Topography-Guided Photorefractive Keratectomy for Postkeratoplasty Astigmatism: Long-Term Outcomes

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Purpose: To evaluate the long-term efficacy and safety of topography-guided photorefractive keratectomy (TG-PRK) for postkeratoplasty refractive error correction.

Methods: A retrospective interventional case series of 54 eyes of 50 patients who underwent previous corneal transplants. Unaided distance visual acuity (UDVA) and best corrected visual acuity (CDVA), manifest refraction, mean central keratometric value, mean keratometric astigmatism, and postoperative complications were reviewed.

Results: Final follow-up was at mean 31 ($\pm$17) months. Sixteen point seven percent of eyes underwent more than 1 surface ablation. Mean UDVA improved from 0.96 $\pm$ 0.06 logarithm of the minimum angle of resolution (LogMAR) preoperatively to 0.46 $\pm$ 0.05 LogMAR of resolution at the final follow-up (Bonferroni, $P < 0.0001$). Mean UDVA improved by 4.4 Snellen lines. Improvement in CDVA was not significant, although a significant improvement was noted when eyes with preoperative CDVA <20/40 were analyzed separately (t test, $P = 0.005$). Mean astigmatism improved from -4.4 ± 0.26 D preoperatively to -2.4 ± 0.26 D at the final follow-up (Bonferroni, $P < 0.0001$), whereas mean SEQ improved from -2.5 ± 0.39 D preoperatively to -1.1 ± 0.25 D (Bonferroni, $P = 0.02$). In total, 9% at the preoperative visit and 55% at the final visit had less than 2 D of astigmatism, respectively. Keratometric astigmatism decreased from 5.24 $\pm$ 0.36 D preoperatively to 2.98 $\pm$ 0.34 D at the final follow-up (t test, $P < 0.0001$). No eyes developed clinically significant haze, 14.8% developed regression, and 13% had a reduction of 2 or more CDVA lines.

Conclusions: Postkeratoplasty topography–guided photorefractive keratectomy has good long-term efficacy and safety, resulting in significant UDVA, refractive, and keratometric improvement. Regression can occur after the first year of treatment, emphasizing the importance of long-term follow-up.

Key Words: topography-guided photorefractive keratectomy, post keratoplasty astigmatism, irregular astigmatism, laser refractive surgery, keratoplasty

Vision after successful penetrating keratoplasty is frequently limited by 4 to 5 D of corneal astigmatism.[1,2] Postkeratoplasty astigmatism is greater than 5 D in 15% to 30% of patients.[3] Postoperatively, most patients require spectacles or contact lens (CL) for the correction of astigmatism and/or ametropia.[4] When the astigmatism is irregular, standard optical correction (eg, spectacles or soft CL) often does not adequately correct vision. The management of irregular astigmatism can be challenging and ranges from rigid CL to surgical and laser refractive interventions.

CLs are an effective method of refractive error correction but can be limited by CL intolerance. Patients are also at risk of CL-related complications, such as infection.[5] Surgical options such as astigmatic keratotomy are popular but only correct astigmatism, and not spherical error.

Excimer laser photoablation is a potential treatment of both astigmatism and spherical refractive error postkeratoplasty. Topography-guided photorefractive keratectomy (TG-PRK) is a customized laser ablation, enabling specific targeting of corneal irregularity. Previous smaller studies have demonstrated a good efficacy and safety profile.[6–8] In this large retrospective interventional study, we examine the long-term visual, refractive, and safety outcomes of TG-PRK for the management of postkeratoplasty refractive error using a high-speed laser with an enhanced beam profile.

