future need for additional surgery for keratectasia or presbyopia.

Parallels may be drawn between ReLEx lenticule reimplantation and epikeratophakia; however, unlike epikeratophakia, lenticule reimplantation does not require epithelial removal, uses autologous tissue, does not require suturing, is unlikely to induce astigmatism, and does not stimulate a significant wound-healing response.²

Lenticule reimplantation may be combined with CXL to increase biomechanical strength and restore stromal volume in eyes with keratoconus or postrefractive surgery ectasia. Stored lenticules also have the potential to be used as refractive inlays for the treatment of presbyopia following modification of their shape, an area we are currently studying.

CONCLUSION

ReLEx lenticule reimplantation may herald the age of reversible refractive surgery, offering patients the reassurance of being able to restore their corneas to their preoperative state and allowing a host of other future treatments. At the SNEC, we have now sought institutional review board approval for reimplantation into our first human patient. Research into lenticular reimplantation continues, and clinical trials are planned. ■

TAKE-HOME MESSAGE

- Lenticule reimplantation is a potential retreatment option to restore stromal volume and near-preoperative refraction after ReLEx.
- During experimental procedures, all eyes achieved complete restoration of corneal thickness to preoperative values, with minimal haze.

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Editors' Note: The Singapore National Eye Centre owns patents for lenticule reimplantation and its various applications.

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