Intracorneal Inlay Complicated by Intrastromal Epithelial Opacification

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Objective: To report epithelial perilenticular opacity as a new complication of intracorneal inlay implantation for the correction of hyperopia.

Design: Prospective observational case series.

Participants: Eleven eyes of 7 patients underwent intracorneal inlay implantation for the correction of hyperopia.

Methods: Intracorneal inlays were implanted onto the stromal bed by using a microkeratome cut to create an inferior hinged corneal flap.

Main Outcome Measures: Postoperative complication occurrence of intracorneal perilenticular opacity, microbiological laboratory analysis, histopathological analysis, and confocal microscopy study.

Results: Of 11 implanted eyes, 5 showed diffuse perilenticular opacity of varying intensity that was unresponsive to steroid use following intracorneal inlay implantation. All patients had moderate to severe loss of best-corrected visual acuity. The inlays showed deposits at the edge and on the surface. Confocal microscopy in all eyes produced images compatible with the confocal morphologic features of epithelial cells. Explantation of inlays was performed in 5 eyes. The histopathologic study showed the presence of epithelial cells, and microbiological analysis and cultures were negative for bacteria, fungi, and mycobacteria.

Conclusion: Epithelial perilenticular opacity is a new and serious complication in patients with intracorneal inlay implantation for the correction of hyperopia.

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Many methods for the surgical correction of hyperopia have been used in recent years. Some of the most common corneal refractive procedures used for the correction of hyperopia are laser-assisted in situ keratomileusis, photorefractive radial keratotomy, laser thermokeratoplasty, and conductive keratoplasty. Now the numbers of clinical indications are increasing, with hundreds of thousands of patients operated on around the world. One of the recently proposed methods is additive refractive keratoplasty. This term refers to a procedure in which a foreign material, either biological or synthetic, is added to the corneal tissue to modify the refractive condition of the eye. This method creates the potential for reversibility; if necessary the implant may be removed, and other treatment may still be available to the patient.

Synthetic stromal inlays or intracorneal implants have been investigated for nearly half a century. Barraquer first, in 1949, followed by many researchers who used an implantable inlay to modify the refraction on the cornea.2-4 They used flint glass and plexiglass in their studies. The implants manufactured from these materials caused anterior stromal necrosis followed by extrusion in eyes implanted with this inlay. The limitations of this impermeable membrane developed in previous studies could be avoided by the use of hydrogel. With its permeability, hydrogel is similar to the corneal stroma, allowing the exchange of water and nutrients between the posterior and anterior layers of the cornea to maintain normal corneal physiologic characteristics.5,6 The first hydrogel to be evaluated for refractive keratoplasty was hydroxyethyl methacrylate, by Dohlman7 in 1967 and later on by other researchers in the area of refractive keratoplasty.8-11 Currently, the method by which intracorneal inlays are implanted within the cornea consists of creating a corneal flap with an automated microkeratome followed by inlay implantation onto the cornea.
neal stroma. It is much easier to predict and maintain a hinged flap of constant thickness and a desired corneal depth for inlay placement. Previous experimental studies have demonstrated that hydrogel lenses need to be placed at a depth between 36% and 60% of the corneal thickness for success.\textsuperscript{12,13}

To our knowledge, no published studies report the implantation of this inlay for the correction of hyperopia in human eyes. The only published studies have been performed on primate eyes. A variety of complications occurred postoperatively following implantation of the hydrogel model in animals. These included corneal opacification,\textsuperscript{12,14} epithelial and stromal thinning,\textsuperscript{9,15,16} keratoctye and fibroblastic changes with or without intra-corneal deposits,\textsuperscript{15,16} epithelial ingrowth,\textsuperscript{17} decentration,\textsuperscript{18} anterior corneal necrosis, and lens extrusion.\textsuperscript{19}

This article describes a new complication arising after implantation of the latest generation of hydrogel corneal inlays for the correction of hyperopia in human eyes. We have termed this complication \textit{epithelial perilenticular opacity}.