MATERIALS AND METHODS

Study Design

This study is a retrospective interventional case series of patients who underwent TG-PRK with mitomycin C for postkeratoplasty astigmatism. The study was granted ethical approval by the Pacific Laser Centre ethical review board and was conducted in adherence with the principles of the tenets of the Declaration of Helsinki. The inclusion criteria

were any patient who underwent postkeratoplasty TG-PRK (once or more times) for any level of astigmatism, with at least 12 months of post-op follow-up. The postkeratoplasty eye was defined as any eye that underwent previous penetrating keratoplasty or deep anterior lamellar keratoplasty. The exclusion criteria were any eye which had another surgical corneal intervention for astigmatism correction before TG-PRK (n = 2), eyes that underwent partial laser ablation treatment (n = 10), eyes that underwent treatment on a different laser platform before 2014 (n = 18), eyes in which TG-PRK was combined with corneal collagen cross-linking (n = 2), and eyes which could not be tracked because of pupil abnormalities (n = 2). Eyes with advanced pellucid marginal degeneration where satisfactory image registration could not be obtained were also excluded (n = 0). Partial laser ablation treatment refers to eyes that underwent treatment to improve corneal irregularity and partially correct refractive error. These are not eyes that underwent treatment for full refractive error correction aiming for emmetropia (plano). This is because these eyes had severe astigmatism/ametropia with inadequate corneal stromal beds, meaning the residual stromal bed would be less than 300 μm if they underwent full treatment.

Data Collection

A medical chart review was conducted to collect the following data: patient demographics, unaided distance visual acuity (UDVA), best corrected distance visual acuity (CDVA), astigmatism, spherical equivalent (SEQ), mean central keratometric value (K central), mean keratometric astigmatism value, and the presence of postoperative complications. The data were collected for the preoperative baseline visit, intermediate follow-up (12 months, but if not available, then any visit between 6 and 18 months posttreatment), and final follow-up. Final follow-up for all eyes (including eyes with repeat surface ablation) refers to the follow-up time since first ablation. Eyes with irregular astigmatism are more prone to variable refractions and therefore CDVA. Eyes with the loss of 2 or more lines of CDVA were considered eyes with true loss of CDVA. To avoid bias in reporting of results, however, we reported all eyes that lost one or more lines of CDVA.

Preoperative corneal topography was preformed by using the Sirius topographer/tomographer with Schwind eye-tech solutions GmbH, Kleinostheim, Germany. Postoperative topography was also performed using a placido-based system (Atlas; Carl Zeiss Meditec, Jena, Germany). Vector analysis assumes a regular toric corneal surface and was therefore not used for the evaluation of astigmatism correction because of the frequent presence of irregular astigmatism.

Post–TG-PRK corneal haze was graded in a method described in the literature by Fantes et al.[9] To minimize bias in the reporting of haze, any haze that was reported in any visit after surface ablation was reported in this study. This includes data from visits to the laser center where the procedure was carried out, visits to the optometrists, or visits to the tertiary cornea service at the Eye Care Center at Vancouver general hospital.

Surgical Technique

Preoperative Assessment

A full ophthalmologic examination was performed on all the patients before surgery, including manifest refraction, cycloplegic refraction, topography, and tomography (SCHWIND Sirius, SCHWIND eye-tech solutions GmbH) performed over a diameter of 4.5 mm. The 4.5 mm of the Sirius refer only to the determination of asphericity, but the scans are 12 mm in width. CDVA and UDVA were measured with a phoropter and Snellen chart.

Surgical Procedure

We used the SCHWIND Custom Ablation Manager (SCHWIND eye-tech solutions GmbH, Kleinostheim, Germany) in the aberration-on mode (ie, full CW). Sirius (C.S.O Frienze, Italy) combines placido-disk topography with Scheimpflug tomography of the anterior segment. Sirius provides information on pachymetry, elevation, curvature, and dioptric power of both corneal surfaces over a diameter of 12 mm. All biometric measurements of the anterior chamber are calculated using 25 sections from the cornea. The devices used in this study meet the standards of European conformity (Conformité Européene or CE marking) but are not approved by the US Food and Drug Administration. The treatment plan was calculated with minimal residual stromal thickness of 300 μm (ie, 300 μm or more). Drops of topical anesthetics were instilled in the upper and lower used. A lid speculum was inserted to allow maximum exposure of the globe.

