Corneal endothelial profile after Ferrara Ring implantation

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PURPOSE: To analyze the long-term corneal endothelial profile after Ferrara ring implantation in keratoconus, post-LASIK ectasia and pellucid degeneration eyes.

METHODS: 102 eyes of 81 patients diagnosed with keratoconus, post-LASIK ectasia or pellucid degeneration, were retrospectively analyzed after a minimum of 1 year of Ferrara ring implantation (45.7±16.4 months, range: 13 to 71 months). Analysis included preoperative and postoperative keratometry, endothelial cell count, average endothelial cell size and coefficient of variation. Surgery was performed using the standard technique for Ferrara ring implantation following the Ferrara ring nomogram.

RESULTS: The mean cell count decreased from 2714±372 to 2562±406 cells/mm^2 (p<0.001). The calculated exponential cell loss rate over the mean interval of follow-up (4 years) was 1.4% per year. The average cell size increased from 375±56 to 399±61 µ^2 (p<0.001). The coefficient of variation increased from 0.22±0.075 to 0.26±0.010 (p=0.001). All corneas remained clear during the follow-up period. There was significant corneal flattening: the mean K decreased from 47.70 ± 2.29 D (range 43.70 to 53.80) to 44.86±2.02 D (range 41.20 to 51.20) (p=0.0001). It was found no correlation between keratometry and endothelial cell count (pre and postoperative). There was a positive correlation between pre and postoperative keratometry and between pre and postoperative cell count.

CONCLUSION: Our study suggests that some endothelial changes occur after Ferrara ring implantation. However, these changes are minimal and non-clinically significant, since the endothelial cell loss rate is not much higher than the normally expected for normal corneas.

INTRODUCTION

Many surgical procedures have been used to treat keratoconus and post-LASIK ectasia, including intrastromal corneal rings[1-6], cross-linking of corneal collagen[7-10], deep anterior lamellar keratoplasty (DALK)[11-15] and penetrating keratoplasty (PK)[16-20]. Preservation of the endothelium is crucial for every treatment involving the cornea; 400 to 800 endothelial cells/mm^2 is the minimum endothelial cell count for a clear cornea[21]. Some studies have evaluated the role of those treatments in the endothelial cells of keratoconus corneas[22-25]. In penetrating keratoplasty patients, there

is evidence of chronic, progressive, low-grade loss of endothelial cells[26-27].

The implantation of intrastromal rings is a minimally invasive surgical option for reshaping the cornea in keratoconus and post-refractive surgery ectasia. Intracorneal ring segments have been used to correct ectatic corneal diseases in order to reduce corneal steepening, reduce the irregular astigmatism and improve the visual acuity[1-6]. Besides, the ring is a surgical alternative to at least delay, if not eliminate, the need of lamellar or penetrating keratoplasty.

The Ferrara intrastromal corneal ring (FICR) are made of PMMA Perspex CQ acrylic segments. They vary in thickness from 150 to 300 µm. The segment cross-section is triangular, and the base for every thickness and diameter is a constant at 600 µm. The segments have 90°, 120°, 160° or 210° of arc.

To investigate the long-term corneal endothelial profile after Ferrara ring implantation in keratoconus and post-LASIK ectasia, we conducted the current retrospective study in which all eyes had a minimum follow-up of one year.
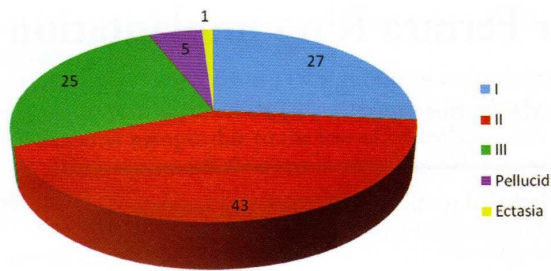
Figure 1. Distribution of diagnosis of operated patients (I, II and III refer to keratoconus classification).
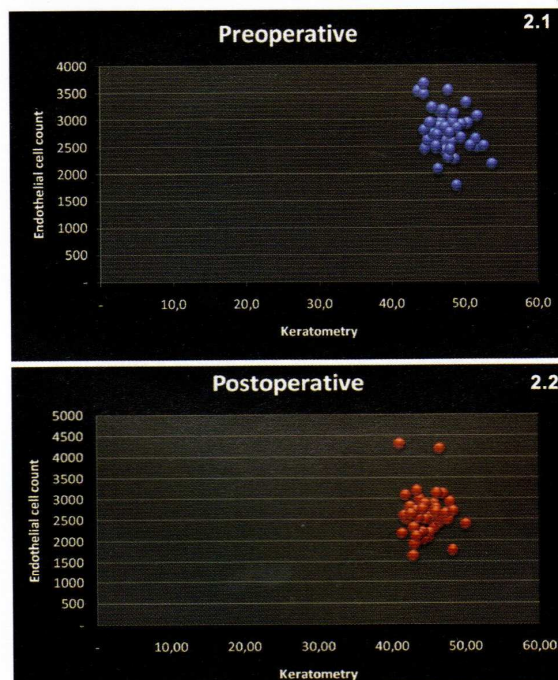
MATERIAL AND METHODS

