STUDIES OF INTRASTROMAL CORNEAL RING SEGMENTS FOR THE CORRECTION OF LOW TO MODERATE MYOPIC REFRACTIVE ERRORS*

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ABSTRACT

Purpose: Intrastromal corneal ring segments (ICRS) were investigated for safety and reliability in the correction of low to moderate myopic refractive errors.

Methods: Initially, 74 patients with spherical equivalent refractive errors between -1.00 and -4.25 diopters (D) received the ICRS in 1 eye. After 6 months, 51 of these patients received the ICRS in the contralateral eye. The total number of eyes investigated was 125.

The outcome measures were uncorrected and best-corrected visual acuity, predictability and stability of the refraction, refractive astigmatism, contrast sensitivity, and endothelial cell morphology.

Results: The 89 eyes with 12-month follow-up showed significant improvement with uncorrected visual acuities of 20/16 or better in 37%, 20/20 or better in 62%, and 20/40 or better in 97%. Cycloplegic refraction spherical equivalents showed that 68% of the eyes were within ±0.50 D and 90% within ±1.00 D of the intended correction. Refractive stability was present by 3 months after the surgery. Only 1 patient had a loss greater than 2 lines or 10 letters of best spectacle-corrected visual acuity, but the patient's acuity was 20/20. Refractive cylinder, contrast sensitivity, and endothelial cell morphology were not adversely affected.

The ICRS was removed from the eyes of 6 patients. Three removals were prompted by glare and double images occuring at night; 3 were for nonmedical reasons. All patients returned to within ±1.00 D of their preoperative refractive spherical equivalent, and no patients lost more than 1 line of best corrected visual acuity by 3 months after ICRS removal.

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Conclusion: The ICRS safely and reliably corrects myopic refractive errors between -1.00 and -4.50 D.

INTRODUCTION

The quest for the ideal keratorefractive surgical procedure has been elusive. Over the last 100 years, the need for improved safety and enhanced efficacy has driven surgical innovation. Yet, every surgical technique under investigation, or in use, has until now been limited by wound healing problems, lack of stability, or poor visual function as assessed by contrast sensitivity.

It is widely agreed among ophthalmologists that wound healing represents a significant problem. The unpredictability of the long-term results of methodologies like photorefractive keratectomy (PRK) or radial keratotomy (RK) is due to the effects of corneal remodeling and wound healing. When these effects participate together as variables in a procedure, it is difficult to achieve a predictable refractive result and the proper amount of flattening across the central optical zone of the cornea.

My concept of an ideal keratorefractive technique evolved from the studies developed to test the safety and efficacy of tissue additive techniques. In the ideal tissue additive technique, the central portion of the host cornea is not incised and, if the additive tissue is removed, the original corneal curvature is restored, making this a potentially reversible and interchangeable procedure. The concept further requires the central visual axis to maintain a positively aspheric or prolate refractive surface. Furthermore, the corneal curvature change must be induced through a mechanical effect that is not influenced by corneal wound healing.

The concept of additive keratorefractive surgery is not new. At the outset of my investigations, it was already recognized that the field of refractive surgery was moving toward tissue additive techniques. The studies that I directed and that are presented in this thesis demonstrate that the 150° intrastromal corneal ring segment (ICRS) is a viable new additive keratorefractive surgery that provides many of the attributes that I ascribed to an ideal refractive surgical procedure.

A brief overview of the experimental and clinical development of tissue additive procedures leading up to the development of the 150° ICRS follows.

TISSUE ADDITIVE TECHNIQUES

Keratophakia

Barraquer's work in developing the use of keratophakia corneal stromal inlays to change the refractive power of the eye illustrated the initial viability of tissue additive techniques.[1] Keratophakia was developed

primarily to correct aphakic refractive errors. In this procedure, an anterior cap of corneal tissue was removed using a microkeratome. A lenticule of donor cornea tissue was then shaped using a Barraquer cryolathe and placed on the exposed stromal bed. The anterior lamellar cap was sutured in place with an antitorque suture technique. By varying the thickness of the donor lenticule, the anterior corneal curvature was steepened and aphakic refractive errors were corrected. The reported clinical experience with keratophakia has been limited, but the results showed the efficacy of this procedure for correcting aphakic refractive errors.[2,3]

Synthetic Central Corneal Stromal Inlays

Barraquer also tried polymethyl methacrylate (PMMA), glass, and colloidin as corneal inlays, but was unsuccessful. The difficulty was that these nonpermeable materials blocked the diffusion of glucose from the aqueous to the layers of the corneal stroma anterior to the lenticules, causing epithelial sloughing and anterior stromal melts. It was established that if an impermeable corneal inlay was greater than 4 mm in diameter, nutrient flow was inhibited and the cornea tended to necrose anterior to the lamellar implant.[4-7]

In an effort to improve permeability, McCarey and Andrews[8] implanted permeable hydrogel keratophakia lenticules in primates. Long-term follow-up of hydrogel implants in primates did not demonstrate any stromal melting overlying the lenticules.[9,10] McCarey also reported that hydrogel inlays produce crystalline deposits hypothesized to be cholesterol produced by stressed keratocytes.[11]

Other corneal inlay materials were also studied, including polysulfone corneal inlays. Lane and associates[13] reported complications including polysulfone lens extrusion, interface opacities, anterior corneal necrosis, refractile particles, and epithelial thinning thought to be due to poor glucose transmissibility.

Several experimental attempts have been made to improve the biocompatibility and tolerance of these lenses by coating them with proteins, [14,15] or placing fenestrations[16] to aid cellular proliferation and movement of nutrients, but there is little reported follow-up in the literature to this additive keratorefractive surgical approach. The benefit of producing a change in the shape of the cornea through a mechanical effect, such as that produced by a biocompatible implant, is obvious and warrants further study.

Epikeratoplasty

Epikeratoplasty evolved from the Barraquer cryolathe techniques in an attempt to simplify the surgical procedure. Formerly termed epikeratophakia, this technique was pioneered by Werblin, Kaufman, and McDonald[17] and was adapted to correct aphakic,[18-28] hyperopic, and

myopic[29,30] refractive errors and keratoconus.[31-34]

Epikeratoplasty differs from Barraquer's keratophakia technique primarily in that the refractive correction was placed on the surface of the cornea. The epikeratoplasty onlay lamellar graft was prepared using donor corneal tissue. The corneal tissue was shaped on a Barraquer cryolathe, cryopreserved, lyophilized, stored, and then rehydrated at the time of surgery. It was then sutured into a peripheral circumferential incision outside of the optical zone in the host cornea.

One of the theoretical advantages of epikeratoplasty was that the central portion of the host cornea was not incised. An additional theoretical advantage was that if the lenticule was removed, the original cornea remains with its original refractive curvature, making this a reversible and potentially interchangeable refractive procedure.

Although initial clinical results with epikeratoplasty were promising, the procedure was fraught with problems. Eventually epikeratoplasty for myopia was abandoned, and epikeratoplasty for keratoconus, pediatric aphakia, and aphakia are rarely performed.

Intracorneal Ring (ICR)

Reynolds' Ring. In 1978, Reynolds hypothesized that a PMMA ring placed within the corneal periphery could be expanded to correct myopia and contracted to correct hyperopia. Fleming and associates[35] conducted the first studies using an early corneal ring design to test the feasibility and safety of Reynolds' original concept. In a pilot rabbit study, a corneal ring was implanted through a 2.5 mm partial-depth, oblique keratotomy incision into a dissected circular peripheral stromal channel that had an inner diameter of 9.4 mm and an outer diameter of 10.9 mm. Two rabbits were implanted and followed for 6 months, during which time the central cornea remained clear. Slight superficial vascularization developed in each eye by month 3 with new blood vessels approaching the outer circumference of the ring. The neovascularization was thought to be a reaction to the suture used to close the oblique incision. Although the vessels were still present at month 6, they did not invade the central cornea. No anterior chamber reaction or other complications were noted.

In 1988, I directed unpublished animal safety studies that focused on improving surgical technique and instrumentation while testing the biocompatibility of the 360° corneal ring. Since it was felt that Bowman's layer was important in achieving the desired flattening of the cornea, I attempted to develop an experimental primate model. However, difficulties with instrumentation and corneal ring design made implantation in the primate impossible. In 1989, Simon reported his early experience with

the intrastromal rings in animal eyes,[36] and later he developed the concept of an injectable intracorneal ring implant.[37] In 1991, D'Hermies also tested the biocompatibility of an intracorneal PMMA ring in rabbit eyes.[38]

Early mathematical modeling studies of corneal ring expansion and contraction demonstrated that minimal changes in the circumference of the corneal ring produced large fluctuations in the central corneal curvature.[39] This extreme sensitivity to minimal changes limited the theoretical predictability of outcome.

Arc-Shortening Theory

In 1989, my colleagues and I considered that using a fixed-diameter ring and simply varying ring thickness could provide titratable corneal flattening. Shortly thereafter, Loomis and Silvestrini developed an arc-shortening model to explain how variations in the thickness of a ring could produce precise changes in central corneal curvature to correct myopic refractive errors.

By 1991, Burris and associates[40] had initiated an in vitro study to further test the expansion model. Rings of various diameters (with 0.3 mm uniform thickness) were inserted into an intrastromal channel (with 8.5 mm fixed outer diameter) in 6 human donor eyes. Results showed that implantation of rings with diameters larger than the outer edge of the dissected channel produced significant corneal flattening. It was also demonstrated that a ring of 0.30 mm thickness with an outside diameter equal to the diameter of the dissected channel induced approximately 3.5 diopters (D) of central corneal flattening. This demonstrated that corneal flattening resulted from the thickness of the corneal ring alone.

There were theoretical concerns about the long-term efficacy of the expansion model when it was concluded that forces exerted on the outer edge of the intrastromal channel might eventually cause further peripheral corneal dissection and loss of refractive effect. In light of the potential unpredictability of the expansion model, and with the demonstration of a more predictable and controllable flattening by virtue of thickness, the original Reynolds' concept was abandoned in favor of the mechanism of action of a fixed-diameter, variable-thickness ring. Only the thickness of the ICR, not the tightening or expansion of a ring, provided the key performance variable that caused varying degrees of corneal flattening.

360° ICR. The viability of using the thickness of a ring to achieve the desired refractive effect was demonstrated through experimental studies carried out by Burris.[41] Using 360° intracorneal rings with fixed diameters and thicknesses ranging from 0.26 to 0.46 mm, this study verified the arc-shortening theory in 33 human donor eyes and showed a linear relationship between the thickness of the ring and the amount of induced central

corneal flattening. Topographic analysis using the Kera-Metrics interferometric system (Kera-Metrics, San Diego, Calif.) additionally demonstrated a positively aspheric or prolate corneal surface after implantation.

Research continued to investigate the mechanism of action whereby ring thickness caused corneal flattening. Pinsky and associates[42] modeled the effects of the 360° ring using a finite-element computer model to predict corneal shape change. This three-dimensional, axisymmetric finite element model took into account the arc-shortening effects of the ring, not just for the central corneal fibers, but also for the shortening of corneal fibers crossing over the ring in all directions. This made it possible to predict the corneal surface deformation over the entire corneal surface and to predict that thicker rings would produce greater degrees of corneal flattening.

360° ICR Blind Eye Studies

Nosé and Belfort[43] performed the first intracorneal ring surgeries on humans in March 1991 in São Paulo, Brazil, when 3 volunteers received corneal ring implants in their nonfunctional blind eyes. The patients ranged in age from 24 to 38 years and had monocular, nonfunctional visual status of 20/800 or less, resulting from noncorneal ocular pathology. All patients received a fixed-diameter, split-end 360° corneal ring with an inner diameter of 6.8 mm, an outer diameter of 7.7 mm, and a thickness of 0.3 mm.

The investigators reported early transient conjunctival congestion and epithelial defects that resolved over 3 to 5 days. The lamellar dissection on either side of the corneal ring implant demonstrated some mild peripheral haze that resolved over 4 to 6 weeks. At 1 year, they reported keratometric corneal flattening of -2.13 D and -2.88 D, and retinoscopic refractive changes of -2.62 D and -2.25 D in the 2 patients who retained the corneal ring.[43] A third patient, who had a keratometric change of -1.74 D 5 months postoperatively, had the corneal ring removed at 6 months according to the protocol. Under topical anesthesia, the corneal ring was extracted from the channel without complication through the original incision site, and 1 month later the patient returned to within 0.12 D of the preoperative refraction. This demonstrated the potential for reversibility of refractive effect with removal of the corneal ring.

Initial experience with the corneal ring demonstrated that the surgical technique and instrumentation were sufficient for positioning the ring at a desired depth with good centration. Furthermore, these studies raised no safety issues and demonstrated stability of refractive effect over the first postoperative year. The investigators reported normal intraocular pressures following ring implantation over the period of the study, although there was a corticosteroid-induced transient intraocular pressure rise between 4 and 8

weeks postoperatively in 1 patient. The long-term follow-up of these initial nonfunctional eyes continued to show stability of refractive effect at 5 years.

FDA Phase I Blind Eye Studies

In July of 1991, Fouraker initiated a study of the corneal ring in 10 nonfunctional eyes. These surgeries constituted the Phase I, US Food and Drug Administration (FDA) clinical trial, which was designed to investigate the safety and efficacy of the corneal ring. All patients received a fixed-diameter, 360° split-end ring with an inner diameter of 6.8 mm, an outer diameter of 7.7 mm, and a thickness of 0.3 mm. The ring was implanted through a superior 2.0 mm incision from the 7 mm to 9 mm optical zones.

Assil and colleagues[44] reported the results of these cases at 1 year documenting an average flattening of the spherical equivalent of 2.5 ± 1.1 D by keratometry and 2.4 ± 1.0 D by cycloplegic retinoscopy. Thus, the average corneal flattening induced by implantation of the 0.3 mm thick corneal ring was within 1 D of the result predicted by Burris and associates[41] from their experimental eye-bank eye studies.

The clinical course in these patients was unremarkable. The re-epithelialization of the incision site was complete within 7 days of the surgery. There was no recurrent epithelial erosion or implant extrusion, and, in general, the corneal ring was well tolerated.

Over the course of the first postoperative year, none of the patients demonstrated any significant changes in intraocular pressure, corneal sensation, or thickness. Transient haze associated with the stromal channel rapidly dissipated over the first 6 to 8 weeks and was barely discernible at the 1 year evaluation. In some patients, small refractile deposits were observed adjacent to the ICR in the lamellar channel. These deposits became evident at the 2 month postoperative examination, stabilized by the 9 month examination, and were not associated with any inflammatory or vascular response. The composition of this material was unknown, but it appeared similar to the deposits observed near other types of intrastromal implants.[11]

Five of the 10 patients from this series developed a unique arcuate pattern of epithelial iron deposition that became evident 8 to 12 months following surgery.[45] Of these 5 patients, 2 had a Hudson-Stahli line in the contralateral eye. The rest of the patients without iron lines in the nonfunctional eye did not have Hudson-Stahli lines in the contralateral eye. Therefore, the appearance of the ICR-associated crescentic iron line was not related to the amount of topographic change, nor was it otherwise considered clinically significant.

Five eyes in the nonfunctional eye study had the corneal ring removed at 1 year as part of the protocol. These patients were observed for 12

months following removal. The mean change in keratometric spherical equivalent at 1 year with the corneal ring was -2.8 D. The mean keratometry returned to within +0.70 ±0.30 D of the preoperative measurement at 3 months, and +0.60 ±0.50 D of the preoperative measurement at 1 year. The mean change in retinoscopic spherical equivalent at 1 year with the ring was also 2.8 D. After corneal ring removal, the retinoscopy returned to within + 0.1 ± 0.2 D of the preoperative measurement at 3 months, and +0.09 ± 0.3 D of the preoperative measurement at 1 year.

This study showed that not only does refractive change return to preoperative levels following removal of the corneal ring but that patients who developed refractile deposits within the lamellar channel also had resolution of these deposits within a few months. Similarly, the series of patients who developed ring-associated crescentic iron lines all had either a disappearance or a reversion of the iron line to a typical Hudson-Stahli line within 3 months.

One of the eyes in the nonfunctional eye study had an enucleation 8 months following ring removal due to pain from preexisting uveitic glaucoma. The histopathology of this cornea was reported by Quantock and associates[46] who found that the ultrastructural remodeling of the stroma had progressed by the time of the enucleation 8 months after removal of the ring. The proteoglycan population was unremarkable, but there were localized, collagen-free regions a few micrometers across that were confined to the midstroma in the region of the lamellar dissection. These collagen-free regions were thought to contribute to the trace stromal haze observed clinically in the region of the lamellar channel.

Sighted Eye Corneal Ring Studies

Experience with a Radial Incision. In Brazil, Nosé and Belfort conducted the first sighted eye studies of the ICR. The 1 year results of the ICR were described in a series of 10 myopic patients who underwent implantation of the 0.3 mm thick, 360° split-end ICR in the nondominant eye. Preoperative refractive error in this group of patients ranged from -2.63 D to -4.25 D. In this series, patients had rapid improvement of uncorrected visual acuity. On the first postoperative day, all patients had 20/40 or better uncorrected visual acuity, which remained stable to the 12-month examination.

At 1 year, 33% of the patients were seeing 20/20 or better without correction. The mean change in spherical equivalent of the manifest refraction compared to preoperative values was -2.25 D (range, -1.62 to -3.25 D). The mean change in spherical equivalent of keratometric readings at 1 year was -2.35 D (range, +1.75 to -5.88 D).

One of the patients had an unrecognized posterior perforation during surgery, and over the first 5 months slowly developed a localized area of stromal edema that induced astigmatism and led to a deterioration of visual acuity. The patient's ring was removed under local anesthesia at the sixth postoperative month. In retrospect, the ring should not have been implanted in this patient. The patient's cornea returned to its preoperative refractive state following ICR removal, and no complications have been reported during the postexplant period.

Two patients in this series developed infiltrates in the channel. Although these receded with the use of antibiotics, they were not felt to be infectious. The postoperative findings included peripheral corneal haze in the lamellar channel that diminished over time, small lamellar channel deposits, stromal neovascularization, and pannus. Long-term follow-up of this initial series of 10 Brazilian sighted eye patients continues, and at 5 years the 9 patients who continue in the study have stable refraction and uncorrected visual acuity of 20/40 or better.[48]

US Sighted Eye Clinical Trials. US sighted eye clinical studies of the ICR began in July of 1993 under an Investigational Device Exemption from the FDA. The study was designed to further test the safety of the ICR and to examine the efficacy of various ICR thicknesses (0.25, 0.30, 0.35, 0.40, and 0.45 mm) for correcting refractive errors between -1.50 to -6.00 D. The study design called for testing the thinner ICR before testing the thicker ICR in order to maximize accuracy and safety.

In my initial series of 10 eyes, 5 were implanted with the 0.25-mm-thick ICR and 5 with the 0.30-mm-thick ICR. The initial refractive response was favorable, and the early postoperative course was unremarkable. At 12 months, all patients had uncorrected visual acuity of 20/40 or better, and 50% of the patients had 20/20 uncorrected visual acuity (unpublished data). All patients maintained a best-corrected visual acuity of 20/20 or better.