Alignment with the laser was achieved with a 1050 Hz infrared eye tracker with simultaneous limbus, pupil, and torsional tracking integrated into the laser system and centered on the corneal vertex. The eye tracker had a response time of 1.7 milliseconds with a system total latency time of 2.9 milliseconds. The ablation profile was centered on the corneal vertex determined by the topography (taking 100% of the pupil offset value[10]), which closely approximates the visual axis.[11,12] Furthermore, the topographic keratometry readings at 3-mm diameter were used for the compensation of the loss of efficiency when ablating the cornea at nonnormal incidences. A 5.5- to 6.5-mm diameter ablation zone and a transition zone of up to 9 mm were used. Patients were requested to look at a pulsing green fixation light throughout the ablation. Mitomycin C 0.02% was applied for 45 to 60 seconds at the conclusions of the ablation; the ocular surface was thoroughly washed with balanced salt solution. Bandage CL was applied, and topical antibiotics and corticosteroid eye drops were instilled.

Patients received topical antibiotic and corticosteroid drops to use 4 times a day for 1 week and lubricating eye drops to use as needed.

Statistical Analysis

Data were recorded in Microsoft Excel (2019). The results are reported as mean ± SD for patient's age and follow-up time and as mean ± standard error of mean for all other measurements. Visual acuity was measured with an

electronic Snellen chart and converted to logarithm of the minimum angle of resolution (LogMAR) values for data analysis. The Kolmogorov–Smirnov test was used to test for the normality of distribution. A repeated measures analysis of variance (ANOVA) was conducted to investigate the effect of TG-PRK on UDVA, CDVA, mean astigmatism, and SEQ. The Mauchly test for sphericity, with subsequent Greenhouse–Geisser correction was used. A Bonferroni correction was conducted for the post hoc analysis to assess for differences at 3 time points (preoperative visit, intermediate follow-up, and final follow-up) and was adjusted in SPSS to compare it with the significance level identified below. A paired samples *t* test was used to evaluate for differences between preoperative and postoperative keratometry values. A paired samples *t* test was also used pre- and post-operative UDVA, CDVA, astigmatism, keratometric astigmatism, K central, and SEQ of eyes undergoing repeat TG-PRK. The univariate linear regression was used to predict the effect of refractive manifest astigmatism on keratometric astigmatism outcomes. The univariate Pearson correlation test was used to analyze the correlation between refractive manifest astigmatism and keratometric astigmatism. A significance level of 0.05 was predetermined ($\alpha = 5\%$), and all data were analyzed using SPSS software, version 22 (SPSS Inc, Chicago, IL).

RESULTS

Fifty-four eyes of 50 patients underwent TG-PRK for postkeratoplasty astigmatism, of which 25 were right eyes and 29 were left eyes. All 54 eyes were studied, rather than 50 eyes of 50 patients only, to avoid selection bias. Seventeen patients were women, and 33 were men. The average age was 52 years (±12.4 years, range: 23–79 years). The most common pre-operative diagnosis was keratoconus, affecting 33 (61%) of 54 eyes. One eye had pellucid marginal degeneration, 5 had Fuchs endothelial dystrophy, 1 had cornea stromal dystrophy, 5 had postrefractive surgery ectasia, 5 had trauma or infection-related corneal scarring, and 4 had unknown pre-keratoplasty diagno-

ses. All eyes undergoing TG-PRK were post-penetrating keratoplasty eyes, except for 1 eye that previously underwent deep anterior lamellar keratoplasty. The mean preoperative central corneal thickness was 552 μm (±7 μm).

The mean postoperative intermediate follow-up visit was at 10.5 ± 2.9 months (range 6–18 months) after TG-PRK. The postoperative final follow-up was at mean 31 months (±17 months, range: 10–70 months) post–TG-PRK. Thirty-six (67%) of 54 eyes had more than 18 months of follow-up, and 52 (96%) of 54 eyes had 12 months or more follow-up. Nine (16.7%) of the 54 eyes required more than 1 surface ablation. Of these, 8 eyes required a total of 2 treatments and 1 eye required 3 treatments.
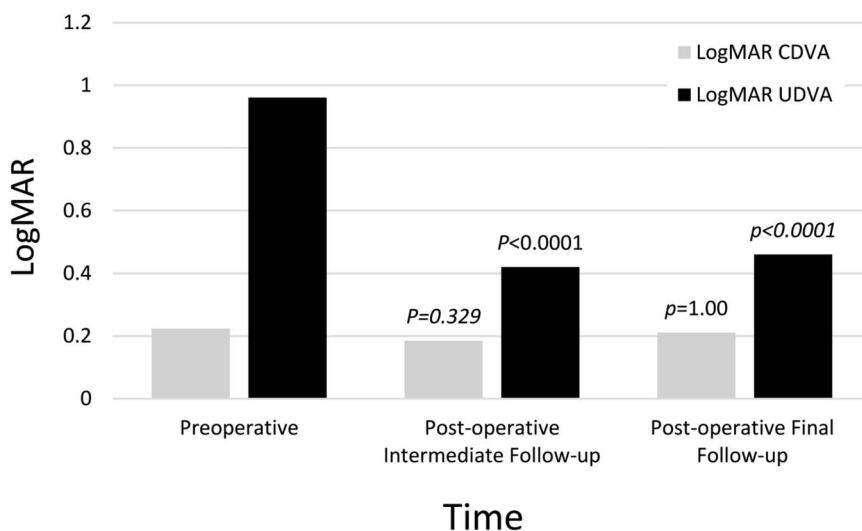
Final Visual Acuity