We retrospectively reviewed patient records of one-hundred and two eyes of 81 patients which were followed for a period of at least 1 year (mean follow-up: 45.7 months, SD: 16.4 months; range: 13 to 71 months). All patients had the diagnosis of keratoconus, post-LASIK ectasia or pellucid degeneration (Figure 1).

The main indication for Ferrara ring implantation was contact lens intolerance and/or progression of the ectasia. Patients were excluded if any of the following criteria applied after preoperative examination: advanced keratoconus with curvatures over 75 diopters and significant apical opacity and scarring, Hydrops, thin corneas, with thickness below 300 μ in the ring track, intense atopia (these should be treated before the implant) and any ongoing infectious process, local or systemic.

Statistical analysis included preoperative and postoperative keratometry and endothelial characteristics (cell count, average cell size and coefficient of variation). The corneal topography was obtained from EyeMap (Alcon®, USA) and Pentacam (Oculus Pentacam®, Germany). Corneal endothelial cell analysis was performed with a non-contact specular microscope (SP-3000, Topcon®, Japan). Endothelial cell images were collected at the central region of the cornea and analyzed later. Statistical analysis was carried out using the XLStat software (2008, Addinsoft Inc.). Wilcoxon test for paired data was used to compare preoperative and postoperative data. Pearson´s test was used to correlate between average pre and postoperative keratometry and pre and postoperative cell count.

All surgeries were performed by the same surgeon (PF) using the standard technique for the FICR implantation, as previously described.[1-5] The rings were implanted according to Ferrara Ring Nomogram (www.ferraring.com). After surgery Ketorolac drops were used every 15 minutes for 3 hours, and a combination of 0.1% dexamethasone and 0.3% moxifloxacin or ciprofloxacin drops was used every 4 hours for 7 days, as well as hypromelose every 6 hours for 30 days.

RESULTS

All patients completed at least 1 year of follow-up (range 13 to 71 months). Mean age was 30.5 ± 8 years. The mean cell count decreased from (mean ± SD) 2714 ± 372 cells/mm^2 to 2562 ± 406 cells/mm^2 (p<0.001). The calculated exponential cell loss rate over the mean interval of follow-up (4 years) was 1.4% per year. The average cell size increased from (mean ± SD) 375 ± 56 μ^2 to 399 ± 61 μ^2 (p<0.001). The coefficient of variation increased from (mean ± SD) 0.22 ± 0.075 to 0.26 ± 0.010 (p = 0.001). All corneas remained clear during the follow-up period.

The mean maximum cell size increased from (mean ± SD) 529 ± 116 μ^2 to 639 ± 225 μ^2 (p<0.001). The mean minimum cell size varied from (mean ± SD) 225 ± 36 μ^2 to 226 ± 54 μ^2 (p = 0.936).

There was significant corneal flattening as showed by keratometry changes. The mean K decreased from 47.70 ± 2.29 (range 43.70 to 53.80) to 44.86 ± 2.02 (range 41.20 to 51.20) (p = 0.0001).

It was found no correlation between keratometry and endothelial cell count (pre and postoperative). There was a positive correlation between pre and postoperative keratometry and between pre and postoperative cell count (Table 1 and Figure 2).

Figures 2.1 and 2.2. Preoperative (2.1) and Postoperative (2.2) Scattergram of Keratometry and Endothelial cell count.

Table 1: Correlation between Pre and Postoperative Keratometry and Pre and Postoperative Endothelial cell count

	Pearson's correlation coefficient			
Parameters	**Preop Km**	**Preop ECC**	**Posop Km**	**Posop ECC**
Preop Km	1	-0.289	0.682	0.060
Preop ECC	-0.289	1	-0.270	0.383
Posop Km	0.682	-0.270	1	-0.005
Posop ECC	0.060	0.383	-0.005	1

ECC = endothelial cell count, Km = mean keratometry.

	p values			
Parameters	**Preop Km**	**Preop ECC**	**Posop Km**	**Posop ECC**
Preop Km	0	0.041	< 0.0001	0.681
Preop ECC	0.041	0	0.058	0.006
Posop Km	< 0.0001	0.058	0	0.972
Posop ECC	0.681	0.006	0.972	0

ECC = endothelial cell count, Km = mean keratometry.