Two of the patients in this initial series, however, developed fluorescein staining along the incision within the first month following suture removal. It was thought that this staining was secondary to a microdehiscence of the wound. In both cases, this most likely was induced by eye rubbing. Although both of these patients had successful resuturing of the wound and they retained the ICR, the dehiscence of the wound was associated with a partial loss of the refractive effect of the ICR. Additionally, these patients developed postoperative astigmatism.

Attempts at a Circumferential Incision

Because the experience with microdehiscence of the radial corneal

incision raised concerns, the surgical procedure was altered to move the incision away from the ICR, using a circumferential incision at a 9 mm optical zone. With this new incision technique, the study was continued with ICR thicknesses of 0.30, 0.35, 0.40, and 0.45 mm.

The visual acuity results from the circumferential incision cases were good, with over 83% of my patients achieving 20/40 or better uncorrected vision (unpublished data). The corneal topography demonstrated a prolate shape, and the patients were relatively free of symptoms of glare, halos, or night myopia.

The results of contrast sensitivity testing of 33 of the total Phase II series revealed that there was no significant loss of contrast sensitivity from preoperative values.[49] The fact that the contrast sensitivity was normal after ICR implantation may explain to some extent why the majority of the patients describe the quality of their vision after the ICR as good to excellent.

The majority of cases in the circumferential incision series did not have any complications (unpublished data). Nonetheless, corneal neovascularization was seen in some cases. This neovascularization was typically characterized as a single vessel extending from the limbus to the incision. Occasionally, a vessel would enter the incision and grow into the lamellar channel. The incidence of this single-vessel neovascularization correlated with either the presence of preexisting pannus or with the passage of the 10-0 nylon through the limbal blood vessels.

Small Diameter 360° Intracorneal Ring Clinical Studies

Nagy and associates[50] recently reported the implantation of an intrastromal corneal ring of their own design in 3 patients with unilateral myopia. The inner diameter of these intracorneal rings was 4 mm, the outer diameter was 5 mm, and the thickness was 0.30 mm. They obtained 10 D of corneal flattening, which was maintained over the follow-up period of 3 to 10 months.

Ferrara of Brazil and Bisantis of Italy have also tested small-diameter intracorneal rings of their own design in patients with high myopia and have obtained corrections of up to 24 D (Ferrara, personal communication, 1997).

Laboratory Studies of Astigmatism

In 1994, I conducted a series of experimental studies using eye-bank eyes to examine the effect of paired partial Intrastromal Corneal Ring Segments (ICRS) for the correction of astigmatism. The segments had the same radius of curvature and cross section as the original ICR but were cut to varying arc lengths including 10°, 45°, 60°, 90°, and 135°. The results of these unpublished experiments demonstrated an interesting phenomenon. The 10° ICRS tended to produce mild steepening in the axis of segment

placement with an equal or greater degree of flattening in the orthogonal axis. The magnitude of the induced curvature changes increased with increasing segment thickness. Similar results were seen with the 45° ICRS, and even greater levels of orthogonal axis flattening were observed with 60° ICRS. With the insertion of 90° ICRS, corneal flattening was observed both in the axis of segment placement and in the orthogonal axis. The 135° ICRS produced a greater degree of corneal flattening over a larger surface area of the cornea. The disparity in the degree of flattening between the two principal meridians was less with the 135° ICRS than with ICRS of smaller arc lengths. In summary, I found a trend toward global flattening of the cornea with a reduction of local effects as the arcuate segment length went beyond 120°.

150° ICRS

Based on the trends that I saw in the astigmatism studies, my colleagues and I experimented with paired 150° ICRS. Since they could be implanted with a simple surgical technique using a radial incision that avoided the problems of neovascularization encountered with the circumferential incision, sighted eye Phase II clinical trials using the 150° ICRS were initiated. These experiments established a performance curve for the 150° ICRS, demonstrating that thicknesses between 0.25 mm and 0.45 mm could induce global corneal flattening between -1.00 and -4.50 D in eye bank eyes.

To date, there have been no published reports with 1 year follow-up of the effectiveness and safety of the ICRS.

In this study, I tested to see whether the ICRS safely, effectively, and reversibly treated low to moderate myopic refractive errors and provided a large refractive optical zone with a normal prolate aspheric surface.

The studies reported here were conducted to see whether:

1. The ICRS is a safe and effective treatment for myopia between –1.00 and –4.25 D
2. The ICRS is a reversible refractive procedure, defined as a return of preoperative best-corrected spectacle visual acuity (BSCVA), uncorrected visual acuity to within 2 Snellen lines, and manifest refraction to within ± 1.00 D within 3 months of removal.

METHODS

STUDY DESIGN

This prospective study of the ICRS was conducted under an FDA Investigational Device Exemption with ongoing review by the Institutional Review Board at the author's university. All patients signed an informed

consent approved by the Institutional Review Board prior to ICRS implantation. I performed the surgeries and follow-up examinations. An independent observer, however, obtained all of the key measurements of the study to eliminate surgeon bias.

The study was divided into 2 phases performed at 2 different universities. The first phase was composed of my cases that were part of a multicenter Phase II FDA clinical trial. Five ICRS thicknesses, 0.25, 0.30, 0.35, 0.40 and 0.45 mm, were implanted in this series of patients. All patients were followed up for at least 12 months after implantation of the ICRS. This study was initiated on May 31, 1995, and was completed in July 1996. All patients initially received the ICRS in 1 eye and were eligible for ICRS surgery in the second eye after 6 months.

The second-phase was composed of my cases that were part of a multicenter Phase III FDA study testing 3 ICRS thicknesses, 0.25 mm, 0.30 mm, 0.35 mm. All patients were followed up for at least 12 months after implantation of the ICRS. This phase was initiated on May 31, 1996, and enrollment was completed on May 5, 1997. All patients initially received the ICRS in 1 eye and were eligible for surgery on the second eye after 6 months. These 2 series of patients have been combined in this report and represent an all-inclusive cohort of my surgical cases with the ICRS.

Trial Objectives

The data were analyzed to evaluate the efficacy and safety of the ICRS. There were 3 efficacy and 5 safety assessments for this study. The efficacy assessments included uncorrected visual acuity, predictability of refractive effect, and stability of refractive effect. The safety assessments included maintenance of best spectacle-corrected visual acuity, loss of best spectacle-corrected visual acuity, induced manifest refraction cylinder, maintenance of contrast sensitivity, and maintenance of endothelial cell counts.

Eligibility Criteria

Patients were eligible for inclusion in the study if they had 2 healthy, normal eyes with best spectacle-corrected visual acuity of 20/20, or better, in each eye; cycloplegic refraction (spherical equivalent) between -1.00 and -4.50 D; and a cylindrical correction of less than or equal to 1.00 D, as measured by manifest refraction. They also needed a stable correction (± 1.00 D), as determined by manifest refraction spherical equivalent (SE), for a minimum of 6 months prior to surgery. If the current method of correction was contact lenses, then they needed a stable refraction (± 1.00 D) as determined by manifest refraction SE, on 2 consecutive examination dates at least 2 weeks apart. Also, they needed to be 21 years or older, be

in good health and mentally sound, and have completed a written informed consent.

Exclusion Criteria

Patients were excluded from participating if one or more of the following criteria were found: pregnancy, as diagnosed by urine hCG no more than 7 days prior to surgery; a history of acute or chronic disease or illness that would increase the operative risk for the patient; or a history of chronic chemical abuse. Similarly, patients were excluded if they had any systemic condition known to affect corneal wound healing, a history of corneal disease, evidence of retinal vascular disease and/or a history of hypercoagulability, or an ocular condition (such as prekeratoconus or keratoconus, recurrent erosion syndrome, or corneal dystrophy) that might predispose them to future complications. Other exclusion criteria included a prior history of herpetic eye disease, untreated lid margin disease, evidence of lagophthalmos or exposure, keratoconjunctivitis sicca, or a history of ophthalmic surgery in either eye. Similarly, patients were excluded if their corneas were steeper than 46 D or flatter than 40 D, or if their corneas had a central thickness of less than 0.48 mm or a peripheral thickness of less than 0.57 mm. Furthermore, cases were excluded if the intraocular pressure was under 10 mm Hg or over 21 mm Hg, or if there was a history of glaucoma, connective tissue disease, such as systemic lupus erythematosus, rheumatoid arthritis, or scleroderma.

Description of ICRS

The ICRS tested consisted of two segments, each having an arc length of 150°. Each segment had a hexagonal cross-section that lies along a conic section. The ICRS was machined into segments from PMMA. The ICRS design has an outer diameter of 8.1 mm and an inner diameter of 6.8 mm.

ICRS thicknesses of 0.25 mm, 0.30 mm, 0.35 mm, 0.40 mm, and 0.45 mm were evaluated in this study. The predicted refractive performance of each thickness was based on a mathematical model and cadaver eye data. The ICRS thicknesses and the predicted dioptric correction for the patients are shown in Table I.

All ICRS were supplied sterile. The ICRS were ethylene oxide (EtO) sterilized and subjected to aeration processing to remove residual EtO.

EXAMINATION SCHEDULE AND DATA COLLECTION

A bank of ophthalmic tests was performed at the preoperative examination and postoperative follow-up examinations. The following section provides a general description of the examination schedule and data collection methods.

TABLE I: PREDICTED PERFORMANCE OF THE ICRS

ICRS THICKNESS (MM)	PREDICTED CORRECTION (D)
0.25	-1.3
0.30	-2.0
0.35	-2.7
0.40	-3.4
0.45	-4.1

Preoperative Examination

The examination included a review of the patient's medical history. Patients with a history of any acute or systemic disease obtained medical clearance from the physician treating the patient for the condition. A pregnancy test (urine hCG) was obtained within 7 days of surgery for female participants of childbearing age.

A complete ocular exam of both eyes was performed. This examination included visual acuity testing using standardized ETDRS (Early Treatment Diabetic Retinopathy Study) visual acuity charts, manifest refraction, cycloplegic refraction, near visual acuity (with and without correction), keratometry, contrast sensitivity testing, ophthalmoscopy, corneal topography, slit-lamp examination, ultrasound pachometry of the central and peripheral cornea, tonometry, and specular microscopy.

Surgical Procedure

I performed the surgical procedure using sterile technique. The patient was prepared using a betadine scrub to the area around the surgical eye. Topical anesthesia was attained with topical tetracaine (0.5%). The eye was draped to fully isolate the eyelashes and lid margin from the surgical field. A Barraquer wire speculum was used to hold the eyelids apart. The geometric center of the cornea was marked with a blunt Sinskey hook. A pre-inked marker was centered on the cornea to provide a visual guide for the placement of the incision at the 12-o'clock position at a 7 mm optical zone. Corneal pachometry (KMI, Philadelphia, PA) was performed over the site of the peripheral incision, and a 15° diamond knife (KMI, Philadelphia, PA) was used to make a 1.8 mm incision at a depth of 67% of the pachometry reading along the superior corneal mark. A modified Suarez spreader was used to begin a lamellar corneal dissection. Specially designed dissecting instruments (KeraVision, Fremont, CA) were inserted into the incision to create curved peripheral corneal tunnels. The intrastromal tunnels were prepared using clockwise and counterclockwise dissecting instruments. Each ICRS was manually rotated into a tunnel until the desired position was reached. The incision was closed using a

single 11-0 nylon suture. The surgical eye received topical dexamethasone 0.1% and tobramycin, and a clear shield was applied overnight.

Postoperative Examinations

The patients in this series were all examined at days 1, 3, 7, 14, and months 1, 3, 6, and 12. At each scheduled follow-up exam, the designated ophthalmic tests were performed (Table II). All observations were recorded on special study report forms.

Contralateral Eye Procedure

After 6 months of follow-up on the operative eye, the patient's contralateral eye was eligible for implantation with the ICRS if refractive stability and safety in the initial eye was established.

DATA MANAGEMENT

The independent observer recorded the clinical data on study report forms, specular microscopy photographs, topography maps, and contrast

TABLE II: SCHEDULE OF TESTS

TEST	PRE	D1	D3	D7	D14	M1	M2	M3	M6	M9	M12
Cycloplegic refraction	X							X	X		X
Manifest refraction	X			X		X	X	X	X	X	X
UCVA	X	X	X	X		X	X	X	X	X	X
BSCVA	X			X		X	X	X	X	X	X
Keratometry	X			X		X	X	X	X	X	X
Slit-Lamp Exam	X	X	X	X	X	X	X	X	X	X	X
Tonometry (IOP)	X	X	X	X	X	X		X	X		X
Pachometry	X							X	X		X
Ophthalmoscopy	X			X					X		
Contrast sensitivity	X							X	X		X
Contrast sens w/gl	X							X	X		X
Topography	X						X	X	X		X
HVF	X								X		
Specular microscopy	X								X		X

BSCVA, best spectacle-corrected visual acuity; HVF, Humphrey visual field ; UCVA, uncorrected visual acuity.

sensitivity plots. The clinical data were sent to the regulatory department of the study sponsor, KeraVision, where the group data were analyzed. The raw data were tabulated and returned to the author for individual reports.

STATISTICAL METHODS

Statistical calculations were performed using StatXact (Cytel Software Corporation, Cambridge, MA) or SAS (SAS Institute Inc., Cary, NC) as appropriate. Differences among ICRS thicknesses were assessed with statistical significance defined as $P < 0.05$. All reported P-values are two-tailed and comparison-wise in that they make no allowance for the number of significance tests performed. In addition to the point estimates of the proportion of patients achieving a designated criterion, 95% confidence limits were calculated for each trial assessment using StatXact. These were calculated for each of the 5 ICRS thicknesses, as well as collectively across the ICRS thicknesses.

Differences among ICRS thicknesses for proportional data were assessed by Fisher's exact or likelihood ratio chi-square tests. For continuous data, analysis of variance or Kruskal-Wallis tests were employed. For ordinal categorical data, Cochran-Mantel-Haenszel methods were used. To evaluate the within-patient changes over time, Wilcoxon signed rank procedures were frequently employed and, unless otherwise specified, tested the null hypothesis that the changes were not different from zero. Changes from the preoperative exam to the month 12 exam were calculated as the month 12 value minus the preoperative value, yielding negative numbers as decreases and positive numbers as increases from the baseline. Safety data and slit-lamp findings were also assessed by ICRS thickness and collectively across all 5 thicknesses.

The specific assessments for this study are described below.

EFFICACY ASSESSMENTS

Uncorrected Visual Acuity

Uncorrected visual acuity was measured in the operative eye using the standardized ETDRS visual acuity charts and light box system at month 12. Individual patients with an uncorrected visual acuity of 20/40, or better, were considered to have a successful visual outcome for this assessment.

Predictability of Refractive Effect

Predictability of the refractive effect was assessed by comparing the patient's intended correction with the achieved correction (cycloplegic refraction spherical equivalent) at month 12.

Stability of Refractive Effect
Stability of the refractive effect was assessed between the month 3 and the month 6 exam and confirmed at subsequent time points, by comparing the change in the patient's refraction (manifest refraction spherical equivalent) for the operative eye between consecutive postoperative exams.

SAFETY ASSESSMENTS

Maintenance of Best Spectacle-Corrected Visual Acuity
Maintenance of BSCVA in the operative eye was evaluated using the ETDRS visual acuity chart at the month 12 postoperative exam. This assessment was made by comparing the patient's preoperative and postoperative BSCVA. A significant loss was considered to be two or more lines or 10 or more letters on the ETDRS chart.

Loss of Best Spectacle-Corrected Visual Acuity
Loss of BSCVA was assessed at month 12. This assessment was made by tabulating the number of eyes that had significant loss of best-spectacle-corrected visual acuity to levels worse than 20/40. This acuity level was picked because it is the legally defined level of vision for a driver's license in most states.

Induced Manifest Refraction Cylinder
Manifest refraction cylinder at month 12 was assessed by measuring the absolute postoperative cylinder minus the absolute preoperative cylinder. The assessment was made on the percentage of eyes that had an increase in absolute cylinder of 1.00 to 2.00 D relative to the preoperative value.

Maintenance of Contrast Mesopic Sensitivity
Contrast sensitivity was tested under mesopic conditions at 5 spatial frequencies, with and without glare, at month 12 for the patients in the second-phase of the study. Contrast sensitivity was assessed using a FACT (Functional Acuity Contrast Test) chart contained within a view-in tester designed and built by Vision Sciences Research Corporation (San Ramon, CA). The test was performed for the initial implant eye at the preoperative, month 6, and month 12 exams, and for the fellow eye at the preoperative and month 6 exams. The test was repeated twice for each eye at each exam to control for variability.

The functional threshold for each eye was used for this analysis. Functional threshold was defined as the lowest contrast grating "patch" on the FACT chart noted as visible by the patient and read correctly. The contrast gratings were read in order of decreasing contrast within each spatial frequency. The mean of the contrast score for the functional

threshold from each of the 2 readings represented the patient's score for the spatial frequency. A log transformation of the mean score was used for analysis, since the contrast scores form an exponential scale and the assessment criterion was specified in log units.

A successful assessment was that the mean change in contrast sensitivity, relative to the preoperative baseline measurements, should not have decreased by more than 0.1 log unit and be outside the accepted normal range for individual readings.

Maintenance of Endothelial Cell Counts

The mean central and peripheral endothelial cell counts for the preoperative, month 6, and month 12 exams were analyzed for the patients in the second-phase of this study. The assessment was made against the criterion that the mean postoperative endothelial cell count for each region should not have significantly decreased from the preoperative value at the month 12 exam. Additionally, the coefficient of variation and the percent of hexagonal cells should not change significantly in the first postoperative year.

Population Analysis

The primary efficacy analyses are reported on the evaluated patients with results available at the specified follow-up exams. Patients who had the ICRS removed, missed a specified exam, did not perform the test, or were lost to follow-up were not included.

Study Population

I enrolled 29 patients and 49 eyes in the first phase of this study, and 45 patients and 76 eyes in the second-phase (Table III). I combined these 2 phases to report on 74 patients as the total study population in this report. Initial eyes and contralateral eyes were combined as well.

The distribution, by ICRS thickness, for the 125 implanted eyes was as follows: 25 implanted with the 0.25 mm ICRS, 39 implanted with the 0.30

TABLE III: ENROLLMENT BY INVESTIGATIONAL SITE

INVESTIGATIONAL SITE	PATIENTS ENROLLED	INITIAL EYES	CONTRALATERAL EYES	TOTAL EYES
First Phase – Institution 1	45	45	31	76
Second-phase – Institution 2	29	29	20	49
Total	74	74	51	125

mm ICRS, 41 implanted with the 0.35 mm ICRS, 9 implanted with the 0.40 mm ICRS, and 11 implanted with the 0.45 mm ICRS.

These 125 eyes completed the preoperative examination and underwent the surgery. Because 3 patients missed the month 3 exam that exam was completed by 122 eyes (74 initial eyes and 48 contralateral eyes). The 6-month exam was completed by 124 eyes (73 initial eyes and 51 contralateral eyes). One patient had the ICRS explanted after the 3-month examination. The month 12 exam was completed by 89 eyes (69 initial eyes and 20 contralateral eyes). Thirty-six patients did not have a month 12 exam. An accounting of these 36 eyes is listed below.