Pre- and post-operative unaided distance visual acuities (UDVA) were available for 49 of 54 eyes. The mean UDVA improved from 0.96 ± 0.06 LogMAR (Snellen equivalent ~ 20/180) preoperatively to 0.42 ± 0.05 LogMAR (Snellen equivalent ~ 20/50) at intermediate follow-up and 0.46 ± 0.05 LogMAR (Snellen equivalent ~ 20/60) at final post-op follow-up (Fig. 1).

When using a repeated measures ANOVA with Greenhouse–Geisser correction, the mean scores for UDVA ($F(1.248, 56.138) = 47.283$, $P < 0.0001$) at the 3 different time points were statistically significantly different.

Post hoc testing using the Bonferroni correction revealed that TG-PRK led to a significant improvement of UDVA when comparing preoperative with intermediate follow-ups ($P < 0.0001$) and to a significant improvement when comparing preoperative to final follow-up measurements ($P < 0.0001$). The level of UDVA was not statistically significantly different when comparing intermediate follow-up with final follow-up UDVA ($P = 0.607$) (Fig. 2A).

UDVA improved by 2 or more lines in 37 (75.5%) of 49 eyes, by 4 or more lines in 25 (51%) of 49, and by 6 or more lines in 18 (36.7%) of 49 eyes. The mean number of lines of improvement in UDVA was 4.4 lines (±3.9 lines).