DISCUSSION

The integrity of the corneal endothelium is one of the most important determinants for the control of corneal hydration. No clinically relevant regeneration mechanisms for the human endothelium in vivo are described in the literature. Wound healing occurs by enlargement, thinning and migration of remaining endothelial cells. The *in vivo* evaluation of the corneal endothelium normally is performed using contact or non-contact specular microscopy.

The topic of corneal endothelial cell loss in healthy subjects with increasing age is of great concern when designing a clinical trial to assess the effects of a surgical procedure on the corneal tissue. The consistent consensus is that a gradual decrease in cell density occurs with increasing age.[28,29,30]

Bourne *et al*[31] rephotographed 2 sets of patients after a 10-year period. The authors grouped the patients who were < 18 years old (5-15 years; n = 10) and > 18 years old (n = 42). The younger patient cohort had a 1.1% ± 0.8% per year loss in endothelial cell density; the older patient cohort had 0.6% ± 0.5% per year loss. The same author showed[32] that 10 years after cataract extraction, eyes continued to lose endothelial cells from the central cornea at the rate of 2.5% per year.

In our study we found a 1.4% loss of endothelial cells per year. Considering that most of the studied patients were young, the rate of endothelial cell loss was slightly higher than in normal eyes (1.1%). Moreover, there is no study in the current literature that shows the profile of the «normal» endothelial loss in keratoconus corneas, which could be higher than in normal corneas. The only report in the literature regarding the endothelium profile of keratoconus is non-prospective and studied only 12 eyes[33].

Endothelial cell loss after penetrating keratoplasty is known to be an ongoing process even years after surgery. It is well known that the cell loss is higher in the early time course after surgery and decreases 3-5 years after surgery. There is great variation of rates of cell loss after PK, ranging from 4.2%[34] to 9.4%[25] per year, at the long-term follow-up. Even after DALK, which is a surgical technique that spares the receptor endothelium, cell loss has been reported[15]. In one study, a decrease in average endothelial cell count from preoperative of approximately 200 cells/mm^2 was observed during the first 12 months after surgery. In patients in whom microperforation occurred during surgery, a loss of approximately 370 cells/mm^2 from preoperative (17%) was recorded 12 months after surgery and remained stable thereafter[15].

The only study[22] which assessed the endothelium after intrastromal rings (Intacs, Addition Technology Inc) implantation, reported that at 24 months after surgery, all corneal regions had a slight decrease in cell density. In all eyes, mean central and peripheral endothelial cell counts remained above 2495 cells/mm^2. Our results are similar, we obtained a higher average postoperative cell count (2562 cells/mm^2) and we had a longer follow-up (4 years).

The polimegatism of endothelial cells is determined by the coefficient of variation (CV). Yee *et al*[35] reported a CV range of ~ 0.22 – 0.31 for normal young adults, with an average of 0.27. In our study, the CV increased from (mean ± SD) 0.22 ± 0.075 to 0.26 ± 0.010 (p = 0.001). Despite the statistically significant change, the values remained normal, according to the major study in normal eyes[35].

Woolensak *et al.*[36], in a collagen cross-linking study in keratoconus, showed that the corneal transparency and the endothelial cell density (P = .45) remained unchanged. The follow-up was 23 months, and the sample was only 23 eyes. The same author, in an experimental study in rabbits[23], showed that riboflavin-UVA treatment should be safe as long as the dose is less than the endothelial cytotoxic dose of 0.65 J/cm2. In human corneas the endothelial cytotoxic UVA dose is reached in corneas thinner than 400 µ, which is not uncommon in keratoconus patients. Moreover, the data obtained from normal corneas of rabbit cannot be extrapolated to human keratoconic corneas, which can have a different metabolism and response to cross-linking. The study has a limitation of measuring the endothelial toxicity only at 4 and 24 hours after treat-

ment. The long-term endothelial cytotoxicity was not evaluated by the study.

Our study suggests that some endothelial changes occur after Ferrara ring implantation. However, these changes are minimal and non-clinically significant, since the endothelial cell loss rate is not much higher than the normally expected for normal corneas. In contrast, the long-term endothelial cell loss after other therapies for keratoconus is much higher (as in PK, or even DALK, in which the receptor endothelium is spared) or unknown (as in cross-linking).

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