- Thirty-one contralateral eyes had not yet reached the 1-year point.
- Two patients (11337-D-1 and 11318-D-1) missed the time window of the month 12 exam; however, they still participate in the study.
- One patient (11319-S-1) was lost to follow-up.
- Two patients (10067-S-1 and 11345-D-1) had the ICRS removed (both segments) prior to the month 12 exam.

An accounting of the implant eyes evaluated at each exam is provided in Table IV. Accountability was excellent for all exams throughout this reporting period. From Table IV, the number of eyes available for analysis per exam represents the total number of evaluable patients' eyes. Any deviations from this number for a specific test have been documented within the "Results" section for the particular test. The denominator used to compute the percentages for a test result was based on the number of patients' eyes evaluated at each exam.

Patient Demographics

Table V summarizes patient demographics and baseline characteristics for the 125 successfully implanted eyes. Patients ranged in age from 22 to 60 years, with a mean of 40.1 years. Thirty-three of the 74 patients (44.6%) were female and 41 (55.4%) were male. Sixty-one (82%) were Caucasian, 6 (8.1%) were Hispanic, 2 (2.7%) were black, 4 (5.4%) were Asian, and 1 (1.4%) was categorized as "other." Surgery was performed on 36 right eyes (48.6%) and on 38 left eyes (51.4%). Eye dominance information was available for the second-phase patients only. Of the 45 second-phase implant patients, 44 (97.8%) had the dominant eye implanted and 1 (2.2%) had the nondominant eye implanted. Recent contact lens use, broken down by type of contact lens, was collected for the second-phase implant patients. Recent contact lens use was as follows: 20 of 45 (44.4%) used soft contact lenses, and 25 (55.6%) were not using contact lenses when they enrolled in this trial.

TABLE IV: CUMULATIVE PATIENTS' EYE ACCOUNTABILITY BY EXAM

	TOTAL ENROLLED EYES	EYES AVAILABLE FOR ANALYSIS	EYES DISCONTINUED	EYES NOT ELIGIBLE°	EYES LOST TO FOLLOW-UP AND MISSED EXAMS	ACCOUNTABILITY† N/N	%
Month 3	125	122	0	0	3	122/125	97.6%
Month 6	125	124	0	1	0	124/124	100%
Month 12	125	89	0	35	1	89/90	98.9%

° Refers to those patients' eyes who had the ICRS removed.

† Accountability is defined as eyes available for analysis divided by total eyes enrolled [eyes enrolled - eyes discontinued - eyes not eligible].

TABLE V: DEMOGRAPHICS FOR IMPLANT PATIENTS

	N/N	%
Sex		
Female	33/74	44.6%
Male	41/74	55.4%
Race		
Caucasian	61/74	82.4%
Hispanic	6/74	8.1%
black	2/74	2.7%
Asian	4/74	5.4%
Other	1/74	1.4%
Implanted eye		
Right	36/74	48.6%
Left	38/74	51.4%
Age (yr)	74/74	100%
Mean	40.08	—
Standard Deviation	7.69	—
Minimum	22	—
Maximum	60	—
Current contact lens use		
None	25/45	55.6%
Soft, RGP, PMMA	20/45	44.4%

Table VI provides the distribution of refractive parameters at the preoperative baseline. All of the patients' eyes had a cycloplegic refraction spherical equivalent (CRSE) and manifest refraction spherical equivalent (MRSE) between -1.00 D and -4.50 D in a fairly equal distribution. This is expected, since patients were recruited to fill the continuous refractive range of corrections for the 5 ICRS thicknesses tested in the study.

All of the patients had less than +1.00 D of manifest refraction cylinder and 66 of 125 (52.8%) did not have any measurable cylinder.

RESULTS

EFFICACY ASSESSMENT

Of the 125 implanted eyes in this study, month 12 follow-up data were available for 89 eyes. The sample size evaluated for each efficacy parameter is specified and may differ from these totals owing to missed ophthalmic tests within the exam.

Uncorrected Visual Acuity

Uncorrected visual acuity data were available for 100% of the eyes for the preoperative exam and the first postoperative exam; 98.4% of the eyes at

TABLE VI: REFRACTIVE PARAMETERS AT PREOP FOR IMPLANT PATIENTS' EYES

A. PREOPERATIVE REFRACTIVE PARAMETERS (CYCLOPLEGIC REFRACTION SPHERICAL EQUIVALENT – CRSE)

	INITIAL EYE		CONTRALATERAL EYE		TOTAL	
SPHERICAL EQUIVALENT	FREQUENCY	%	FREQUENCY	%	FREQUENCY	%
1.00 – 1.99 D	21	28.4	12	23.5	33	26.4
2.00 - 2.99 D	27	36.5	21	41.2	48	38.4
3.00 – 3.99 D	14	18.9	9	17.6	23	18.4
4.00 – 4.50 D	12	16.2	9	17.6	21	16.8

B. PREOPERATIVE REFRACTIVE PARAMETERS (MANIFEST REFRACTION SPHERICAL EQUIVALENT – MRSE)

	INITIAL EYE		CONTRALATERAL EYE		TOTAL	
SPHERICAL EQUIVALENT	FREQUENCY	%	FREQUENCY	%	FREQUENCY	%
1.00 – 1.99 D	21	28.4	10	19.6	31	24.8
2.00 - 2.99 D	24	32.4	22	43.1	46	36.8
3.00 – 3.99 D	18	24.3	10	19.6	28	22.4
4.00 – 4.50 D	11	14.9	9	17.6	20	16.0

C. PREOPERATIVE REFRACTIVE PARAMETERS (MANIFEST CYLINDER)

	INITIAL EYE		CONTRALATERAL EYE		TOTAL	
CYLINDER	FREQUENCY	%	FREQUENCY	%	FREQUENCY	%
0.00 D	35	47.3	31	60.8	66	52.8
0.25 D	9	12.2	4	7.8	13	10.4
0.50 D	12	16.2	9	17.6	21	16.8
0.75 D	16	21.6	7	13.7	23	18.4
1.00 D	2	2.7	0		2	1.6

the 1 month exam; 97.6% of the eyes at the month 3 exam; 99.2% of the eyes at the month 6 exam; and 100% of the 89 evaluable eyes at the month 12 exam. Table VII provides the distribution of UCVA results for the preoperative, day 1, month 1, month 3, month 6, month 9, and month 12 exams. Figure 1 plots the percentage of eyes that were ≤ 20/16, ≤ 20/20, and ≤ 20/40 at each of these time points.

On the first postoperative day, 112/125 (89.6%) eyes had UCVA of

TABLE VII: UNCORRECTED VISUAL ACUITY OVER TIME

	PREOP		DAY 1		MONTH 1		MONTH 3		MONTH 6		MONTH 12	
UCVA	N/N	%*	N/N	%	N/N	%	N/N	%	N/N	%	N/N	%
20/12.5 or Better	0/125	0%	2/125	1.6%	9/123	7.3%	21/122	17.2%	16/124	12.9%	14/89	15.7%
20/16 or Better	0/125	0%	13/125	10.4%	36/123	29.3%	53/122	43.4%	54/124	43.5%	32/89	36%
20/20 or Better	0/125	0%	41/125	32.8%	67/123	54.5%	89/122	73%	87/124	70.2%	55/89	61.8%
20/25 or Better	1/125	0.8%	68/125	54.4%	85/123	69.1%	106/122	86.9%	107/124	86.3%	78/89	87.6%
20/40 or Better	11/125	8.8%	112/125	89.6%	103/123	83.7%	117/122	95.9%	117/124	94.4%	86/89	96.6%
20/50 to 20/100	47/125	37.6%	12/125	9.6%	18/123	14.6%	5/122	4.1%	6/124	4.8%	3/89	3.4%
20/125 or Worse	67/125	53.6%	1/125	1%	2/123	1.6%	0/122	0%	1/124	.8%	0/89	0%
Total Evaluated	125	--	125	--	123	--	122	--	124	--	89	--
Not Reported	0	--	0	--	2	--	3	--	1	--	0	--
Total Evaluable	125	--	125	--	125	--	125	--	125	--	89	--

*Cumulative percentages.

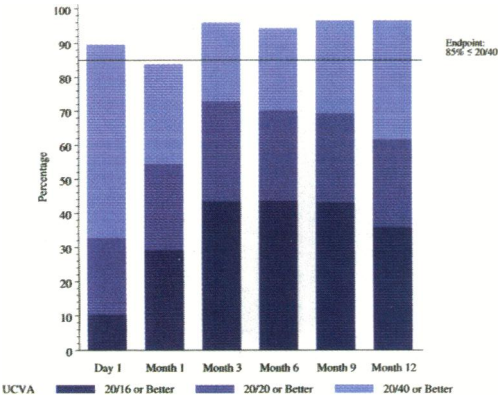

FIGURE 1
Percentage of eyes that are ≤ 20/16, ≤ 20/20, and ≤ 20/40 at day 1, and months 1 ,3, 6 ,9, 12.

20/40 or better, 41/125 (32.8%) eyes had UCVA of 20/20 or better, 13/125 (10.4%) eyes had UCVA of 20/16 or better, and 2/125 (1.6%) eyes had UCVA of 20/12.5 or better.

By the month 1 exam, 103/123 (83.7%) eyes had UCVA of 20/40 or better, 67/123 (54.5%) eyes had UCVA of 20/20 or better, 36/123 (29.3%) eyes had UCVA of 20/16 or better, and 9/123 (7.3%) eyes had UCVA of 20/12.5 or better.

By the month 3 exam, 117/122 (95.9%) eyes had UCVA of 20/40 or better, 89/122 (73%) eyes had UCVA of 20/20 or better, 53/122 (43.4%) eyes had UCVA of 20/16 or better, and 21/122 (17.2%) eyes had UCVA of 20/12.5 or better.

By the month 6 exam, 117/124 (94.4 %) eyes had UCVA of 20/40 or better, 87/124 (70.2 %) eyes had UCVA of 20/20 or better, 54/124 (43.5 %) eyes had UCVA of 20/16 or better, and 16/124 (12.9 %) eyes had UCVA of 20/12.5 or better.

By the month 12 exam, 86/89 (96.6 %) eyes had UCVA of 20/40 or better, 55/89 (61.8 %) eyes had UCVA of 20/20 or better, 32/89 (36 %) eyes had UCVA of 20/16 or better, and 14/89 (15.7 %) eyes had UCVA of 20/12.5 or better.

Of the 89 eyes evaluated at the month 12 exam, 3 eyes (3.4 %) had UCVA worse than 20/40. Table VIII provides a listing of visual acuity and refractive data for these 3 patients' eyes.

Table IX summarizes the number and percentage of evaluated patients with UCVA results of 20/40 or better and 20/20 or better at month 12, by ICRS thickness and combined. Overall, 86 of 89 eyes (97%) had UCVA of 20/40 or better. The results by ICRS thickness range from 89% to 100%.

TABLE VIII: PATIENTS' EYES WITH UNCORRECTED VISUAL ACUITY WORSE THAN 20/40 AT MONTH 12 (N/N = 14/410)

PATIENT'S ID	ICRS (MM)	AGE/ SEX	EXAM	UCVA	BSCVA	MANIFEST REFRACTION	MRSE	CYCLOPLEGIC REFRACTION	CRSE	PREDICTED RESIDUAL ERROR°
10043-S-1	0.45	43/F	Preop	20/200	20/12.5	-5.00 + 0.75 x 105°	-4.63	5.25 + 0.75 x 110°	-4.88	-
			Month 6	20/63	20/20	-3.00 + 2.25 x 115°	-	-2.75 + 1.75 x 125°	-1.88	-0.78
			Month 12	20/50	20/16	-2.25 + 2.00 x 105°	-1.88 - -1.25	-1.75 + 1.25 x 95°	-1.13	-0.78
10050-S-2	0.35	46/F	Preop	20/160	20/16	-3.00 + 0.00 x 0°	-3.00	-3.25 + 0.00 x 0°	-3.25	-
			Month 6	20/50	20/16	-1.00 + 0.00 x 0°	-1.00	-1.00 + 0.00 x 0°	-1.00	-0.55
			Month 12	20/63	20/16	-1.50 + 0.00 x 0°	-1.50	1.00 + 0.50 x 90°	-0.75	-0.55
10071-D-2	0.40	45/M	Preop	20/160	20/12.5	-4.00 + 0.00 x 0°	-4.00	-4.00 + 0.00 x 0°	-4.00	-
			Month 6	20/50	20/16	-1.25 + 0.0 x 0°	-1.25	-1.25 + 0.00 x 0°	-1.25	-0.60
			Month 12	20/50	20/16	-1.25 + 0.50 x 105°	-1.00	-1.00 + 0.00 x 0°	-1.00	-0.60

Predicted Residual Error is calculated by subtracting the predicted correction for the ICRS thickness from the Preoperative Manifest Refraction Spherical Equivalent (MRSE)

BSCVA, best spectacle-corrected visual acuity; CRSE, cycloplegic refraction spherical equivalent; ICRS, intrastromal corneal ring segments; MRSE, manifest refraction spherical equivalent; UCVA, uncorrected visual acuity.

° Calculated by subtracting predicted correction for ICRS thickness from preoperative MRSE.

TABLE IX: ANALYSIS OF UNCORRECTED VISUAL ACUITY AT MONTH 12 ALL EVALUATED PATIENTS

ICRS THICKNESS	N	20/40 OR BETTER N	%	(95% CI)	20/20 OR BETTER N	%	(95% CI)
0.25 mm	18	18	100%	(78.1%, 99.5%)	13	72%	(46.4%, 89.3%)
0.30 mm	24	24	100%	(82.8%, 99.6%)	19	79%	(57.3%, 92.1%)
0.35 mm	27	26	96%	(79.1%, 99.8%)	15	56%	(35.6%, 74%)
0.40 mm	9	8	89%	(50.7%, 99.4%)	4	44%	(15.3%, 77.3%)
0.45 mm	11	10	91%	(57.1%, 99.5%)	4	36%	(12.4%, 68.4%)
All	89	86	97%	(89.8%, 99.1%)*	55	62%	(50.8%, 71.7%)†

* P = .199, two-tailed Fisher's exact test, comparing the 5 ICRS sizes.
† P = .074, two-tailed Fisher's exact test, comparing the 5 ICRS sizes.

The difference in the results for 20/40 or better among ICRS thicknesses was not statistically significant (P= 0.199). Fifty–five of 89 eyes (62%) had UCVA of 20/20 or better. The difference in the results for 20/20 or better among ICRS thicknesses was not statistically significant (P=.074).

Figure 2 plots the number of patients' eyes for which UCVA was 20/16 or better, 20/20 or better, or 20/40 or better at month 12. There were no patients' eyes worse than 20/100 at the month 12 exam.

Predictability of Refractive Outcome

By comparing the patients' intended correction with the achieved correction based on the difference in the CRSE, I assessed the predictability of the refractive effect of the ICRS. One hundred twenty-two of 125 study eyes (97.6%) were assessed for predictability of refractive effect at the

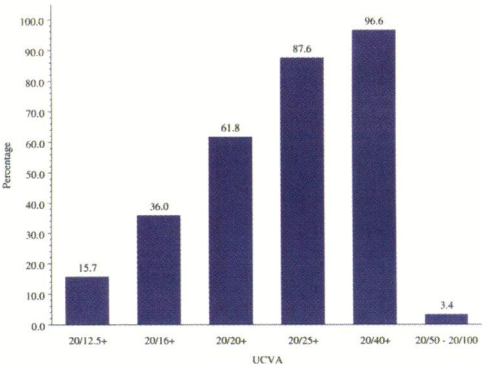

FIGURE 2

Uncorrected visual acuity at month 12.

month 3 exam. One hundred twenty-four of 125 study eyes (99.2%) were assessed for predictability of refractive effect at the month 6 exam. Eighty-nine of 89 study eyes (100%) were assessed for predictability of refractive effect at the month 12 exam. Three patients at the month 3 exam and 1 patient at the month 12 exam did not have cycloplegic refraction testing performed.

Figure 3 shows the percentage of patients' eyes within ± 1.00 D and ± 0.50 D at the month 3, month 6, and month 12 exams. Table X provides a summary of predictability of refractive effect at months 3, 6, and 12. Table X also provides the number of patient's eyes who were overcorrected by more than 1.00 D, overcorrected by more than 2.00 D, undercor-

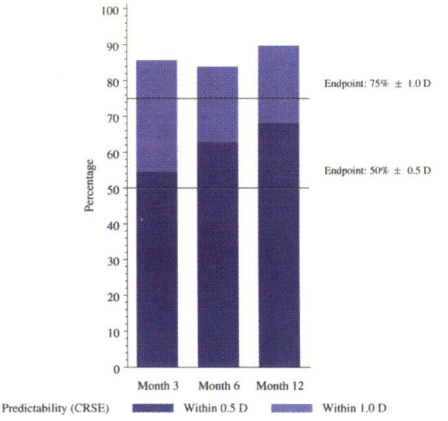

FIGURE 3
Percentage of patients ± 1.00 D and ± 0.50 D at the month 3, month 6, and month 12 exams.

rected by more than 1.00 D, and undercorrected by more than 2.00 D.

Based on CRSE, 9 (10%) of 88 evaluated eyes had a greater than 1.00 D deviation from the intended correction at month 12. Of these 9 eyes, 3 (33%) were undercorrected and 6 (67%) were overcorrected. Of the 3 patients' eyes that were undercorrected by more than 1.00 D, all 3 (100%) had UCVA of 20/40 or better. Of the 6 patients' eyes that were overcorrected by more than 1.00 D, all 6 (100%) had UCVA of 20/40 or better, and 4 of 6 (67%) had UCVA of 20/20 or better. Of the 9 patients' eyes that had a greater than 1.00 D deviation from their intended correction at month 12, 9 of 9 (100%) had UCVA of 20/25 or better, and 5 of 9 (56%) had UCVA of 20/20 or better.

Table XI summarizes the average correction achieved for each ICRS

TABLE X: PREDICTABILITY OF REFRACTIVE EFFECT BASED ON CRSE°

	MONTH 3		MONTH 6		MONTH 12	
DEVIATION FROM INTENDED CORRECTION (D)	N/N	%	N/N	%	N/N	%
± 0.50 D	65/119	55%	78/124	63%	60/88	68%
± 1.00 D	102/119	86%	104/124	84%	79/88	90%
± 1.50 D	116/119	97%	120/124	97%	88/88	100%
± 2.00 D	119/119	100%	123/124	99%	88/88	100%
>2.00 D	0/119	0%	1/124	1%	0/88	0%
Total Evaluated	122	–	124	–	89	–
Not Reported	3	–		–	1	–
Total Evaluable	119	–	124	–	88	–
Overcorrected >+1.00 D	12/119	10%	14/124	11%	6/88	7%
Overcorrected >+2.00 D	0/119	0%	1/124	1%	0/88	0%
Undercorrected <-1.00 D	5/119	4%	6/124	5%	3/88	3%
Undercorrected <-2.00 D	0/119	0%	0/124	0%	0/88	0%
Total Evaluated	122	–	124	–	89	–
Not Reported	3	–	0	–	1	–
Total Evaluable	119	–	124	–	88	–

°CRSE, cycloplegic refraction spherical equivalent.

thickness based on CRSE at month 12. The difference between the predicted correction and the average achieved correction for each ICRS size ranges from within 0.02 D for the 0.45 mm ICRS thickness to within 0.27 D for the 0.35 mm ICRS thickness. The standard deviation ranges from 0.37 D for the 0.25 mm ICRS thickness to 0.91 D for the 0.45 mm ICRS thickness.