FIGURE 1. Mean best-corrected distance visual acuity (CDVA) and UDVA in LogMAR at the pre-operative visit, intermediate follow-up, and final follow-up.
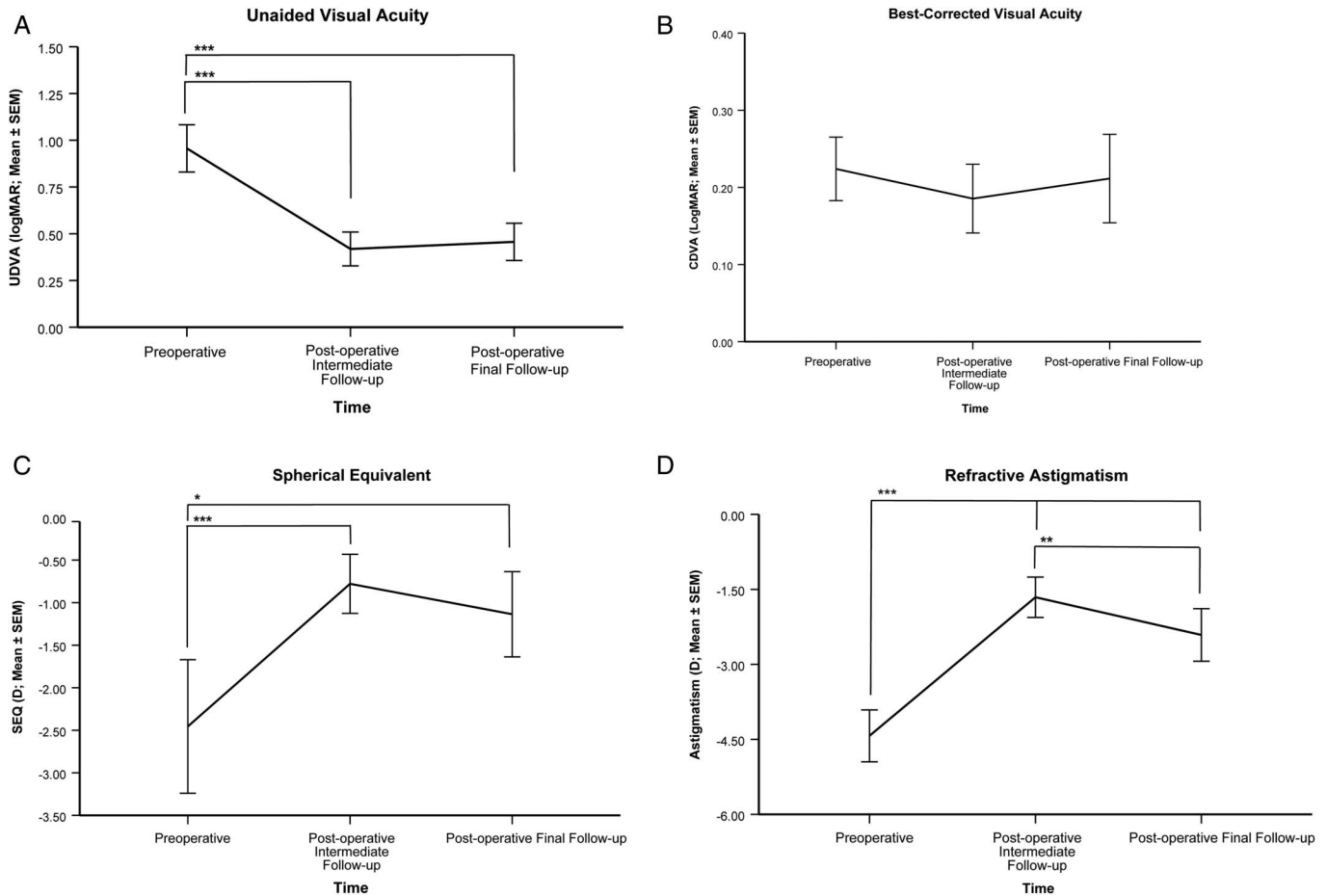
FIGURE 2. A, Change in mean LogMAR UDVA over time. B, Change in mean LogMAR CDVA over time. C, D, Change in SEQ and refractive astigmatism over time.

The median improvement was 4 lines. No eyes had a UDVA better than 20/40 preoperatively, and only 3 (6%) eyes had a UDVA of 20/40 preoperatively. Twenty-three (46%) of the 47 eyes with known UDVA at final follow-up post–TG-PRK had a UDVA of 20/40 or better.

Preoperative and final follow-up CDVA was available for all eyes and for 48 of 54 eyes for the intermediate follow-up.

The mean CDVA changed from 0.22 ± 0.02 LogMAR preoperatively to 0.19 ± 0.02 LogMAR at intermediate follow-up and 0.21 ± 0.03 LogMAR at the final follow-up. CDVA was 20/40 or better in 85.2% (46 of 54 eyes), 87.5% (42 of 48 eyes), and 83.3% (45 of 54 eyes) of eyes at preoperative, intermediate, and final follow-up, respectively.

When using a repeated measures ANOVA with Greenhouse–Geisser correction, there was no significant difference of CDVA measures at preoperative versus intermediate and versus final follow-ups ($F(1.602, 75.296) = 1.223$, $P = 0.299$) (Fig. 2B).

Two eyes developed visually significant cataracts, 1 eye had worsened glaucoma, 1 eye had a significant epiretinal membrane (ERM), and another eye underwent ERM surgery, followed by corneal decompensation. When these were excluded from post-op analysis, a nonsignificant improve-

ment in CDVA to 0.18 LogMAR at final follow-up was noted, and CDVA was 20/40 or better in 88% (43 of 49) of eyes.

In the 8 eyes with preoperative CDVA worse than 20/40 (ie, 20/50 or worse), the mean LogMAR improved from 0.46 LogMAR preoperatively to 0.21 LogMAR at final follow-up. A paired samples *t* test revealed statistically significant improvement of CDVA ($P = 0.005$). Six (75%) of the 8 eyes had a final CDVA of 20/32 or better.