### METHODS

**PATIENTS**

The hydrogel intracorneal inlays were implanted in 11 hyperopic eyes of 7 patients (4 women and 3 men). The mean±SD age was 42.3±8.1 years (range, 24-60 years). Mean±SD preoperative cyclopegic hyperopia was 4.6±1.1 dipters (D) (range, 2.5-6.0 D). All patients had less than 1 D of keratometric astigmatism. Mean±SD preoperative uncorrected visual acuity (UCVA) was 20/80±20/200 (range, 20/40-20/200). Mean±SD preoperative best spectacle-corrected visual acuity (BSCVA) was 20/25±20/100 (range, 20/20-20/40). The patients showed no systemic or ocular health problems. Results of preoperative biomicroscopy examination of the anterior segment and fundus were normal. The preoperative evaluation also included corneal pachymetry using ultrasonic pachymetry (DGH-500 pachymeter; DGH Technology, Inc, Exton, Pa) and the determination of scotopic pupil size (Colvard Pupillometer; Oasis Medical, Inc, Glendora, Calif). Approval from the Ethical Board Committee was obtained, and all patients read and signed an informed consent document explaining the surgical procedure and possible risks in accordance with the Declaration of Helsinki.

Nine eyes (5 patients) were implanted with inlays (Permalens; PermaVision, Anamed Inc, Lake Forest, Calif). The Permalens inlay is made of hydrogel with a water content of more than 70% and a refractive index of 1.3. The thickness is from 20 to 50 µm, and its diameter is 4.5 mm. The power of the inlay ranges from +3.00 D to +6.00 D. The other 2 eyes (2 patients) were implanted with another inlay design made of hydrogel with a water content of 78% and a refractive index of approximately 1.3. The thickness is between 48 and 92 µm, and the diameter is from 4.75 to 5.25 µm. The power of the inlay ranges from +2.00 D to +8.00 D.

### RESULTS

All patients underwent the same surgical protocol to implant the corneal inlay. An automated microkeratome (M2; Moria, Antony, France) was used to tentatively create a 180-µm corneal flap with a diameter of 8.5 mm and a 4-mm inferior hinged corneal flap. During the procedure, corneal pachymetry was used to measure the cornea and residual stromal bed by using an ultrasonic pachymeter. Following the manufacturer's indications, a "dry technique" was used for the implantation of the inlay. Hence, the interface was not irrigated after the microkeratome cut or the implantation. Immediately after the microkeratome cut was performed, the stromal bed was dried using a sponge (Merocel; Oasis Medical, Inc), and the inlay was placed on the pupil zone by means of a specific manual vacuum device as recommended by the manufacturer. The hinged corneal flap was replaced onto the bed using a nonstitch technique. The gutter around the edge of the flap was also dried with a sponge. After the fluid was squeezed from the interface, the flap was left to settle for 2 minutes. All surgical procedures were successful. At the end of the procedure, the eye was occluded for 24 hours. Postoperative treatment included 0.3% ofloxacin 4 times per day for 1 week and combined tobramycin and 0.1% dexamethasone 4 times a day for 1 week. Four cases required inlay reposition owing to different degrees of decentration. Follow-up was carried out at 1 to 2 days, 1 week, 1 month, 3 months, and 6 months. Figure 1 shows a successful inlay implant.

![Figure 1. Slitlamp examination. Arrows indicate a successful inlay implant, which is almost imperceptible because of its extreme thinness.](image-url)
of fluorescein staining of the gutter were positive for the first 3 days but became negative afterward. Peripheral flap interface epithelial nets or sheets of cells were not observed in any of the cases in the present series, including those in which perilenticular opacification did not develop.

All patients complained of similar symptoms: night glare, moderate photophobia, starbursts, and blurry vision. They received treatment with 0.3% ofloxacin and with tobramycin and dexamethasone 4 times a day. A study of the corneal stroma using confocal microscopy (ASL model 500; Advanced Scanning, New Orleans, La) was performed the second postoperative week in all eyes (5/5) with similar results. Scanning was performed from the epithelium to the endothelium, paying special attention to the stroma interface and inlay edges. The corneal epithelium and the stroma behind the basal membrane were normal. The keratocytes of the anterior stroma were activated, and a zone of apoptotic keratocytes was found on the anterior inlay surface. At this level, stromal edema, nonmetallic particles, and the extracellular matrix were clearly seen using this technique (Figure 6). Just behind the inlay, epithelial cells were found lying over the stromal bed with nonmetallic particles and epithelioid cells (Figure 7). We observed many epithelial cells in the posterior inlay and around the edge and epithelioid cells. The edge of the corneal inlay is clearly seen in Figure 8. The posterior stroma and endothelium were normal, and this finding was similar in all cases. No improvement in biomicroscopic appearance or in the patient’s symptoms was noticed after 3 weeks of treatment. Central flap thickness was deducted by subtraction of the perspective pachymetry measurement from the stromal measurement obtained immediately after flap lifting. The mean ± SD thickness was 169 ± 20 µm. There were no significant differences in flap thickness between patients who did or did not develop postoperative perilenticular opacity.