Table XII provides an analysis of predictability of refractive effect (based on CRSE) for evaluated eyes across the 5 ICRS thicknesses at

TABLE XI: SUMMARY OF CORRECTION ACHIEVED AT MONTH 12 BASED ON CRSE°

ICRS THICKNESS (MM)	NO. OF PATIENTS	NOMINALLY PREDICTED CORRECTION(D)	AVERAGE ACHIEVED CORRECTION(D)	SD
0.25	18	-1.30	-1.53	0.45
0.30	24	-2.00	-2.09	0.37
0.35	26	-2.70	-2.97	0.54
0.40	9	-3.40	-3.29	0.61
0.45	11	-4.10	-4.08	0.91

°CRSE, cycloplegic refraction spherical equivalent.

TABLE XII: ANALYSIS OF PREDICTABILITY OF REFRACTIVE EFFECT (CRSE) AT MONTH 12 EVALUATED PATIENTS' EYES

		WITHIN ± 0.50 D			WITHIN ± 1.00 D		
ICRS THICKNESS	N	N	%	(95% CI)	N	%	(95% CI)
0.25 mm	18	12	67%	(41.2%, 85.6%)	17	94%	(70.6%, 99.7%)
0.30 mm	24	22	92%	(71.5%, 98.5%)	24	100%	(82.8%, 99.6%)
0.35 mm	26	16	62%	(40.7%, 79.1%)	22	85%	(64.3%, 95%)
0.40 mm	9	6	67%	(30.9%, 91%)	8	89%	(50.7%, 99.4%)
0.45 mm	11	4	36%	(12.4%, 68.4%)	8	73%	(39.3%, 92.7%)
All	88	60	68%	(57.3%, 77.5%)*	79	90%	(81%, 94.9%)†

MRSE, manifest refraction spherical equivalent.

* $P = .012$, two-tailed Fisher exact test, comparing the 5 ring sizes.

† $P = .069$, two-tailed Fisher exact test, comparing the 5 ring sizes.

month 12. Overall, 60 of 88 eyes (68%) were within 0.50 D of their intended correction at month 12. Seventy-nine of 88 eyes (90%) were within 1.00 D of their intended correction at month 12. There was a statistically significant difference among the 5 ICRS thickness groups at the month 12 exam for those patients' eyes corrected to within ±0.50 D of intended correction (P=.012). There was no significant difference for those patients' eyes corrected to within ±1.00 D of intended correction (P=.069).

Predictability of Refractive Effect Based on MRSE. Predictability of refractive effect was also analyzed based on manifest refraction spherical equivalent (MRSE) to evaluate whether a difference in predictability exists between MRSE and CRSE. Table XIII provides an analysis of predictability based on MRSE at months 3, 6, and 12.

Table XIV provides an analysis of predictability of refractive effect (based on MRSE) for eyes across the 5 ICRS thicknesses at month 12. Overall, 58 (65%) of 89 eyes were within ±0.50 D of their intended correction at month 12. Eighty-one of 89 eyes (91%) were within ±1.00 D of their intended correction at month 12. The differences among the 5 ICRS thickness groups at the month 12 exam in the proportions of patients' eyes within ±0.50 D and ±1.00 D were not statistically significantly different (P = .612 and P=.111, respectively).

The manifest refraction data demonstrate that the ICRS product, grouping the 5 thicknesses evaluated, has predictable refractive outcomes. The performance of the 0.45 mm ICRS in this limited number of eyes, however, was less predictable.

TABLE XIII: PREDICTABILITY OF REFRACTIVE EFFECT BASED ON MRSE

	MONTH 3		MONTH 6		MONTH 12	
DEVIATION FROM INTENDED CORRECTION (D)	N/N	%	N/N	%	N/N	%
± 0.50 D	77/122	63%	85/124	69%	58/89	65%
± 1.00 D	108/122	89%	111/124	90%	81/89	91%
± 1.50 D	113/122	93%	118/124	95%	86/89	97%
± 2.00 D	118/122	97%	122/124	98%	89/89	100%
>2.00 D	4/122	3 %	2/124	2 %	0/89	0%
Total Evaluated	122	--	124	--	89	--
Not Reported	0	--	0	--	0	--
Total Evaluated	122	--	124	--	89	--

MRSE, manifest refraction spherical equivalent

The proportions of evaluated patients' eyes corrected to within ±1.00 D were comparable for both MRSE and CRSE at month 12. Furthermore, analyses of the discordance between MRSE and CRSE predictability revealed no statistically significant difference for any and all ICRS thicknesses ($P > .15$, goodness of fit, chi square). The results clearly demonstrate that manifest refraction provides comparable predictability to cycloplegic refraction.

Table XV charts the average correction of the manifest refraction for

TABLE XIV: ANALYSIS OF PREDICTABILITY OF REFRACTIVE EFFECT (MRSE) AT MONTH 12

	WITHIN ± 0.50 D				WITHIN ± 1.00 D		
ICRS THICKNESS	N	N	%	(95% CI)	N	%	(95% CI)
0.25 mm	18	12	67%	(41.2%, 85.6%)	18	100%	(78.1%, 99.5%)
0.30 mm	24	17	71%	(48.8%, 86.6%)	23	96%	(76.9%, 99.8%)
0.35 mm	27	17	63%	(42.5%, 79.9%)	24	89%	(69.7%, 97.1%)
0.40 mm	9	7	78%	(40.2%, 96.1%)	8	89%	(50.7%, 99.4%)
0.45 mm	11	5	45%	(18.1%, 75.4%)	8	73%	(39.3%, 92.7)
All	89	58	65%	(54.3%, 74.8%)°	81	91%	(82.6%, 95.8%)†

MRSE, manifest refraction spherical equivalent.

° $P = .612$, two-tailed Fisher's exact test, comparing the 5 ICRS sizes.

† $P = .111$, two-tailed Fisher's exact test, comparing the 5 ICRS sizes.

TABLE XV: SUMMARY OF CORRECTION ACHIEVED AT MONTH 12 BASED ON MRSE

ICRS THICKNESS (MM)	NO. OF PATIENTS	NOMINALLY PREDICTED CORRECTION (D)	AVERAGE ACHIEVED CORRECTION (D)	SD
0.25	18	-1.30	-1.61	0.37
0.30	24	-2.00	-2.00	0.55
0.35	27	-2.70	-2.75	0.57
0.40	9	-3.40	-3.39	0.55
0.45	11	-4.10	-3.85	0.94

MRSE, manifest refraction spherical equivalent.

each of the 5 ICRS thicknesses. The standard deviation in the manifest refraction appeared to be larger in the thicker ring sizes, but the sample sizes are small and not statistically significant.

Stability of Refractive Effect

Stability of refractive effect was assessed as the change in manifest refraction spherical equivalent (MRSE) for 4 time intervals: the month 1 to month 3 exams, the month 3 to month 6 exams, the month 6 to month 9 exams, and the month 9 to month 12 exams. The MRSE for each eye was utilized because this measurement best represented the patients' natural state of vision correction.

Figure 4 illustrates the stability of refractive effect for all evaluable eyes across all thicknesses combined. The change in MRSE is summarized for the 4 analysis time intervals. The mean change in MRSE was plotted for each time interval with the vertical bars representing two standard deviations above and below the mean, or an estimate of the 95% distribution. Table XVI provides the descriptive statistics used in Figure 4, as well as the number of patients' eyes with a change of 1.00 D MRSE or less and 0.50 D MRSE or less between consecutive exams. Ninety-nine of 120 eyes (83%) were within 1.00 D of the previous exam at month 3. At the month 6 exam, 116 of 121 eyes (96%) were within 1.00 D of the month 3 exam. At the month 9 exam 85 of 88 eyes (97%) were within 1.00 D of the month 6 exam, and at the month 12 exam 85 of 85 (100%) were within 1.00 D of the month 9 exam. The result for this subset of patients' eyes was the same as, or slightly better than, the overall result for all evaluated patients' eyes. The refractive stability, therefore, for the month 3 to the month 6 interval exceeded the study assessment criterion. Refractive stability was also demonstrated for all subsequent exams.

Table XVII summarizes the stability of refractive effect by ICRS thickness and across all thicknesses combined at the following intervals:

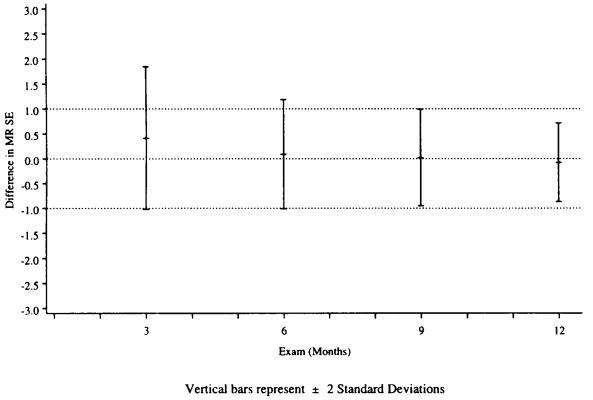

FIGURE 4
Stability of refractive effect for all evaluable eyes at the month 3, month 6, month 9, and month 12 exams,

between the month 3 and the month 6 exams, the month 6 and month 9 exams, and the month 9 and month 12 exams. Overall, 116 of 121 of evaluated eyes (96%) had a change in manifest refraction of 1.00 D or less from their month 3 to month 6 exams. The results by ICRS thickness ranged from 78% to 100% during this interval. There was no statistically significant difference in stability among thicknesses over the month 3 to month 6 time interval (P=.130), nor for the subsequent time intervals. Eighty-five of 88 eyes (97%) had a change in manifest refraction of 1.00 D or less from month 6 to month 9, and the results by ICRS thickness ranged from 91% to 100%. Eighty-five of 85 eyes (100%) had a change in manifest

TABLE XVI: SUMMARY OF STABILITY OF MRSE ALL EVALUATED PATIENTS' EYES OVER TIME

CHANGE IN SE BETWEEN	MONTH 1 TO MONTH 3	MONTH 3 TO MONTH 6	MONTH 6 TO MONTH 9	MONTH 9 TO MONTH 12
Within ± 0.50 D	74/120 (62%)	97/121 (80%)	71/88 (81%)	71/85 (84%)
Within ± 1.00 D	99/120 (83%)	116/121 (96%)	85/88 (97%)	85/85 (100%)
Mean Difference (D)	0.41	0.09	0.02	-0.08
Std Dev (D)	0.72	0.55	0.49	0.40
95% CI (D)	0.28 to 0.54	-0.01to 0.19	-0.08 to 0.12	-0.16 to 0.01
95% Distribution (D)	-1.02 to 1.85	-0.99 to 1.17	-0.95 to 0.99	-0.87 to 0.72

MRSE, manifest refraction spherical equvalent.

TABLE XVII: ANALYSIS OF STABILITY OF REFRACTIVE EFFECT MRSE ALL EVALUATED PATIENTS' EYES

	MONTH 3 TO MONTH 6 WITHIN ± 1.00 D			MONTH 6 TO MONTH 9 WITHIN ± 1.00 D			MONTH 9 TO MONTH 12 WITHIN ± 1.00 D		
ICRS THICKNESS	N/N	%	(95% CI)	N/N	%	(95% CI)	N/N	%	(95% CI)
0.25 mm	23/24	96%	(-0.08 to 0.15)	19/21	91%	(-0.10 to 0.20)	18/18	100%	(-0.14 to 0.14)
0.30 mm	36/38	95%	(-0.15 to 0.13)	24/24	100%	(-0.14 to 0.24)	24/24	100%	(-0.12 to 0.07)
0.35 mm	39/39	100%	(-0.15 to 0.15)	23/23	100%	(-0.10 to 0.28)	23/23	100%	(-0.41 to –003)
0.40 mm	7/9	78%	(0.12 to 0.59)	9/9	100%	(-0.11 to 0.25)	9/9	100%	(-0.59 to 0.07)
0.45 mm	11/11	100%	(-0.15 to 0.52)	10/11	91%	(-0.20 to 0.50)	11/11	100%	(-0.27 to 0.54)
All	116/121	96%	(-0.03 to 0.12)°	85/88	97%	(-0.01 to 0.16)†	85/85	100%	(-0.16 to 0.01) ‡

MRSE, manifest refraction spherical equivalent.

° P = .130, Two-Tailed Fisher's exact test, comparing the 5 ICRS sizes.

† P = .197, Two-Tailed Fisher's exact test, comparing the 5 ICRS sizes.

‡ Two-tailed Fisher exact test not applicable.

refraction of 1.00 D or less from month 9 to month 12, and the results by ICRS thickness were also 100%. Refractive stability was achieved at the month 3 time point and maintained through the month 12 time point for all 5 ICRS thicknesses.

Constant "N" Analysis. The results of the refractive stability analysis were further confirmed for the subset of patients who had manifest refraction data available at each of the month 1, 3, 6, 9, and 12 exams. A total of 85 eyes in this cohort had manifest refraction data available at all 5 of these exams. Figure 5 plots the mean MRSE change and the standard deviation for the mean change between consecutive exams for these 85 eyes. Table XVIII provides a summary of the number and percentage of patients with a change in MRSE of 1.00 D or less and 0.50 D or less between exams, and the mean change between exams for this subset of patients.

Refractive stability was achieved at month 3 as demonstrated by the proportion of patients with a change of 1.00 D or less MRSE from the month 3 to the month 6 exam. Eighty of 85 patients (94%) had an MRSE at the month 3 exam within 1.00 D of the month 6 MRSE. Refractive stability was also demonstrated for all subsequent time intervals.

Keratometry

The change in keratometry was tabulated at 1 year after ICRS implantation (Table XIX). There was a progressive flattening of the corneal curvature with each increase in ICRS thickness ($P<.0001$). In general, the mean change in keratometry correlated with the mean change in refraction for

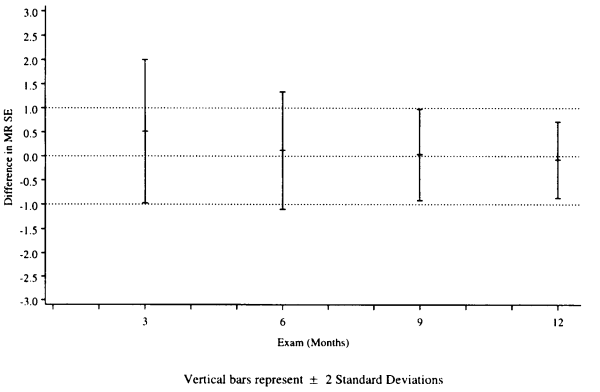

FIGURE 5

Stability of refractive effect of eyes that were evaluated at all time points (N=85) with a change of 1.00 D MRSE or less between consecutive exams.

TABLE XVIII: SUMMARY OF STABILITY OF MRSE SUBSET OF PATIENTS' EYES PRESENT AT ALL EXAMS CONSTANT "N" ANALYSIS

CHANGE IN SE BETWEEN	MONTH 1 TO MONTH 3	MONTH 3 TO MONTH 6	MONTH 6 TO MONTH 9	MONTH 9 TO MONTH 12
Within ± 0.50 D	49/85 (58%)	67/85 (79%)	69/85 (81%)	71/85 (84%)
Within ± 1.00 D	67/85 (79%)	80/85 (94%)	83/85 (98%)	85/85 (100%)
Mean Difference (D)	0.51	0.12	0.03	-0.08
Std. Dev. (D)	0.74	0.61	0.47	0.40
95% CI (D)	0.35 to 0.68	-0.01 to 0.25	-0.07 to 0.14	-0.16 to 0.01
95% Distribution (D)	-0.97 to 2.00	-1.10 to 1.34	-0.92 to 0.98	-0.87 to 0.72

MRSE, manifest refraction spherical equivalent.

each of the ICRS thicknesses. The standard deviation of the postoperative keratometry as well as the change in keratometry at 12 months increased with thicker ICRS.

Corneal Topography

Corneal topography was collected by the independent observer as part of this trial for the purpose of providing additional information in the event of an anomalous result. The corneal topography following ICRS implantation is unique to myopic refractive surgical procedures. In general, the prolate shape of the cornea is maintained over the central optical zone (Fig 6). The topography with the 0.40 mm and 0.45 mm ICRS is more variable with occasional enhancement of the prolate shape with enhancement of asphericity (Fig 7). Analysis of the surface quality using the Holladay diagnostic software package (Version 3.1, Eye Sys, Inc., Houston, TX) demonstrated a high-quality anterior corneal surface (Fig 8). The predicted corneal acuity for this eye was 20/10.

TABLE XIX: CHANGE IN KERATOMETRY°

RING SIZE	EYES N=89	MEAN PREOP K (SD)		MEAN-12 MO. POST-OP K (SD)		MEAN 12-MO. CHANGE (SD)	
0.25 mm	18	43.57	(1.33)	42.08	(1.56)	-1.47	(0.38)
0.30 mm	24	43.47	(1.11)	41.57	(1.34)	-1.89	(0.47)
0.35 mm	27	43.31	(1.69)	40.57	(1.95)	-2.77	(0.65)
0.40 mm	9	43.46	(1.86)	40.33	(2.61)	-3.13	(0.96)
0.45 mm	11	44.16	(1.42)	40.16	(1.82)	-3.94	(1.06)

°K, keratometry; Kruskal-Wallis among groups ($P < .0001$).

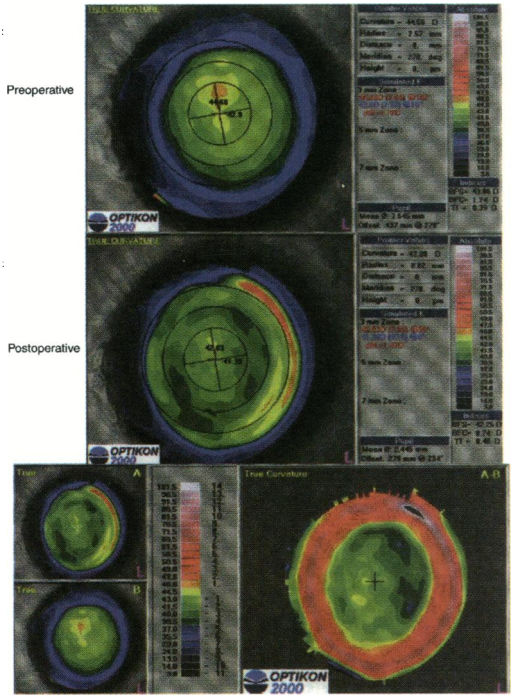

FIGURE 6
Typical corneal topography following ICRS implantation. It is unique among myopic refractive surgical procedures in that prolate shape of the cornea is maintained over the central optical zone.