Refractive Correction

Refractive astigmatism and SEQ measurements were available for all 54 eyes preoperatively, 51 eyes at intermediate follow-up, and 53 eyes at final follow-up. The mean astigmatism improved from −4.4 ± 0.26 D preoperatively to −1.7 ± 0.20 D at intermediate follow-up and −2.4 ± 0.26 D at the final follow-up. The mean SEQ improved from −2.5 ± 0.39 D preoperatively to −0.8 ± 0.17 D at intermediate follow-up and −1.1 ± 0.25 D at the final follow-up. When using a repeated measures ANOVA with Greenhouse–Geisser correction, the mean scores for astigmatism ($F(1.724, 84.453) = 55.312$, $P < 0.0001$) and SEQ ($F(1.399, 68.556) = 11.412$, $P < 0.0001$) at

the 3 different time points were statistically significantly different (Figs. 2C, D).

The mean astigmatism decreased by 2.1 D between preoperative visit and final follow-up. The mean SEQ decreased by 1.1 D between preoperative visit and final follow-up. Post hoc testing using the Bonferroni correction revealed that TG-PRK led to a significant improvement of astigmatism and SEQ when comparing preoperative visit with intermediate follow-up ($P < 0.0001$ and $P < 0.0001$, respectively) and to a significant improvement when comparing preoperative visit to final follow-up ($P < 0.0001$ and $P = 0.02$, respectively). The mean astigmatism and SEQ regressed by 0.7 D and 0.4 D between intermediate and final follow-up, respectively. Change of astigmatism and SEQ between intermediate follow-up and final follow-up was noted, this was statistically significant for astigmatism ($P = 0.005$) but was not statistically significant for SEQ ($P = 0.429$).

Preoperatively, 9% had 2 D or less of astigmatism, and 28% had 3 D or less of astigmatism. At the intermediate visit, 76% had 2 D or less of astigmatism and 84% had 3 D or less of astigmatism. At the final follow-up, 55% of eyes had 2 D or less of astigmatism and 78% had 3 D or less of astigmatism. This is summarized in Figure 3.

The SEQ was within 0.5 D of emmetropia for 6% of eyes preoperatively, 33% at intermediate follow-up, and 33% of eyes at the final follow-up. The mean SEQ was within 1D of emmetropia for 22% of eyes at preoperatively, 52% at intermediate follow-up, and 40% of eyes at final follow-up.

Keratometry

The mean K central values were recorded preoperatively and at final follow-up for all 54 eyes preoperatively and 52 eyes at the final follow-up. The keratometric astigmatism values were recorded preoperatively and at the final follow-up for 53 eyes preoperatively and 52 eyes at the final follow-up. K central decreased from 45.51 ± 0.30 D preoperatively to 44.13 ± 0.39 D at the last follow-up visit. The keratometric astigmatism value decreased from 5.24 ± 0.36 D preoperatively to 2.98 ± 0.34 D at the final follow-up. A paired samples t test revealed statistically significant differences of the mean final follow-up measurements of K central ($P < 0.0001$) and keratometric astigmatism ($P < 0.0001$) from preoperative measurements (Table 1).

Retreatment

Nine (16.7%) of 54 eyes required TG-PRK retreatment. The average age of patients was 53 years, and 8 were men. The average follow-up was 36 months (3 years, ± 21 months), and the median follow-up was 40 months. The reason for additional surface ablation enhancement was regression in 4 eyes, residual astigmatism in 4 eyes, and for overcorrection in 1 eye. For the 3 eyes that had regression, preoperative CCT, SEQ, and astigmatism were 526 μm, +0.375 D, and 2.25 D for the first eye; 560 μm, −4.5 D, and 2.0 D for the second eye; and 620 μm, −1.75 D, and 4.25 D for the third eye. Of the 4 eyes requiring astigmatism correction, 1 eye had untracked treatment becase of iris trauma, 1 eye had preoperative temporal corneal graft haze limiting the effect of treatment, 1 eye had very high preoperative astigmatism (7.5 D), and 1 eye had unknown cause for poor response to the first TG-PRK treatment.