Explantation of the inlay was performed after 1 month of follow-up in all 5 cases. During the explantation procedure, when the flap was lifted, a thin membrane was observed between the posterior inlay surface and the stromal bed in 5 of 5 eyes (Figure 9). This membrane was carefully removed and sent for histopathologic and microbiological study. After explantation, an intensive topical steroid (0.1% dexamethasone) and an antibiotic (ofloxacin) were used for 5 days. Corneal transparency improved in all eyes, although 2 of 5 eyes still showed mild stromal peripheral opacity around the cen-
tral cornea; however, this did not interfere with central corneal transparency. The membrane and inlay were inoculated using several media including blood, chocolate, MacConkey agar, Thayer-Martin agar, Lowenstein-Jensen medium, and Sabouraud agar for bacterial, mycobacterial, and fungal cultures. Gram and Giemsa stains and histopathologic studies were also carried out. Microbiological analysis and cultures of corneal specimens from all patients were negative for bacteria, fungi, and mycobacteria. Although pathologic study was performed for all explanted inlays together with adherent tissues attached to the inlay obtained during surgery, only 2 pathologic results were obtained because the other 3 samples had insufficient material to be processed. There was 1 case of abnormalities with the Permalens inlay and 1 for the other type of inlay. In all cases, the postoperative BCVA and refraction were nearly the same as initial preoperative levels after 3 months of follow-up. Removal of the inlay showed a positive effect on the recovery of corneal transparency, which returned to nearly normal levels in all cases. In 3 cases a faint ring-shaped peripheral opacity, which did not affect the central cornea, was still visible 6 months after explantation.

One case involved a 39-year-old man who had hyperopia in his right eye. The UCVA was 20/125 OD, and the BSCVA was 20/25 OD. The refraction was +6.00 D of spherical defect and −0.5 D × 50° of cylinder defect, and his scotopic pupil size was 4.0 mm. A +6.00 D intracorneal hydrogel inlay was selected for insertion in this case. The surgery was performed as previously described.

Five days after surgery the intracorneal inlay had migrated 1.0 mm temporally, so the patient underwent surgery to reposition the inlay by lifting the flap. One week later, the patient complained of photophobia, starbursts, blurry vision, and night glare. The UCVA was 20/100 OD, and the BSCVA was 20/50 OD with +3.50 D of spherical defect and −0.5 D × 90° of cylinder defect. There were several whitish deposits on the edge of the inlay, which was decentrated 1.0 mm temporally (Figure 3). Mild corneal edema and moderate diffuse haze were also apparent. There was no anterior chamber reaction. Initially the patient was diagnosed as having DLK, and treatment was started with 0.1% fluorometholone every 4 hours and cyclopentolate hydrochloride every 8 hours. The patient showed no improvement, and we decided to explant the intracorneal inlay after 3 weeks of observation.
Confocal microscopy was performed using a tandem scanning confocal microscope (ASL model 500). The corneal epithelium and the stroma behind the basal membrane were normal. The inlay was found to be between 134 and 173 μm. Keratocyte activation and apoptosis anterior to the inlay surface were found as described previously. Epithelial cells were found lying over the stromal bed with few nonmetallic particles and epithelioid cells (Figure 7). We observed many epithelial cells in the posterior inlay and around the edge and epithelioid cells. The posterior stroma and endothelium were normal.

The patient improved rapidly, with regression of the ocular inflammation and corneal deposits; the topical steroids were slowly reduced. After 2 weeks of treatment the UCVA was 20/125 OD, and the patient's BSCVA was 20/40 OD. The refraction was +6.00 D of spherical defect and −2.00 D × 75° of cylinder defect. Biomicroscopy examination showed peripheral leukoma around the corneal flap. Because of the loss of 4 lines of BSCVA as well as the patient's reported symptoms, the inlay was finally removed and sent for microbiological and pathologic study.