Predictors of Efficacy Outcome
Efforts to identify predictors of positive efficacy outcomes were made by 2 approaches:

1. A univariate approach that sought to identify the strength of association between each demographic or preoperative variable and the outcomes of predictability and visual acuity.
2. A multivariate approach that employed a stepwise logistic regression model.

Table XX summarizes the results of the univariate analyses. There were no associations between any of the demographic or preoperative variables and the two efficacy outcomes. In other words, no preoperative

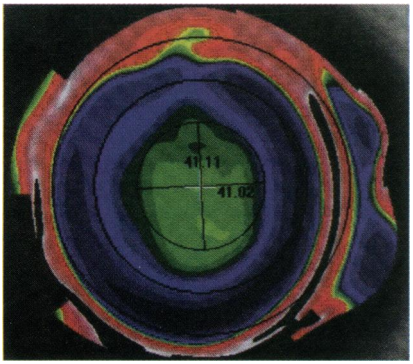

FIGURE 7

Topography with 0.40 mm and 0.45 mm ICRS may occasionally show enhancement of prolate shape with enhanced asphericity.

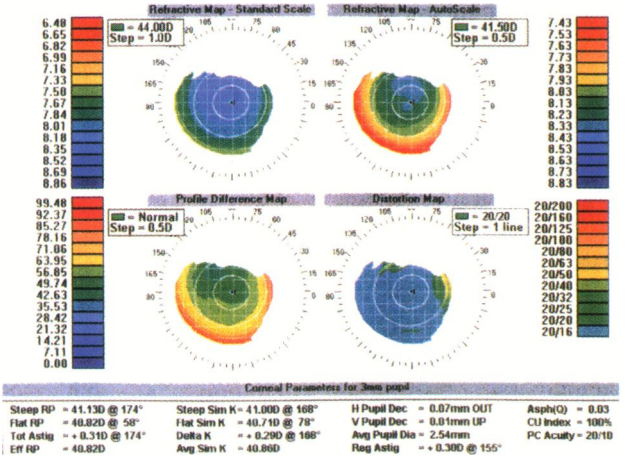

FIGURE 8

Holladay Diagnostic Summary from a 0.25 mm ICRS at 1 year demonstrating a smooth prolate anterior corneal surface. Predicted corneal acuity was 20/10.

subset of patients was identified as having a statistically higher (or lower) probability of positive outcome.

Multivariate analyses were also performed using stepwise logistic models in which the predicted outcomes were predictability based on CRSE and UCVA. None of the parameters tested showed a differential effect on efficacy outcomes.

TABLE XX: UNIVARIATE ASSOCIATIONS WITH EFFICACY OUTCOMES

	PREDICTABILITY (CRSE)		UCVA	
	± 1.00 D	*P*-VALUE	20/40 OR BETTER	*P*-VALUE
Sex				
Male (%)	45/52 (87%)	0.398, Chi	51/52 (98%)	0.763, Chi
Female (%)	34/36 (94%)		35/37 (95%)	
Ethnicity				
White (%)	67/75 (89%)	1.000, Chi	73/76 (96%)	1.000, Chi
Non-white (%)	12/13 (92%)		13/13 (100%)	
Implanted Eye				
Right (%)	42/46 (91%)	0.885, Chi	46/47 (98%)	0.921, Chi
Left (%)	37/42 (88%)		40/42 (95%)	
Age, yrs				
21-29 (%)	5/5 (100%)	0.840, LR	5/5 (100%)	0.190, LR
30-39 (%)	36/40 (90%)		41/41 (100%)	
40-49 (%)	29/33 (88%)		30/33 (91%)	
50-59 (%)	8/9 (89%)		9/9 (100%)	
60-69 (%)	1/1 (100%)		1/1 (100%)	
Contact Lens Use				
Yes (%)	17/18 (94%)	1.000, Chi	18/18 (100%)	N/A
No (%)	21/23 (91%)		23/23 (100%)	

Chi, chi-square, Yate's correction; LR, likelihood ratio.

Efficacy Assessments Summary

The efficacy assessments examined in this study were UCVA, predictability of refractive effect, and stability of refractive effect. A summary of the results of these variables and a comparison, where applicable, to the criteria specified in the FDA guidance document for assessment of new laser refractive surgical procedures is listed in Table XXI.

SAFETY ASSESSMENTS

There were 5 safety assessments for this study: Maintenance of BSCVA, loss of BSCVA, induced manifest cylinder refraction, maintenance of contrast sensitivity, and maintenance of endothelial cell counts.

Maintenance of Best Spectacle-Corrected Visual Acuity (BSCVA)

Maintenance of BSCVA in the operative eye was evaluated using the ETDRS system at month 3, month 6, and month 12. This assessment was made by comparing the patient's preoperative and postoperative BSCVA. A significant loss of BSCVA is considered to be two or more lines on the ETDRS chart in the first-phase group or 10 or more letters in the second -phase group.

TABLE XXI: SUMMARY OF KEY EFFICACY VARIABLES–EVALUATED IMPLANT PATIENTS' EYES

	MONTH 3		MONTH 6		MONTH 12		
EFFICACY VARIABLES	N/N	%	N/N	%	N/N	%	FDA GUIDANCE ASSESSMENT*
UCVA 20/20 or better	89/122	73%	87/124	70%	55/89	62%	NA
UCVA 20/40 or better	117/122	96%	117/124	94%	86/89	97%	85%
CRSE ± 0.50 D	65/119	55%	78/124	63%	60/88	68%	NA
CRSE ± 1.00 D	102/119	86%	104/124	84%	79/88	90%	NA
MRSE ± 0.50 D	77/122	63%	85/124	69%	58/89	65%	50%
MRSE ± 1.00 D	108/122	89%	111/124	90%	81/89	91%	75%
MRSE Stability ±0.50 D†	74/120	62%	97/121	80%	71/85	84%	NA
MRSE Stability ±1.00 D†	99/120	83%	116/121	96%	85/85	100%	95%

* Food and Drug Administration guidance document entitled, "Checklist of Information Usually Submitted in an Investigational Device Exemptions (IDE) Application for Refractive Surgery Lasers," October 10, 1996.

† Stability assessed from month 1 to month 3, month 3 to month 6, month 6 to month 9, month 9 to month 12, using all evaluated patients' eyes for each exam.

TABLE XXII: SUMMARY OF BEST-SPECTACLE CORRECTED VISUAL ACUITY OVER TIME

	PREOP		MONTH 6		MONTH 12	
BSCVA	N/N	%	N/N	%	N/N	%
20/10	4/125	3.2%	4/124	3.2%	2/89	2.3%
20/12.5	42/125	33.6%	39/124	31.5%	25/89	28.1%
20/16	67/125	53.6%	59/124	47.6%	46/89	51.7%
20/20	12/125	9.6%	22/124	17.7%	16/89	18.0%
20/25	0/125	0%	0/124	0%	0/89	0%
20/32	0/125	0%	0/124	0%	0/89	0%
20/40	0/125	0%	0/124	0%	0/89	0%
20/50	0/125	0%	0/124	0%	0/89	0%
Total Evaluated	125	—	124	—	89	—
Not Reported	0	—	0	—	0	—
Total Evaluable	125	—	124	—	89	—

TABLE XXIII: CHANGE IN BEST-SPECTACLE CORRECTED VISUAL ACUITY OVER TIME: ALL EVALUATED EYES

	MONTH 6		MONTH 12	
	N/N	%	N/N	%
Loss of >10 letters or >2 lines	1/124	0.8%	1/89	1.1%
Loss of 10 letters or 2 lines	4/124	3.2%	3/89	3.4%
Loss of 5 to 9 letters or 1 line	22/124	17.7%	24/89	27%
Within 4 letters or No line Change	80/124	64.5%	46/89	51.7%
Gain of 5 to 9 letters or 1 line	16/124	12.9%	15/89	16.9%
Gain of 10 letters or 2 lines	1/124	0.8%		
Total Evaluated	124	—	89	—
Not Reported	0	—	0	—
Total Evaluable	124	—	89	—

Table XXII provides the distribution of BSCVA measurements at the preoperative, month 6, and month 12 time points. At the month 6 and month 12 exams, no patient eyes had a BSCVA worse than 20/20.

Table XXIII provides a summary of the increase or decrease in BSCVA at the month 6 through month 12 exams. The number of patients' eyes that lost two or more lines, or ten or more letters, was comparable to the number of patients' eyes that gained two or more lines, or ten or more letters. At the month 6 exam, 1 in 124 eyes (0.8%) had a decrease from the preoperative BSCVA of 10 or more letters, or of two or more lines. The patient (11341-D-2) who had this decrease had a BSCVA of 20/20. One of 124 eyes (0.8%) had a corresponding increase of BSCVA. The month 12 exam showed a similar trend, as 1 in 89 eyes (1.1%) had a decrease of BSCVA and no eyes had an increase of BSCVA. The one patient with a decrease (11344-D-1) had a BSCVA of 20/20 or better at the month 12 exam.

Table XXIV provides a listing of patients who lost 10 or more letters, or two or more lines, of BSCVA in the initial eye at the month 12 postoperative exam.

Loss of Best Spectacle-Corrected Visual Acuity

The safety assessment for loss of BSCVA was defined as the percentage of the patients who had a BSCVA worse than 20/40 at 1 year. Table XXV provides an analysis of BSCVA at month 12. No patients in this study had a BSCVA worse than 20/40.

Induced Manifest Refraction Cylinder >2 Diopters

The safety assessment for induced manifest refraction cylinder was based

TABLE XXIV: PATIENTS WITH 10 OR MORE LETTERS OR 2 OR MORE LINES LOSS OF BEST SPECTACLE-CORRECTED VISUAL ACUITY AT MONTH 12

PATIENT'S ID	ICRS	AGE	EXAM	UCVA	BSCVA	CHANGE FROM PREOP	MRSE	CRSE
KCB-10052-1	0.45	39	Preop	20/160	20/12.5	-	-4.625	-4.625
			Month 3	20/20	20/12.5	no change	-1.25	-1.25
			Month 6	20/20	20/12.5	no change	-0.875	-
			Month 9	20/20	20/16	1 line		
			Month 12	20/25	20/20	decrease	-0.125	0.625
						2 line		
						decrease	-0.75	-0.75
PAM-10064-2	0.45	35	Preop	20/400	20/12.5	-	-5.00	-5.25
			Month 3	20/80	20/20	2 line		
			Month 6	20/100	20/20	decrease	-2.75	-2.75
			Month 9	20/80	20/20	2 line		
			Month 12	20/25	20/20	decrease	-2.625	-2.25
						2 line		
						decrease	-2.125	-
						2 line		
						decrease	-1.375	-0.25
CCH-11309-1	0.25	54	Preop	20/63	20/12.5	-	-1.25	-1.38
			Month 3	20/20	20/20	10 letter		
			Month 6	20/20	20/12.5	decrease	+0.38	+0.75
			Month 9	20/32	20/16	3 letter		
			Month 12	20/25	20/20	decrease	+0.25	+0.25
						5 letter		
						decrease	+0.75	-
						10 letter		
						decrease	+0.63	+0.63
DLF-11344-1	0.30	43	Preop	20/200	20/12.5	-	-3.00	-2.50
			Month 3	20/32	20/20	9 letter		
			Month 6	20/16	20/16	decrease	-1.00	-0.75
			Month 9	20/16	20/16	4 letter		
			Month 12	20/20	20/20	decrease	-0.50	-0.63
						6 letter		
						decrease	-0.25	-
						11 letter		
						decrease	-0.50	-0.50

BSCVA, best spectacle-corrected visual acuity; CRSE, cycloplegic refraction spherical equivalent; MRSE, manifest refraction spherical equivalent; UCVA, uncorrected visual acuity.

on the percentage of eyes that had an increase in absolute cylinder relative to the preoperative value. Analysis was made first on induced cylinder of greater than 2.00 D to provide a comparison with other keratorefractive procedures. Additional analysis of the distribution of the induced

TABLE XXV: ANALYSIS OF BEST SPECTACLE-CORRECTED VISUAL ACUITY AT MONTH 12

		BSCVA 20/40 OR WORSE		
ICRS THICKNESS	N	N	%	(95% CI)
0.25 mm	18	0	0%	(0.0%, 21.9%)
0.30 mm	24	0	0%	(0.0%, 17.2%)
0.35 mm	27	0	0%	(0.0%, 15.5%)
0.40 mm	9	0	0%	(0.0%, 37.1%)
0.45 mm	11	0	0%	(0.0%, 32.1%)
All	89	0	0%	(0.0%, 5.2%)*

*Two-tailed Fisher's exact test not applicable.

manifest cylinder was also made.

Table XXVI provides an analysis of induced cylinder greater than 2.00 D for month 6 and 12. One eye had an induced cylinder greater than 2.00 D at month 6, but at 1 year there were no eyes with this level of astigmatism.

Analysis of Induced Cylinder. Figure 9 and Table XXVII provide the change in magnitude of manifest refractive cylinder from month 6 through month 12. Induced cylinder greater than 1.50 D was infrequent at month 6 and 12. No patient eyes had induced cylinder greater than 1.50 D at the month 12 exam.

Table XXVIII provides the mean standard deviation and median induced manifest refractive cylinder for all ICRS thicknesses, combined and individually. The magnitude of preoperative cylinder statistically correlated with the ICRS thickness (P=.016). This was expected, since ICRS

TABLE XXVI: ANALYSIS OF INDUCED MANIFEST REFRACTION CYLINDER PROTOCOL ASSESSMENT: LESS THAN 5% > 2.00 D

		> 2.00 D (PREOPERATIVE TO MONTH 6)			>2.00 D (PREOPERATIVE TO MONTH 12)			
ICRS THICKNESS	N	N	%	(95% CI)	N	N	%	(95% CI)
0.25 mm	25	0	0.0%	(0.0%, 16.6%)	18	0	0.0%	(0.0%, 21.9%)
0.30 mm	38	0	0.0%	(0.0%, 11.4%)	24	0	0.0%	(0.0%, 17.2%)
0.35 mm	41	0	0.0%	(0.0%, 10.7%)	27	0	0.0%	(0.0%, 15.5%)
0.40 mm	9	1	0.1%	(0.6%, 49.3%)	9	0	0.0%	(0.0%,37.1%)
0.45 mm	11	0	0.0%	(0.0%, 32.1%)	11	0	0.0%	(0.0%,32.1%)
All	124	1	0.8%	(0.0%, 5.1%)	89	0	0.0%	(0.0, 5.2%)

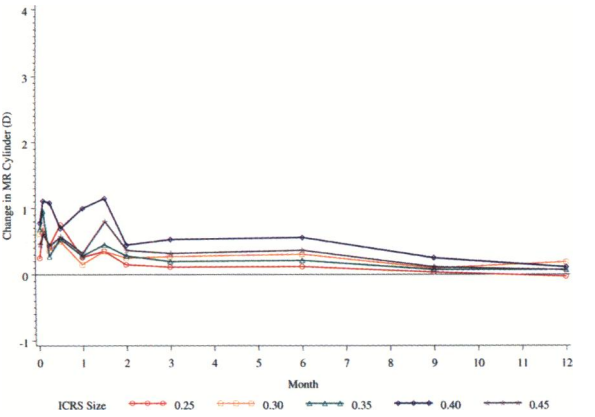

FIGURE 9
Change in magnitude of manifest refractive cylinder from month 1 through month 12.

thickness correlates with increasing refractive error. At month 12, the mean change in the manifest cylinder was 0.087 D with a standard deviation of ±0.5 D. There was no statistically significant difference in the induced astigmatism among the 5 ICRS thicknesses (P=.486).

Maintenance of Mesopic Contrast Sensitivity

Mesopic contrast sensitivity, with and without glare, was tested only on the

TABLE XXVII: CHANGE IN MAGNITUDE OF MANIFEST REFRACTION CYLINDER OVER TIME

	MONTH 6		MONTH 12	
INDUCED ASTIGMATIC CYLINDER (D)	N/N	%	N/N	%
-0.75 to -1.00	6/124	4.8%	11/89	12.4%
-0.25 to -0.50	20/124	16.1%	11/89	12.4%
No change	37/124	29.8%	32/89	36.0%
+0.25 to +0.50	32/124	25.8%	23/89	25.8%
+0.75 to +1.00	18/124	14.5%	10/89	11.2%
+1.25 to +1.50	9/124	7.3%	2/89	2.2%
+1.75 to +2.00	1/124	0.8%	0/89	0.0%
>2.00	1/124	0.8%	0/89	0%
Total evaluated	124	—	89	—
Not reported	0	—	0	—
Total evaluable	124	—	89	—

TABLE XXVIII: MANIFEST REFRACTION—CYLINDER (D)(PREOP–MONTH 12)

		ICRS THICKNESS (MM)					
	ALL THICKNESSES	0.25	0.30	0.35	0.40	0.45	AMONG GROUPS P-VALUE, TEST
Preop							
Mean (SD)	0.284 (0.327)	0.264 (0.315)	0.156 (0.242)	0.306 (0.328)	0.25 (0.395)	0.568 (0.318)	0.016 KW
Median	0.00	0.125	0.00	0.250	0.00	0.750	
Min, max	0.00, 1.00	0.00, 0.75	0.00, 0.75	0.00, 1.00	0.00, 1.00	0.00, 0.75	
n	89	18	24	27	9	11	
Month 12							
Mean (SD)	0.371 (0.454)	0.236 (0.277)	0.344 (0.382)	0.380 (0.487)	0.361 (0.333)	0.636 (0.728)	
Median	0.250	0.125	0.250	0.250	0.250	0.750	
Min, max	0.00, 2.00	0.00, 0.75	0.00, 1.00	0.00, 1.75	0.00, 0.75	0.00, 2.00	
n	89	18	24	27	9	11	
Change between: Preop and month 12							
Mean (SD)	0.087 (0.500)	-0.028 (0.352)	0.188 (0.385)	0.074 (0.532)	0.111 (0.614)	0.068 (0.751)	0.486 KW
Median	0.00	0.00	0.00	0.00	0.250	0.000	
n	89	18	24	27	9	11	
WSR *P*-value	0.160	0.871	0.037	0.616	0.688	0.824	

KW = Kruskal-Wallis; WSR = Wilcoxon signed rank

second-phase patients. The safety assessment for maintenance of mesopic contrast sensitivity was defined as the mean change relative to the preoperative contrast sensitivity measurement that should not decrease by more than 0.1 log unit.

Of the 45 initial patients' eyes implanted in the second-phase, 41 completed the month 12 exam. The analyses that follow include only patients who had data available for their initial operative eyes at the preoperative, month 6 and month 12 exams and their nonoperative fellow eyes at the preoperative and month 6 exams. A total of 40 eyes had results at all required time points for contrast sensitivity without glare and 41 patients' eyes for contrast sensitivity with glare. Five of 45 initial eyes did not have a result for contrast sensitivity without glare for one or more of the required time points, and 4 initial eyes were missing a result for contrast sensitivity with glare.

Figure 10 presents the contrast sensitivity of the initial implant eyes without glare for all thicknesses combined for the preoperative, month 6, and month 12 exams. The figure plots the mean score at each spatial frequency under mesopic conditions. The gray area of the graph represents the normal range for mesopic lighting conditions without glare, based on the 90% distribution of the fellow eye at the preoperative exam.

Table XXIX summarizes the change in contrast sensitivity between the

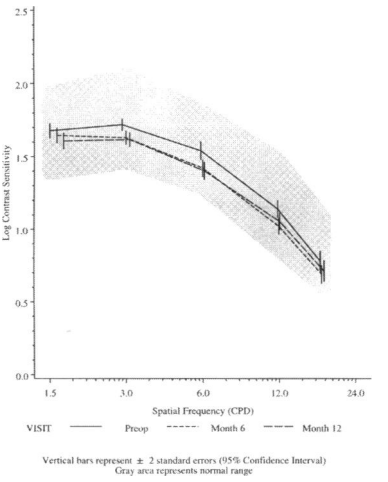

FIGURE 10

Contrast sensitivity of initial implant eyes without glare for all ICRS thicknesses combined for preoperative, month 6, and month 12 exams. Mean score is plotted at each spatial frequency under mesopic conditions. Gray area represents normal range for mesopic lighting conditions without glare, based on 90% distribution of fellow eye at preoperative exam.

TABLE XXIX: CONTRAST SENSITIVITY WITHOUT GLARE: MEAN CHANGE IN LOG CONTRAST SENSITIVITY FROM PREOPERATIVE EXAM FOR THE INITIAL OPERATIVE EYE AT MONTH 6 AND MONTH 12

SPATIAL FREQUENCY (CPD)		MONTH 6 N = 40	MONTH 12 N = 41
1.5	Mean (SD)	-0.013 (0.127)	-0.072 (0.193)
	95% CI	-0.091, 0.064	-0.134, -0.011
	n	28	40
3.0	Mean (SD)	-0.093 (0.174)	-0.110 (0.187)
	95% CI	-0.15, -0.037	-0.170, -0.049
	n	39	39
6.0	Mean (SD)	-0.119 (0.232)	-0.143 (0.285)
	95% CI	-0.192, -0.046	-0.234, -0.052
	n	41	40
12.0	Mean (SD)	-0.111 (0.180)	-0.122 (0.203)
	95% CI	-0.198, -0.025	-0.223, -0.021
	n	19	18
18.0	Mean (SD)	-0.116 (0.205)	-0.150 (0.247)
	95% CI	-0.274, 0.041	-0.379, 0.079
	n	9	7

CPD, cycles per degree.

preoperative and postoperative month 6 and month 12 exams by spatial frequency for the initial implant eye. The mean change in contrast sensitivity without glare ranged from -0.072 log units for 3 cpd at month 12 to a decrease of -0.119 log units for 6.0 cpd at month 6. There was a substantial drop-off in sample size, however, as spatial frequency increased owing to the inability of many patients to read even the first patch at the higher spatial frequencies (12 cpd and 18 cpd) both preoperatively and postoperatively. Changes in contrast sensitivity could only be calculated for a spatial frequency if the patient was able to read at least the first patch both preoperatively and postoperatively. The resultant decreased sample size was also reflected in the wider confidence limits among the higher spatial frequencies.

Figure 11 presents the contrast sensitivity at the preoperative and month 6 exams of the nonoperative fellow eye without glare for all thicknesses combined. Month 12 data for the nonoperative fellow eye are not provided, since the patients were eligible for a contralateral eye procedure and the majority of fellow eyes had been implanted before the month 12 exam of the initial operative eye. The change in contrast sensitivity without glare for the nonoperative fellow eye ranged from an increase of 0.010 log units at 1.5 cpd to a decrease of -0.148 log units at 18 cpd. The changes in the nonoperative fellow eye, reported in Table XXX, were largely similar to those seen in the initial operative eye, as demonstrated by the overlap of the corresponding 95% confidence intervals.

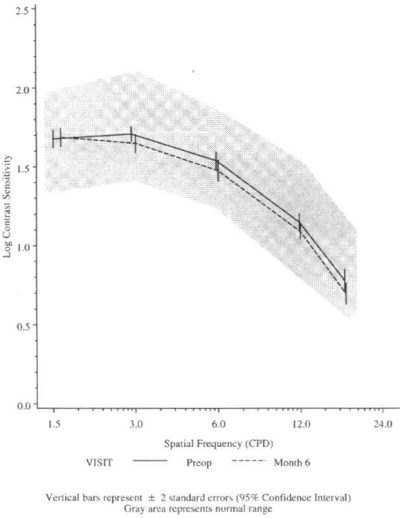

FIGURE 11

Contrast sensitivity at preoperative and month 6 exams of nonoperative fellow eye without glare for all thicknesses combined.

TABLE XXX: CONTRAST SENSITIVITY WITHOUT GLARE MEAN: CHANGE IN LOG CONTRAST SENSITIVITY FOR THE INITIAL OPERATIVE EYE AND NONOPERATIVE FELLOW EYE AT MONTH 6

SPATIAL FREQUENCY (CPD)		INITIAL EYE N = 41	FELLOW EYE N = 41
1.5	Mean (SD)	-0.032 (0.195)	0.010 (0.164)
	95% CI	-0.093, 0.030	-0.055, 0.075
	n	41	41
3.0	Mean (SD)	-0.093 (0.174)	-0.063 (0.187)
	95% CI	-0.150, -0.037	-0.125, -0.002
	n	39	38
6.0	Mean (SD)	-0.119 (0.232)	-0.067 (0.236)
	95% CI	-0.192, -0.046	-0.144, 0.009
	n	41	39
12.0	Mean (SD)	-0.111 (0.180)	-0.081 (0.156)
	95% CI	-0.198, -0.025	-0.147, -0.015
	n	19	24
18.0	Mean (SD)	-0.116 (0.205)	-0.148 (0.273)
	95% CI	-0.274, 0.041	-0.40, 0.104
	n	9	7

CPD, cycles per degree.

Mesopic Contrast Sensitivity with Glare

The results for mesopic contrast sensitivity with glare were similar to those without glare. Figure 12 plots the mean mesopic contrast sensitivity with glare by spatial frequency for the preoperative, month 6 and month 12 exams. Table XXXI presents the initial eye changes in contrast sensitivity with glare under mesopic conditions. The mean changes in contrast sensitivity score with glare at month 6 ranged from an increase of 0.078 log units at 18 cpd to a decrease of 0.0.08 log units at 12.0 cpd. At month 12 the mean contrast sensitivity loss ranged from -0.00 log units at 1.5 cpd to -0.104 log units at 3 cpd.

The changes in the nonoperative fellow eye, reported in Table XXXII, were largely similar to those seen in the initial operative eye, as demonstrated by the overlap of the corresponding 95% confidence intervals. This points out the difficulty in interpreting the data, since both the initial and the control fellow eye have small decreases in contrast sensitivity with glare.

Contrast Sensitivity Results Summary. These results indicate ICRS implant patients generally have mild decreases in contrast sensitivity, with and without glare, at month 6 and month 12 in both the operative eye as well as the control fellow eye as compared to preoperative vision. All of

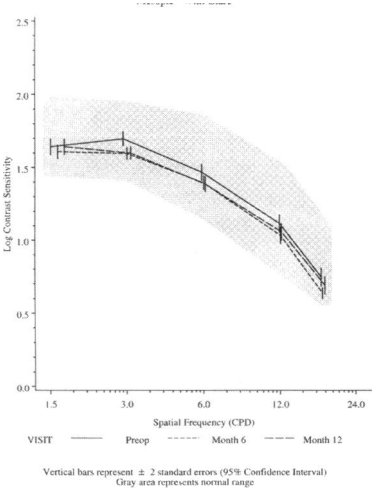

FIGURE 12

Mean mesopic contrast sensitivity with glare by spatial frequency for preoperative, month 6 and month 12 exams. Changes in nonoperative fellow eye were largely similar to those seen in initial operative eye, as demonstrated by overlap of corresponding 95% confidence intervals.

TABLE XXXI: CONTRAST SENSITIVITY WITH GLARE: MEAN CHANGE IN LOG CONTRAST SENSITIVITY SCORE FOR THE INITIAL OPERATIVE EYE AT THE MONTH 6 AND MONTH 12 EXAMS

SPATIAL FREQUENCY (CPD)		MONTH 6 N = 41	MONTH 12 N = 41
1.5	Mean (SD)	-0.034 (0.232)	-0.00 (0.232)
	95% CI	-0.107, 0.039	-0.073, 0.074
	n	41	41
3.0	Mean (SD)	-0.103 (0.204)	-0.104 (0.189)
	95% CI	-0.169, -0.037	-0.165, -0.043
	n	39	39
6.0	Mean (SD)	-0.073 (0.211)	-0.084 (0.241)
	95% CI	-0.139, -0.006	-0.162, -0.005
	n	41	39
12.0	Mean (SD)	-0.08 (0.199)	-0.068 (0.244)
	95% CI	-0.176, 0.016	-0.198, 0.062
	n	19	16
18.0	Mean (SD)	0.078 (0.145)	-0.018 (0.135)
	95% CI	-0.212, 0.056	-0.123, 0.160
	n	7	6

CPD, cycles per degree.

TABLE XXXII: CONTRAST SENSITIVITY WITH GLARE: MEAN CHANGE IN LOG CONTRAST SENSITIVITY SCORE FOR THE INITIAL OPERATIVE EYE AND NONOPERATIVE FELLOW EYE AT MONTH 6

SPATIAL FREQUENCY (CPD)		INITIAL EYE N = 41	FELLOW EYE N =41
1.5	Mean (SD)	-0.034 (0.232)	-0.028 (0.204)
	95% CI	-0.107, 0.039	-0.092, 0.037
		41	41
3.0	Mean (SD)	-0.103 (0.204)	-0.096 (0.180)
	95% CI	-0.169, -0.037	-0.154, -0.037
		39	39
6.0	Mean (SD)	-0.073 (0.211)	-0.110 (0.191)
	95% CI	-0.139, -0.006	-0.171, -0.049
		41	40
12.0	Mean (SD)	-0.08 (0.199)	-0.059 (0.167)
	95% CI	-0.176, 0.016	-0.137, 0.019
		19	20
18.0	Mean (SD)	0.078 (0.145)	-0.113 (0.187)
	95% CI	-0.212, 0.056	-0.286, 0.059
		7	7

CPD, cycles per degree

the contrast sensitivity scores were within the normal range. These results suggest that the ICRS does not adversely affect the patient's functional vision, as measured by contrast sensitivity, both with and without glare, under mesopic lighting conditions. Nonetheless, the size of this statistical sample is too small to ensure that there is not a significant loss in contrast sensitivity both with and without glare. Obtaining results from a larger sample will be necessary to draw a statistical conclusion.

Maintenance of Endothelial Cell Counts

Specular microscopy was performed in the second-phase study using a Konan Robo noncontact specular microscope with a digital image storage system. The mean central and peripheral endothelial cell counts were evaluated at month 6 and month 12. Emory Eye Center of the Emory University School of Medicine, Atlanta, was the independent reading center for the specular microscopy images. Images were read from the central region and the peripheral region at the 6-o'clock and 10-o'clock positions. The cell density, coefficient of variation in cell size, and percentage hexagonal cells were read for each region. An image needed to have had a minimum of 50 analyzable cells to be considered valid and included in the analysis.

There were a total of 45 initial eyes enrolled and successfully implanted that had specular microscopic evaluation. The month 12 exam was completed by 39 of 45 initial eyes (86%). Specular images were taken at the preoperative, month 6, and month 12 exams for the initial operative eye and nonoperative fellow eye. Only limited data were available from the nonoperative fellow eye at the month 12 exam, and they were not included in this summary, since the fellow eyes were eligible for implant beginning at the month 6 exam. Data are presented here for those subjects with complete data available for all required exams.

Endothelial Cell Density. Table XXXIII provides the mean cell density at the preoperative and postoperative exams as well as the mean change in cell densities, the mean percent change in cell counts, and 95% confidence interval for the change. The mean change in cell density was computed as the mean of the paired difference within each subject eye between the preoperative and the postoperative exam. Positive values indicated an increase in cell density, and negative values indicated a decrease. The percentage change in endothelial cell densities was computed as the paired change from the preoperative exam as a percentage of the preoperative count. A 95% confidence interval was computed for the percent change.

The mean percent change in cell density ranged from decrease of 0.8% for the central region at month 6 to a decrease of 3.7% for the 10-o'clock

TABLE XXXIII: SUMMARY OF CHANGE IN ENDOTHELIAL CELL COUNTS (CELLS/MM²)

REGION	EXAM	PREOP MEAN (SD)	POSTOP MEAN (SD)	MEAN CELL CHANGE	PERCENT CHANGE	95% CI
Central	Month 6	2652(36)	2629(36)	-23	-0.8%	-2.2%, +0.6%
n = 36	Month 12	2652(36)	2612(36)	-40	-1.5%	-2.8%, -0.2%
Peripheral @ 6:00	Month 6	2659(35)	2600(35)	-59	-2.0%	-3.8%, -0.2%
n = 35	Month 12	2659(35)	2612(35)	-47	-1.5%	-3.1%, 0.02%
Peripheral @ 10:00	Month 6	2819(37)	2730(37)	-89	-3.1%	-5.0% ,-1.2%
n = 111	Month 12	2819(37)	2711(37)	-108	-3.7%	-5.2%, -2.3%

position of the peripheral region at month 12. The maximum decrease in cell density was less than 4% for all regions and time points.

Endothelial cell densities for the nonoperative fellow eyes were similar to the operative eye at the preoperative exam and slightly higher at the month 6 postoperative exam, as shown in Table XXXIV.

Coefficient of Variation. Coefficient of variation was assessed as a measure of polymegathism. The mean coefficient of variation for the initial operative eye at each time point can be found in Table XXXV. The mean change in coefficient of variation at the postoperative exams ranged from 0.1% for the central region at month 6 to an improvement of -1.7% for the peripheral regions at month 12. Statistically significant improvement in the coefficient of variation was seen at the month 12 exam for the peripheral

TABLE XXXIV: SUMMARY OF CHANGE IN ENDOTHELIAL CELL COUNTS (CELLS/MM) FOR THE INITIAL IMPLANT EYE AND NONOPERATIVE FELLOW EYE AT MONTH 6

REGION	EYE	PREOP MEAN	POSTOP MEAN	MEAN CHANGE	PERCENT CHANGE	WSR	95% CI
Central	Initial	2652	2629	-23	0.8%	*P*=0.07	-2.2%,+0.6%
n = 36	Fellow	2673	2664	9	0.2%		-1.4%,+1.0%
Peripheral @ 6:00	Initial	2659	2600	-59	-2.0%	*P*=0.08	-3.8%,-0.2%
n = 35	Fellow	2685	2658	-27	-0.7%		-2.7%,+1.4%
Peripheral @ 10:00	Initial	2819	2730	-89	-3.1%	*P*=0.054	-5.0%,-1.2%
n = 37	Fellow	2841	2800	-41	-1.5%		-3.8%,+0.7%

WSR = Wilcoxon signed rank

TABLE XXXV: SUMMARY OF CHANGE IN COEFFICIENT OF VARIATION (%): INITIAL IMPLANT EYE

REGION	EXAM	PREOP MEAN	POSTOP MEAN	MEAN CHANGE	WSR
Central	Month 6	34.1	34.2	0.1	$P = 0.834$
n = 36	Month 12	34.1	33.4	-0.7	$P = 0.367$
Peripheral @ 6:00	Month 6	35.3	35.2	0.0	$P = 0.899$
n = 35	Month 12	35.3	33.5	-1.7	$P = 0.005$
Peripheral @ 10:00	Month 6	35.8	35.3	-0.5	$P = 0.504$
n = 37	Month 12	35.8	34.1	-1.7	$P = 0.027$

WSR = Wilcoxon signed rank

regions, -1.7% ($P = 0.005$) and -1.7% (P = 0.027) for the 6-o'clock and 10-o'clock peripheral regions, respectively.

Hexagonality. The percentage of hexagonal endothelial cells was assessed as a measure of pleomorphism. Preoperatively, 57.6% of the cells for the initial operative eyes were hexagonal in the central region, 56.3% at the 6-o'clock position in the peripheral region, and 56.8% at the 10-o'clock position in the peripheral region (Table XXXVI). The mean percentage of hexagonal cells remained between 56.8% and 59.0% at the month 6 and month 12 exams for all regions. The mean change for all regions and time points was less than 2.7%, and the only statistically significant change was the peripheral region at 6-o'clock at month 12, +2.7% ($P = .006$).

Endothelial Cell Loss Summary. The changes in endothelial cell densities for all regions was less than 4% in any of the regions examined.

TABLE XXXVI: SUMMARY OF CHANGE IN HEXAGONALITY (%)

REGION	EXAM	PREOP MEAN	POSTOP MEAN	MEAN CHANGE	WSR
Central	Month 6	57.6	57.6	0.0	P = 584
n = 42	Month 12	57.6	57.7	+0.1	P = 785
Peripheral @ 6:00	Month 6	56.3	58.0	+1.7	P = 136
n = 40	Month 12	56.3	59.0	+2.7	P = 006
Peripheral @ 10:00	Month 6	56.8	56.8	0.0	P = 867
n = 41	Month 12	56.8	57.5	+0.7	P = 614

WSR, Wilcoxon signed rank

Furthermore, there were no statistically significant increases in the coefficient of variation, polymegathism, or statistically significant decreases in the percent hexagonal cells, pleomorphism, associated with the ICRS and implant surgery. These results suggest that the ICRS implant does not significantly affect the corneal endothelium. Nonetheless, the sample size used in this analysis is relatively small and the lack of statistical significance could result from this alone.

Ocular Complications

Complications Not Related to ICRS. In the first phase of this study, a few complications occurred that were not felt to be the result of the ICRS. One patient moved during the making of the radial incision with the diamond knife, resulting in a 2 mm incision that extended to the limbus. The wound was closed with an extra 11-0 nylon suture. There were no sequella.

One patient (10044.D.1) complained of itching for the first 2 weeks after the surgery. This symptom resolved after topical Tobradex was discontinued. One patient (10045.D.2) had conjunctival injection and chemosis for the first 2 weeks after surgery. I felt that this was due to the trauma of the Vacuum Centering Guide and to irritation from topical Tobradex. Two patients (10052.S.1, 10053.D.1) developed conjunctivitis during the course of the study. I did not feel that this was caused by the ICRS surgery. The conjunctivitis resolved without sequella. One patient (10059.D.2) developed a corneal abrasion from blunt trauma. I did not believe that this was related to the ICRS, and the problem resolved without sequella.

Three eyes (10044.D.1, 10064.D.2, and 10065.D.1) developed filamentary keratitis in the first postoperative week. These filaments appeared near the incision site and were felt to be due to healing of the epithelial defects. All resolved without sequella.

One patient (10046.S.1) had induced astigmatism that caused visual symptoms for the first 6 months. This problem eventually resolved. Two eyes in 1 patient (10065.S.2, 10065.D.1) developed mild flare and cell in the anterior chamber 6 and 8 weeks after ICRS surgery. I did not feel that this mild iritis was due to the ICRS. The iritis responded to topical corticosteroids.