Microbiological analysis and cultures of the corneal specimen showed no abnormalities. Histopathologic studies showed that the membrane consisted of epithelial cells (Figure 10). There was no presence of granulocytes such as polymorphonuclear cells, eosinophils, or basophils, ruling out acute infection. The inlay dissolved during the histopathologic process.

**COMMENT**

The correction of moderate and high hyperopia with corneal refractive surgical procedures presents substantial challenges for refractive surgeons. Phakic intraocular lenses, both anterior and posterior chamber, have potential intraocular complications such as secondary glaucoma, endothelial cell loss, complicated cataract, and uveitis and are still being investigated in hyperopic eyes.20-23

This study describes a new and unique complication termed epithelial perilenticular opacity, which occurred in 5 eyes following intracorneal inlay implantation. Symptoms such as photophobia, blurry vision, and starbursts as well as clinical course were similar in all patients. These symptoms began in the first week, and biomicroscopy examination results were similar in all cases. Patients did not improve with topical steroids, with progression of the opacity and worsening of the BSCVA, leading to inlay explantation. The differential diagnosis of this complication was DLK. This consists of noninfectious diffuse interface inflammation after corneal lamellar surgery, characterized by infiltration of inflammatory cells at the interface.24 As in DLK, the diffuse aspect of the infiltrate (the absence of a single focus and the confinement of the infiltrate to the interface) suggests a noninfectious etiology. During the inlay explantation procedure, samples were obtained in all 5 eyes for microbiological analysis and produced negative results in all cases. In DLK cases, an allergic or toxic inflammatory reaction is the most likely cause; in general, such cases respond well to topical steroids.24

The complication of epithelial perilenticular opacity is distinctly different from DLK: the infiltration was confined to the limits of the inlay, did not respond to steroids, and had a different clinical evolution from DLK. A possibility that could be considered in our cases is a hypersensitivity reaction type 4.25 Immunological rejection depends on whether the host recognizes the implanted material as foreign and produces specific persistent antigens, as in the case of the intracorneal inlay. This might be the stimulus for macrophage cells to migrate, surrounding the foreign object, and then to transform into epithelial-like cells (known as epithelioid cells), causing an inflammatory response on the stromal bed. This was ruled out because our histopathologic studies did not show the presence of this kind of cell.

According to pathologic and confocal microscopy analysis, the implantation of epithelial cells and their further ingrowth on the inlay surface was the cause of the perilenticular opacity. The implantation of epithelial cells in the interface occurs by mechanical dragging of the keratome blade during keratectomy; backflow during irrigation, carrying floating epithelial cells; ingrowth at the junction of the epithelium and keratome; and migration under the flap.26 When already present at the interface, the adequate condition of the inlay surface and its isolation from other tissues will probably promote the ingrowth of the layer formed on the hydrophilic surface of the inlay. The migrating epithelial cells may further contribute to stromal melting of the flap, but no evidence of corneal melting was observed in any of our cases. Epithelial ingrowth at the interface is more common after enhancement procedures because the lifting of the flap can induce adjacent epithelial abrasions with increased cell proliferation.27 In our study, 3 of 5 eyes had the flap lifted to reposition the inlay as a result of decentration. Epithelial cells were on the posterior inlay surface and around the edge. This induced a hyperopic shift with loss of BSCVA caused by the whitish deposits. No evidence was observed in any of the cases that the epithelial cells were growing around the inlay or invading the interface from the edge of the flap. This supports the idea that such cells were implanted at the interface by the keratome cut. The dry technique used in these cases likely influenced the development of this complication. Use of these inlays should be adequately reevaluated in the future as a potential source of epithelial perilenticular opacity.

This article forms part of a multicenter study of the correction of hyperopia with intracorneal inlays. The new
generation of soft intracorneal inlays offers an alternative for the correction of hyperopia with potential reversibility and implant removal. Therefore, we report a new specific complication of intracorneal epithelial inlay implantation called intracorneal perilenticular opacity, a finding that could have a significant effect on the future consideration of inlays in refractive surgery. This complication should be distinctly differentiated from DLK. The lack of a positive response to steroids and the confinement of the interface opacity to the limits of the implanted inlay are the most remarkable differentiating clinical signs. A careful review of the surgical process involved in inlay implantation should be conducted. The causes and prevention of epithelial perilenticular opacity should be carefully investigated in future research into additive refractive keratoplasty with intracorneal inlay implantation.

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