In the second-phase of the study, the following complications occurred that were not felt to be the result of the ICRS. Two eyes (11317-2,11315-1) had a noninfectious infiltrate. These infiltrates typically appeared between days 7 and 14 in the superior channel. Both eyes were treated with topical Tobradex, and the infiltrates resolved rapidly in one case and over a period of a few months in the second case. The infiltrates did not lead to loss of corneal stroma or problems with the refraction.

One eye (11314-1) developed deep stromal neovascularization. In this

case, the incision contacted a preexisting pannus that was the result of soft contact lens wear. The superficial pannus grew into the incision in the first postoperative month and extended 2 clock hours in the channel. It was nonprogressive, and the caliper of the vessels continued to decrease.

Complications Related to the ICRS. In the first phase of the study, some complications occurred that I felt were secondary to the ICRS. One patient (10043.S.1) had glare secondary to the original implant being too close to the pupil margin. Although repositioning of the ICRS was attempted, the ICRS continued to migrate to its original position, and it was eventually removed. Another patient (10056.S.1) had glare and double images due to ICRS malposition at the original surgery. Repositioning of the ICRS was attempted, but it returned to its original location causing the return of symptoms. The ICRS was eventually removed. A third patient had a large pupil in mesopic conditions and complained that he could see the ICRS at night. The ICRS was removed, and the symptoms resolved.

One patient developed a sterile infiltrate in the superior channel near the incision site. This was initially treated with topical antibiotics with slow resolution. Subsequently, the incision site developed linear fluorescein staining and neovascularization. Wound revision was performed, the wound gape resolved, and neovascularization receded over the following 6 months.

In the second-phase of the study, the following complications occurred, which I felt were due to the ICRS. One patient (11308-1) had a decentered ICRS noted on day 1. The patient was able to see the ICRS at night. The ICRS was repositioned in the first postoperative week by creating a slightly deeper lamellar channel, and the symptoms resolved. One patient (11345-1) had the ICRS explanted because of an undercorrection and fluctuating visual acuity. During the day his visual acuity was 20/20, but it dropped to 20/60 at night. Another patient had both ICRS removed (11347-1,11347-2) due to his desire to comply with a restriction set by the Federal Aviation Administration (FAA). The patient had uncorrected visual acuity of 20/15 in each eye, but the FAA would not reissue his pilot license if his vision was corrected by an investigational device.

Reversibility

In the course of this study, 6 ICRS were explanted for the reasons listed above. It should be noted that 3 of the 6 had ICRS removal after the close of the database in May 1998 for this report. These cases are included here, in part, to demonstrate the unique feature of reversibility of refractive effect.

Surgical Technique. The explantation of the ICRS was easy. The patient was prepared and draped in the same fashion as in the original surgery.

Topical anesthesia (Tetracaine 0.5%) was applied. A speculum was inserted to hold the eyelids apart. The wound was opened usually with a blunt instrument like a Sinskey hook and the original channel was opened. A Sinskey hook was then used to engage the hole in the tip of the ICRS, and the ICRS was pulled from the channel. After removal of the ICRS, the wound was closed with 11-0 nylon suture.

Table XXXVII lists the preoperative and 3-month postexplant visual acuities and manifest refractions for the patients that had ICRS removals.

The ICRS was removed in 6 of 125 eyes (5%) in the total series. In the first phase of the study, the incidence of removals was 3 in 49 (6%), and the primary reason for removal was glare and double images, especially at night. These symptoms were related to two principal problems:

1. Inclusion of patients in the study with mesopic pupils larger than 7 mm.
2. Poor centration of the ICRS over the pupil at the time of surgery.

These problems were corrected in the second-phase of the study, where eyes with mesopic pupils larger that 7 mm were excluded from the study, and where caution was exercised in centering the surgery properly. In the second-phase of the study, the incidence of removal was 3 in 79 (3.7%). However, 2 of these explants were performed for nonmedical reasons:

1. In a patient who had no complaints, was happy with the outcome, and was enjoying 20/15 visual acuity.
2. In a patient who was undercorrected and did not want to wait for an exchange procedure.

The latter patient asked for ICRS removal and within 6 weeks had a PRK by another surgeon.

DISCUSSION

My research on 125 eyes implanted with the 150° ICRS with 1 year follow-up on 89 eyes demonstrated the viability of this new additive refractive surgical procedure to correct low to moderate myopic refractive errors. The results from this series of patients documented good visual acuity, rapid visual recovery, predictability, and refractive stability. Furthermore, the ICRS did not cause significant loss in best spectacle-corrected visual acuity, or contrast sensitivity did not induce astigmatism, and did not significantly alter endothelial cell counts or morphology. The ICRS achieved these results without surgically altering the center of the cornea and

TABLE XXXVII: VISUAL ACUITY AND REFRACTIVE ERROR IN CASES OF ICRS REMOVALS: PREOP VERSUS 3-MONTH POSTOP

EYE	ICRS (MM)	PRE-UCVA	POST-UCVA	PRE-BSCVA	POST-BSCVA	PRE-MANIFEST REFRACTION	POST-MANIFEST REFRACTION (3 MO)
10067-1	0.25	20/40	20/63	20/10	20/12.5	-1.75 + 0.75 X 75°	-2.00 + 0.75 X 45°
10043-1	0.45	20/200	20/100	20/12.5	20/20	-5.00 +0.75 X 105°	-4.25 + 1.25 X 105°
10056-1	0.40	20/200	20/200	20/16	20/12.5	-4.75	-4.00 + 0.25 X 135°
11345-1	0.30	20/60	20/60	20/16	20/20*	-2.50 + 0.50 X 070	-2.25*
11347-1	0.35	20/200	20/60	20/16	20/12.5	-3.25 + 0.25 X 025	-2.75 + 0.50 X 050
11347-2	0.25	20/200	20/160	20/20	20/20	- 2.50	-2.25

* Datapoints are taken from the medical record of ophthalmologist who performed PRK on this patient 6 weeks post-explant. Post PRK the patient achieved 20/20 uncorrected visual acuity.

without sacrificing the cornea's normal prolate aspheric corneal topography. For the most part, the ICRS met the criteria that I set forward at the outset of this thesis for an ideal refractive procedure.

My ICRS data either equaled or surpassed the reported results of other practiced keratorefractive procedures, radial keratotomy (RK), photorefractive keratectomy (PRK), and laser assisted in situ keratomileusis (LASIK) in the follow-up measures that were assessed in this report. These results fared even better if compared against the early results of these other procedures. Nonetheless, even where my data only marginally surpassed the reported experience with other procedures, it is my opinion that the demonstrated removability of the ICRS, with its resultant potential for reversibility and adjustability, created a strong case for the ICRS, since it provides a safety net that other procedures cannot offer.

Although my experience with ICRS removals during this study was limited, reversibility of the refractive effect was demonstrated with the return of BSCVA and manifest refraction to preoperative levels. Reversibility of refractive effect following ICRS explantation was recently presented by Burris and associates, (ISRS, November 7, 1998). In a series of 31 explants, 92% of the eyes returned to within 1.00 D, and 81% to within 0.50 D of their original refraction. No patients lost best spectacle-corrected visual acuity. Additionally, Asbell and colleagues presented the cumulative experience in the United States for ICRS exchanges (ISRS, November 7, 1998). There were a total of 12 exchange procedures. All of them were performed for undercorrections of greater than 1.00 D after the ICRS had been in position for at least 6 months. After the exchange, more than 50% of the patients had refractions of less than 1.00 D. At this time, follow-up on these cases has been minimal, but the concept of adjustability of the ICRS has been demonstrated.

COMPARISON OF ICRS WITH OTHER KERATOREFRACTIVE TECHNIQUES

While the ICRS appears to be a viable alternative procedure, the acceptance of this surgical approach will depend on how it compares to currently practiced keratorefractive procedures. Ultimately, patients and surgeons will compare this new technology on the basis of procedure ease, and long-term refractive and safety results. Even though the ICRS is a new keratorefractive technique and, to date, has only been performed under investigational protocols, the results can be compared to RK, PRK, and LASIK.

Surgical Procedure

The ease and simplicity of the surgical procedure provided another line of evidence supporting the viability of the ICRS. Based my experience

within this study, and the experiences of other surgeons, the procedure was simple to perform. It required only topical anesthetic in most cases and did not cause pain or discomfort. The peripheral lamellar channels were created with a suction ring that produced only mild discomfort and a sensation of pressure comparable to a LASIK procedure. In my hands, the surgical procedure took between 7 and 12 minutes, and it was similar in difficulty to other refractive surgeries.

Postoperatively, I observed that the patients experienced only minimal discomfort that quickly resolved when any epithelial defect around the incision healed. Moreover, because there was almost never any intraocular inflammation, patients were treated with topical corticosteroids and antibiotics for only 7 days, which was a shorter course than I have typically used with photorefractive keratectomy. The postoperative management of the ICRS patients was similar to that with RK or LASIK, but less intensive than with PRK.

Visual Acuity and Recovery

ICRS. Visual recovery after the ICRS procedure was rapid. In this series of patients, on the first postoperative day, 90% of the eyes were 20/40 or better; 33% were 20/20 or better; 10% were 20/16 or better; and 2% were 20/12.5. Visual acuities continued to improve over the subsequent weeks, and by 1 month 84% of eyes were 20/40 or better, 55% of eyes were 20/20 or better, 29% of eyes were 20/16 or better, and 7% of eyes were 20/12.5. At 1 year 97% of the eyes were 20/40 or better, 62% were 20/20 or better, 36% were 20/16 or better, and 16% were 20/12.5 or better.

The visual acuity and visual recovery results were equal to, or slightly higher than, the results reported with other keratorefractive procedures, which gave the ICRS, on the average, a visual outcome advantage. This advantage was demonstrated in the percentage of patients that could see better than 20/20. Specifically, at 1 year, over one third of the eyes achieved 20/16 or better unaided visual acuity. To date, no other keratorefractive procedure has achieved such a high percentage of eyes at such a high level of visual acuity. I believe that this represents a clear advantage of this surgical modality, and I attribute this finding to the fact that the surgery does not alter the cornea's visual axis.

Radial Keratotomy. ICRS visual acuity data were compared to the reports of the Prospective Evaluation of Radial Keratotomy (PERK) study. The establishment of this multicentered, prospective, randomized clinical trial set the standard for how radial keratotomy and future refractive surgery advances would be evaluated.[51] The PERK study provided perhaps the best comparison of RK and my results with the ICRS, since both of these

studies were prospective evaluations of new and relatively untested keratorefractive procedures that were carried out under a rigorous protocol.

At 1 year after radial keratotomy, the PERK study group reported uncorrected visual acuity of 20/40 or better in 78% of the eyes. The procedure was found to be most effective in eyes with refraction between -2.00 D and -4.25 D.[52] At 3 years[53] and 4 years,[54] 76% were 20/40 or better. The percentage of eyes that achieved 20/40 visual acuity with the ICRS surpassed the results of the early procedure of radial keratotomy.

In 1992, Assil[55] and Casebeer independently designed a bi-directional diamond knife to be used in the combined-incision radial keratotomy technique.[56] The use of the bi-directional or combined technique provided the enhanced efficacy of the Russian-style incision while providing the safety of the American-style incision. Studies utilizing the combined incision technique provided documentation of ongoing improvements in this modality.[56,57]

Initial results of radial keratotomy using the Casebeer combined technique demonstrated effective reduction of myopia with a high degree of safety.[58] Waring, and associates[59] reported that 93% of the eyes achieved an uncorrected visual acuity of 20/40 or better and 54% achieved 20/20 or better. Verity and colleagues,[60] in a study of the combined technique using the Genesis diamond knife (Alcon, Fort Worth, TX), reported that 97% of the patients had 20/40 or better visual acuity after a single radial keratotomy procedure.

The ICRS visual acuity results also compared favorably to the modern combined technique of radial keratotomy. While the percentage of eyes that achieved 20/40 acuity was roughly similar in the ICRS cases, the percentage of eyes reported at the 20/20 level was higher in the ICRS group.

PRK. Since Trokel and coworkers[61] reported using the 193 nm excimer laser for corneal ablation in 1983, this procedure underwent the transition from experimental work in the laboratory to clinical acceptance. The results of the US FDA clinical trials of the excimer laser were favorable and were summarized in a recent review by Seiler and McDonnell.[62] The Phase III FDA clinical trial conducted by VISX (Santa Clara, CA) provided good data to compare PRK and the ICRS, since the data were collected under similar protocols that tested the respective technologies at an early stage in development. At 1 year, VISX reported that 94% of 480 eyes were 20/40 or better and 54% were 20/20 or better. In a recent report, Tuunanen and Tervo[63] found that 88% of the eyes with myopia between – 1.50 D and – 6.00 D achieved 20/40 or better visual acuity. While my results with the ICRS were comparable at the 20/40 level, the results at the 20/20 level were even better (62% versus 54%) than these reports.

The visual recovery after PRK was reported to be slower than the

visual recovery reported in this series of ICRS eyes. The delay in visual recovery following PRK was believed to be secondary to the healing of the epithelial defect that was created at the time of the procedure. By comparison, the ICRS visual recovery was faster, in part, because there was no epithelial healing in the visual axis.

LASIK. In recent years, the photoablative properties of the excimer laser have been applied to the technique of in situ keratomileusis with promising results. Laser assisted in situ keratomileusis, termed LASIK by Pallikaris[64,65] uses a microkeratome to make an anterior corneal flap. The excimer laser then ablates tissue from the exposed stromal bed and the flap is repositioned without sutures.

LASIK has recently come to the forefront as the procedure of choice for most ophthalmologists.[66-68] Most surgeons prefer LASIK because of the rapid visual recovery. Comparative studies between PRK and LASIK have shown that overall improvement in uncorrected visual acuity was more rapid in LASIK than PRK, although long-term efficacy was similar.[69]

In a review article, Farah and associates[70] summarized the reported experience with LASIK. In the published literature, he found that an average of 49.2% of eyes achieved 20/40 or better visual acuity, whereas in the published abstracts, an average of 82.5% of eyes achieved this visual acuity level. Additionally, an uncorrected visual acuity of 20/20 was achieved in 22% of the eyes in published papers, as opposed to 56% of the eyes in published abstracts. The performance of the ICRS surpassed all averaged data from the reported LASIK literature.

In a recent report by Dulaney and colleagues[71] on visual recovery after LASIK, 81% of the eyes on day 1 and 91% of the eyes by month 1 achieved visual acuity of 20/40 or better. Rapid visual recovery after LASIK was confirmed by other investigators.[72-76] In a study of LASIK treatment of low myopia between -1.00 to -3.50 D, Pirzada[77] reported rapid visual recovery, with 20/40 acuity achieved in 52% by 1 week, 80% by 1 month, and 93% by 6 months following LASIK. This LASIK study of low myopia was the best study to compare with ICRS results, since the range of preoperative myopia was similar. Once again, the visual recovery with the ICRS eyes was more rapid than the reported LASIK results. No less than 80% of the ICRS eyes achieved 20/40 from the first postoperative day through month 1, and 96%, 94%, and 97% of the eyes had achieved this level of acuity at 3, 6, and 12 months, respectively. Furthermore, Durrie presented a comparison of the visual recovery between ICRS and LASIK in a matched series of patients between -1.00 D and -4.00 D where he found that visual recovery was faster and more patients saw 20/16 or better with the ICRS than with LASIK (ISRS presentation, November 7, 1998).

Summary of Visual Acuity and Recovery Comparison. The visual acuity and recovery performance of the ICRS was better than the reported experience with RK, PRK, or LASIK. This was the case for the percentage of eyes that achieved 20/40 and 20/20 visual acuity, and more important, the ICRS had a higher percentage of eyes that achieved 20/16 or better visual acuity. Furthermore, the ICRS eyes achieved these better levels of visual acuity rapidly after the surgery.

Predictability of the Refractive Outcome

While it is essential for a refractive procedure to provide good visual acuity, the ability of a procedure to perform in a predictable manner is important. The assessment of the precision of a procedure gives the surgeon a guideline for how to apply the technique.

ICRS. At 1 year, 90% of the eyes in my ICRS series were within 1.00 D of the intended cycloplegic correction and 68% were within 0.50 D of the intended cycloplegic correction. The results for predictability using the manifest refraction were similar. These data demonstrated that the ICRS had a predictable refractive outcome.

RK. Numerous clinical studies have shown that a variety of factors affect the predictability of the refractive outcome after radial keratotomy. The most significant factors have included the patient's age; the amount of preoperative myopia; the number, length, and depth of the incisions; the size of the optical zone; and corneal curvature.[78-81]

In the PERK study at 1 year, only 60% of the eyes were within 1.00 D of emmetropia.[52] Of the patients outside of this target, 30% were undercorrected and 10% were overcorrected. Similar results were reported in the PERK study at 3 and 4 years.[53,54] At 1 year, where 90% of the eyes were within 1.00 D of the desired correction, the predictability of the ICRS was better than the 1 year PERK data. Similarly, of the eyes outside of this target, 3% were undercorrected and 7% were overcorrected.

The ICRS results also compared well to the modern techniques of radial keratotomy. Using the Casebeer system and including all enhancement cases, Waring, and associates[59] reported 89% of eyes within 1.00 D of emmetropia, and 68% within 0.50 D of emmetropia at 1 year. Similarly, Werblin and Stafford[82] reported that 84% were within 1.00 D and 66% were within 0.50 D of emmetropia at 3 years following the surgery. The predictability of the ICRS procedure at 1 year was similar to these results if radial keratotomy enhancements were included. In this series of ICRS patients, however, there were no enhancements or exchange procedures performed.

PRK. PRK has good predictability. The results for the Phase III VISX FDA clinical trial for the correction of myopia less than 6.00 D demon-

strated that 92% of the eyes were within 1.00 D of the desired correction and 68% were within 0.50 D of the desired correction at 1 year. In a recent paper, Wang and associates[73] reported that 83% of the eyes in his PRK series were within 1.00 D of emmetropia and 61% were within 0.50 D. These results appeared to be similar to my ICRS results; however, the fact that the PRK reports included a wider range of preoperative correction made the comparison more difficult.

LASIK. Farah and colleagues[70] in a retrospective review of the literature of myopic LASIK, reported that the mean percentage of patients within ± 1.00 D was 67% in published papers and 83.2% in published abstracts. Predictability of the procedure decreased with higher preoperative myopia. Wang and associates[73] found that 89% of the LASIK eyes were within 1.00 D of emmetropia and 71% of the LASIK eyes were within 0.50 D of emmetropia. The increase in the predictability with LASIK was presumably due to the minimal epithelial insult caused by the LASIK procedure. The predictability in this LASIK report surpassed the predictability of the ICRS. However, the ICRS predictability compared favorably with the average predictability of LASIK found in the literature.

Summary of Predictability of the Refractive Outcome. The predictability of the ICRS was better than comparative early reports of RK, PRK, and LASIK. When the predictability of the ICRS was compared to recent reports of these techniques, the results were more equivalent. It should be noted, however, that the ICRS eyes had low to moderate myopic refractive errors from -1.00 to - 4.50 D, whereas the other procedures treated to higher levels of myopia.

Stability of the Refractive Outcome

Beyond providing a good and predictable visual outcome, a refractive surgical procedure's result should be stable over time.

ICRS. In this ICRS series, I found that 96% of the eyes had a change in manifest refraction of 1.00 D or less from the month 3 to month 6 exams. Eighty-five of 88 eyes (97%) had a change in manifest refraction of 1.00 D or less from month 6 to month 9, and 85 of 85 (100%) had a change in manifest refraction of 1.00 D or less from month 9 to month 12. It appeared that refractive stability was achieved by month 3 and maintained through the first year. Long-term refractive stability of the ICRS was reported by Nosé at 5 years.[47]

RK. Poor stability of the refractive correction after radial keratotomy has been the most significant complication of this procedure. The 10 year results of the PERK study published by Waring and associates[83] documented the incidence of progressive hyperopic drift, which occurred over time following the procedure.

The complication of progressive hyperopic drift was not eliminated by the combined technique of radial keratotomy. Werblin and Stafford[84] reported a 3-year follow-up on 128 patients treated with radial/astigmatic keratotomy using Casebeer combined technique nomograms in which he found an average magnitude of hyperopic shift of +0.6 D. Scorolli and associates[85] reported a study of 51 patients who underwent 4-8 incision radial keratotomy for myopia ranging from - 2.00 to - 7.25 D. After 8 years, 66.2% showed a refractive error within ±0.50 D, 17.4% were more myopic by 0.50 D, and 16.2% were more hyperopic by 0.50 D. The mean hyperopic shift was higher (+0.78 D) in eyes with keratometry less than 36 D compared with eyes with readings greater than 36 D (+0.38 D) 6 months after surgery.

Another PERK study documented the diurnal change in refraction, corneal curvature, visual acuity, and intraocular pressure after radial keratotomy.[86] The PERK Study Group reported persistent diurnal fluctuation in refraction in some patients 11 years after the original surgery.[87] Persistent diurnal change in the corneal curvature was felt to result from corneal instability.

I found no significant change in the mean refractions of the ICRS eyes over the 12 month follow-up period. This was a good indication that the corneal instability seen with radial keratotomy would not develop with the ICRS. Additionally, Twa and associates[88] recently reported a diurnal variation study and found no significant change in the refraction over the course of the day in a series of 79 eyes from 45 patients who were at least 6 months from their surgery.

PRK. PRK appeared to provide a stable postoperative result in most cases with less than 6 D of preoperative myopia.[62] Haze formation and associated myopic regression were complications following PRK. In the Phase III PRK study, 1.5% of the eyes had moderate haze and 0.5% of the eyes had marked haze.[89] Haze was maximal between 3 and 6 months after PRK and correlated with the degree of preoperative myopia and regression.[90,91] While patient age had no statistically significant effect on refractive stability or corneal haze 1 year after PRK,[92,93] greater attempted correction was associated with less predictability and less stability of refraction.[93] Late-onset corneal haze occurred in 1.8% of the eyes after PRK, which resulted in a decrease visual acuity and regression. Treatment with topical steroids, or reoperation, resulted in partial reversibility of haze and regression.[94] However, the reported prospective, randomized, double-masked studies did not demonstrate any statistically significant long-term beneficial effect on refractive outcome, stability, or stromal haze with the use of topical corticosteroids after PRK.[91,95]

LASIK. Farah and colleagues[70] found regression of -0.50 D in 90% of

low and moderate myopes and 80.9% in high myopes. Factors responsible for postoperative regression are still unknown, but it was thought that the degree and mechanism of regression after LASIK in mild to moderate myopes was a consequence of epithelial hyperplasia associated with central corneal steepening.[96,97]

Another cause of late regression after LASIK was corneal ectasia. Corneal ectasia was reported in two studies as a complication of LASIK that limited the range of myopic correction.[98,99] In general, the risk of ectasia was higher in the treatment of high myopia, but was also seen in the treatment for low myopia, if the preoperative corneal thickness was less than 500 μm. It was suggested that a residual stromal bed of 250 μm should remain for corneal stability.

Summary of Stability of the Refractive Outcome. The ICRS results were stable and did not have regression or loss of the refractive effect, as was seen in the reported RK and LASIK studies. Nonetheless, the follow-up of the ICRS cases was only 1 year, and the long-term effects cannot be established at this time. It is unlikely that the ICRS would have any severe regression due to ectasia, since the ICRS is an additive technique rather than a tissue removal technique. Theoretically, the cornea should be strengthened, rather than weakened, by the ICRS procedure.

Loss of BSCVA

Refractive surgery is generally performed on normal eyes that have excellent preoperative BSCVA. A procedure that minimizes the chance for loss of BSCVA should be preferred over a procedure that has a higher incidence of this problem.

ICRS. At 1 year, no patients had a BSCVA of less than 20/20. Only 1 of the 89 patients (1.1%) at 1 year had a loss of greater than 2 lines or 10 letters of BSCVA. This patient lost a total of 11 letters but had a preoperative best-corrected visual acuity of 20/12.5, and at 1 year, it was 20/20. I had an additional 3 cases (3.9%) with a two-line or 10-letter loss in BSCVA; however, all of these patients had BSCVA of 20/20.

RK. The reported loss of 1 line of BSCVA in the PERK study at 1 year was 13%.[53,52,83] At 3 years, the reported two-line loss of BSCVA was 1.3%, and at 10 years the reported two-line loss was 3%. Sawelson and Marks[101] reported a loss of best-corrected visual acuity in 8% of his patients 5 years after radial keratotomy. Verity and associates[60] reported a 0.3% incidence and Waring and associates[59] a 1% incidence of loss of 2 lines of BSCVA using the combined incision radial keratotomy technique. The incidence of BSCVA loss with the ICRS was similar to the loss seen in the newer radial keratotomy techniques.

PRK. The loss of BSCVA following PRK may result from corneal haze,

decentered ablations, central island, and irregular astigmatism. The incidence of loss of BSCVA following PRK was reported between 0.9% and 2.7% in eyes with less than 6 D of preoperative myopia.[102-104] The incidence of haze and loss of BSCVA increased with increasing preoperative myopia.

LASIK. Eccentric ablation, flap irregularities, interface debris, and epithelial islands can cause loss in BSCVA after LASIK.[105-107] Condon and associates[108] reported a loss of one Snellen line of BCVA in 14.5%, and 3 eyes (3.6%) lost two or more lines of spectacle-corrected visual acuity. In the myopic LASIK review article by Farah and colleagues[70] the proportion of eyes that lost two or more lines of best-corrected visual acuity was 8% in the reviewed papers and 0.9% in the reviewed abstracts.

Summary of Loss of BSCVA. The ICRS had a very low incidence of loss of BSCVA, and when it occurred, it was not always clinically significant. The ICRS was safer than other refractive surgery procedures; however, since the center of the cornea was untouched by this form of refractive surgery, a low incidence of loss of BSCVA was expected.

Induced Cylinder

Induced astigmatism needs to be avoided if a new refractive surgical procedure for the treatment of low and moderate myopia is to be accepted.

ICRS. With the ICRS, most eyes had some degree of suture-induced with-the-rule cylinder in the first few weeks after surgery. This regressed in most cases after the 11-0 nylon suture was removed from the 12 o'clock incision site. Sutures were removed anytime after 2 weeks if with-the-rule cylinder of more than 1.00 D was noted. In general, long incisions, tight wound apposition of the incision with 1 or more sutures, and sutures left in too long were felt to be possible causes of astigmatism with this procedure. Astigmatism, when present, tended to decrease over time.

Only 1 patient had 2.00 D of induced cylinder at 6 months, and by 1 year, no patients had this level of astigmatism. Overall, for all 5 ICRS thicknesses, I found a mean induced cylinder of +0.09 D at 1 year, and there was no significant difference in the change in manifest cylinder among the ICRS thicknesses.

PRK. PRK for myopia creates a low degree of unpredictable surgically induced astigmatism, possibly due to irregular epithelial thickening during postoperative healing.[109] In a recent report, Schmidt and Hennekes[110] found that an average induced astigmatism of 0.58 D was seen after PRK. This cylinder was not correlated with preoperative astigmatism or with the depth of the ablation.

LASIK. Factors such as variable flap healing, minimal decentration of ablation, and epithelial cells under the flap can result in regular

astigmatism following LASIK. In one study, the mean surgically induced astigmatism was 0.93 D in the astigmatic myopic LASIK series.[108] In another study, Pallikaris and Siganos[65] found no statistically significant difference between preoperative and postoperative astigmatism 1 year after LASIK.

Summary of Induced Cylinder. The ICRS did not appear to induce any significant cylinder. The initial effect of suture-induced cylinder resolved after the suture was removed. Although PRK and LASIK induced higher average astigmatism than the ICRS, this comparison is probably not justified, since the ICRS study population probably had a lower level of preoperative myopia or astigmatism.

Endothelial Cell Counts

ICRS. The assessment of endothelial cell counts and morphology in the ICRS patients was undertaken to ascertain if this corneal implant would cause damage to the corneal endothelium. The two issues that needed to be addressed were:

1. Was there a significant loss of cells caused by the surgical technique?
2. Was there any evidence of ongoing or progressive endothelial cell loss?

The endothelium was assessed centrally and peripherally at the 6-o'clock and 10-o'clock positions. Peripheral endothelial cell counts were performed to assess cell morphology and hexagonality, since these parameters would have to change first if there was any ongoing damage to the endothelium from the ICRS. Peripheral digital images taken with a non-contact Konan Robo endothelial camera were not of sufficient quality for accurate measurement of cell counts. This resulted from posterior flexion of the endothelium caused by the ICRS. There was no significant change in the peripheral endothelial cell morphology assessed with either coefficient of variation or percentage of hexagonality.

A mean decrease in the central endothelial cell count of 0.8% at 6 months and 1.5% at 1 year was seen in this study. This did not represent a statistically significant loss of endothelial cells. The sample size was too small, however, to ascertain if there was a significant progressive central endothelial cell loss over this period of time. Longer follow-up of a larger study population would be necessary to determine if cell loss exceeded the recent reported annual cell loss of 0.6%.[111]

RK. MacRea and Rich[112] reported on the long-term effects of radial keratotomy on the corneal endothelium. A series of 25 eyes were followed after radial keratotomy for a period of 4 to 10 years. The mean central endothelial cell loss was 0.4% per year, and there was no change in either hexagonality or coefficient of variation of the cells. Evaluation of the

mid-peripheral endothelial cell counts demonstrated a 1% cell loss per year.

PRK. No detectable changes in central corneal endothelial cell density were found up to 2 years following PRK treatments of up to 6.0 D of myopia.[113] However, a transient modest loss (6.2%) of peripheral corneal endothelial cells was noted at 1 year, which resolved at the 2 year postoperative exam. Variations in endothelial cell shape caused by contact lens wear resolved after PRK. Other studies showed no long-term corneal endothelial damage, even in highly myopic eyes, 1 to 2 years after PRK.[114,115]

LASIK. Perez-Santonja and associates[116] reported that LASIK caused no damage to the central corneal endothelial cells. Postoperative improvements in endothelial cell density and coefficient of variation in cell size values were related to the discontinuance of contact lens use after surgery. LASIK to correct myopia up to -18.50 D caused no damage to the central corneal endothelium 6 months after the surgery. Pallikaris and Siganos[117] reported an average of 2.43% endothelial cell loss at 24 months. Recently, Jones and colleagues[118] reported the 3 month follow-up of a prospective study of 98 eyes from 68 consecutive patients and found no significant central endothelial cell loss, change in the coefficient of variation or percentage of hexagonality.

Summary of Endothelial Cell Counts. Endothelial cell loss after ICRS, RK, PRK, and LASIK did not appear to be a major safety concern. Nonetheless, further follow-up of the ICRS eyes should be done to document stability of the central endothelial cell counts.

Contrast Sensitivity Results

ICRS. Contrast sensitivity was measured using the Functional Acuity Contrast Test housed within a special view-in tester. The test was difficult to perform and hard to reproduce. Additionally, the normal range of response is broad, and there was no standard reference for a clinically significant loss. The mean loss in contrast sensitivity without glare across all spatial frequencies ranged from -0.07 to -0.15 log units for the operative eye and +0.01 to -0.148 in the fellow eye. The changes in the fellow eye, therefore, were not significantly different that those seen in the operative eye.

Similar results were obtained with contrast sensitivity with glare. The plots of the contrast sensitivity that graph the preoperative versus postoperative measurements demonstrated the important point that any changes seen were well within the normal range of response to the test. This was true for contrast sensitivity without glare and with glare.

RK. Tomlinson and Caroline[119] carried out a small study in 6 PERK patients. Contrast sensitivity was measured in both the operative and fellow eye. In this series, they found that in 50% of the patients, there was a significant decrease in contrast sensitivity. Ginsburg and associates[120]

reported contrast sensitivity under photopic conditions in 69 patients from the PERK study who had the procedure in only 1 eye. They found that 40% of the patients had 50% more loss of contrast sensitivity in the operative eye than in the fellow control eye in the higher spatial frequencies of 12 cpd and 18 cpd.

PRK. Transient loss of near contrast sensitivity was noted at 7 months after PRK and then returned to baseline within 1 year after PRK.[121] Eyes that have undergone PRK may have long-term impairment of mesopic vision compared to soft contact lens use.[122] The loss of low-contrast visual acuity 1 year after PRK was higher than the loss of high-contrast visual acuity. These losses were greater when the pupils were dilated and a glare source was used. The reduction of low-contrast sensitivity was positively correlated with the decentration of the ablation zone.[124] Pupil size was also correlated with decreased contrast sensitivity after PRK.[124]

LASIK. Paerez-Santonja and associates[125] tested 14 eyes from 10 patients after LASIK for the correction of myopia ranging from -6.00 to -19.50 D and found that contrast sensitivity was initially decreased. At 1 month postoperatively, there was significant loss of contrast sensitivity at the low and intermediate spatial frequencies of 3 and 6 cpd. By 3 months postoperatively, there was improvement to the point that there was no longer any statistically significant loss in contrast, and by 6 months, all tests had returned to baseline.

Summary of Contrast Sensitivity Results. Contrast sensitivity results were difficult to interpret and even more difficult to compare, since the measurement techniques were not standardized and were not correlated to any functional assessment of patient satisfaction. Even with these caveats, the result of the ICRS reported in this series of patients appeared at least as good as, if not better than, other keratorefractive surgical procedures.

Prolate Asphericity

The ICRS produced a positively aspheric corneal refractive surface that minimized refractive myopic shift in dim light conditions. The maintenance of a prolate topography was a unique advantage of the ICRS over other keratorefractive procedures where the postoperative cornea had an oblate shape. Fleming[126,127] reported the advantages of maintaining prolate topography after refractive surgery. He pointed out that the oblate corneal topography seen with radial keratotomy produced certain visual side effects, including myopic shift and loss of contrast sensitivity in mesopic conditions.

ICRS Postoperative Complications

There were no serious complications in the ICRS patients reported in this

thesis. Minor problems included 1 case of transient conjunctivitis, 3 cases of filamentary keratitis, and 1 case of transient iritis.

One patient developed deep stromal blood vessels. In my experience, the risk factors for neovascularization after the ICRS procedure have included:

1. An incision that made contact with a preexisting pannus or limbal blood vessel.
2. An incision that dehisced because of eye rubbing or abnormal wound healing.

In the case reported in my investigation, the incision went into a region of superior pannus. When the incision came in contact with an area of pannus, the blood vessels became inflamed and grew to the superficial wound in the first postoperative week. Left unchecked, they grew down into the incision and into the channel. Topical corticosteroids may have helped to stop vessel growth during the active growth stage. Once the blood vessels were in the channel, they grew to the ICRS and became quiescent.

Miscellaneous Findings. Other findings that were seen with the ICRS (that were not considered significant) included channel haze, lamellar channel deposits, ring hole deposits, and sterile channel infiltrates. Channel haze was seen in most eyes in the first postoperative month. This was presumably caused by the separation of the corneal lamellae, and it disappeared in most cases by month 3. Lamellar channel deposits were seen in approximately 70% of eyes. These were fine to coarse, white crystalline deposits, which never developed outside of the lamellar channel. They appeared between 1 and 2 months after surgery and peaked by 6 months. In many cases, they began to recede after 12 months. Only rarely were they noticeable, and they never limited visual acuity.

These lamellar channel deposits were similar to the deposits reported by McCarey[5] adjacent to hydrogel corneal inlays. Ring hole deposits developed at 4 to 6 weeks after surgery, which probably represented collagen and proteoglycan accumulation in the potential space.[46] Finally, sterile infiltrates occurred rarely in the superior channel 7 to 21 days after surgery. These infiltrates were fluffy in nature, and they receded in 7 to 14 days with mild corticosteroid treatment.

Reversibility

No refractive surgical procedure is without complications. It is an advantage, therefore, for a surgical procedure to be reversible. The ability to restore a patient to preoperative refraction, if the patient is dissatisfied or if the visual needs change, is comforting for the physician as well as the patient.

During the course of this study, and up to the present time, I have performed 6 ICRS removals. In the first phase of the study, I removed 3 in 49, representing a rate of 6%. These ICRS were removed because of patient complaints of visual disturbances, especially at night. Two of these patients had very large pupils (>7 mm) under mesopic conditions, and the patients complained of seeing the ICRS at night. In the second-phase of the study, I removed a total of 3, but 2 were from a patient who had good visual acuity and no symptoms. He was forced to have the ICRS removed because of FAA regulations that disqualified him from obtaining his pilot's license renewal as long as he had an experimental device in his cornea. The other patient was undercorrected and did not want to attempt an exchange procedure.

Although the ICRS is easily removable, I believe that if cases with large mesopic pupils are avoided and care is taken to properly position the ICRS evenly around the pupil, the incidence of ICRS removals should be significantly reduced.

Nonetheless, some patients may desire ICRS removal if their visual needs change. In the low-myopic patient, for instance, the onset of presbyopia might be addressed by ICRS removal or exchange in 1 eye.

CONCLUSION

An analysis of the data shows that the ICRS is effective in improving uncorrected visual acuity in patients with low to moderate myopia. Because it is an implant that mechanically flattens the cornea without affecting the central optical zone, the ICRS circumvents the problem of corneal remodeling and wound healing response and achieves a predictable, safe result.

I also found the ICRS product to be easily removed and/or exchanged. This means that if a patient is undercorrected, a thicker ring may be exchanged to produce the desired refractive outcome. Moreover, if a patient needs to remove the ICRS permanently, the eye returns to its original condition.

Over the last several years, my colleagues and I have envisioned a wide variety of treatment applications for this additive keratorefractive technology. It has been proposed, for instance, that future developments may include use of radial segments placed in the periphery of the cornea, like spokes of a wheel, as a treatment for low degrees of hyperopia. This additive keratorefractive technology is still clearly in its infancy.

In this study, 150° intrastromal corneal ring segments reliably and predictably corrected myopia and provided good visual acuity with predictable and stable refractive correction. There was a low incidence of

vision-threatening complications. This combination, coupled with the unique feature of reversibility and potential adjustability of the refractive effect, afforded the patients a favorable risk-benefit ratio. These features hold promise for widespread use of this new surgical modality.

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