There was a statistically significant improvement in CDVA, astigmatism, and keratometric astigmatism, but not in UDVA, SEQ, or K central (Table 2) compared with the initial preoperative visit. The mean CDVA improved from Snellen equivalent of ~ 20/80 to ~ 20/40, as shown in Table 2.

SAFETY

Haze Development

None of the 54 eyes developed clinically significant haze (grade 2 or higher)[13], and in total, 9 (17%) of 54 eyes developed post–TG-PRK corneal haze. Of these, 7 eyes developed grade 0.5 corneal haze after TG-PRK, and 1 eye developed grade 1 haze. In the eye with grade 1 haze, the UDVA improved from 20/200 to 20/40 and the CDVA from 20/50 to 20/30. No cause or risk factors for the development of haze were identified. Only 2 of the 9 eyes that developed haze had more than 1 surface ablation, graded as trace haze.
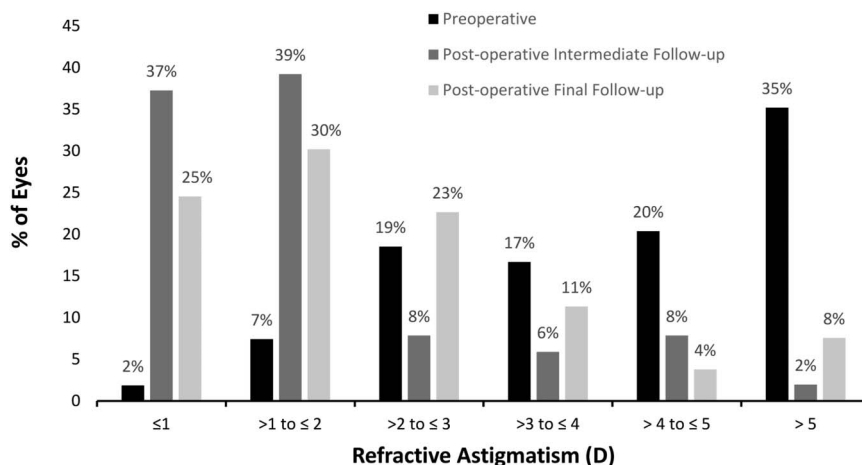
FIGURE 3. Distribution of refractive astigmatism (D) at pre-operative and post-operative intermediate and final follow-up visits.

TABLE 1. Comparison Between Preoperative and Postoperative Visual, Refractive, and Topographic Measurements

	Preoperative	Intermediate	Final Follow-up	
	Mean ± SEM	Mean ± SEM	Mean ± SEM	*P*
SEQ (D)	−2.5 ± 0.39	−0.8 ± 0.17	−1.1 ± 0.25	<0.0001*
RA (D)	−4.4 ± 0.26	−1.7 ± 0.20	−2.4 ± 0.26	<0.0001*
CDVA (LogMAR)	0.22 ± 0.02	0.19 ± 0.02	0.21 ± 0.03	0.299*
UDVA (LogMAR)	0.96 ± 0.06	0.42 ± 0.05	0.46 ± 0.05	<0.0001*
KA (D)	5.24 ± 0.36	†	2.98 ± 0.34	<0.0001
K Central (D)	45.51 ± 0.30	†	44.13 ± 0.36	<0.0001

*Greenhouse–Geisser Correction.
†Data not available.
KA, keratometric astigmatism; LogMAR, logarithm of the minimum angle of resolution; RA, refractive astigmatism; SEM, standard error of mean.

Regression

Eight (14.8%) of 54 eyes developed regression, 3 of which underwent repeat surface ablation. Six of 8 eyes were of male patients; the average age was 53 ± 10 years. Seven of 8 eyes originally underwent penetrating keratoplasty (PKP) for keratoconus, and 1 underwent PKP for trauma-related corneal scarring. The average preoperative CCT was 553 ± 12 μm. The mean last follow-up was 3.5 ± 1.3 years. UDVA improved from 1.2 at the mean preoperative visit to 0.8 LogMAR at the final follow-up. The mean CDVA changed from 0.2 to 0.3 LogMAR. At preoperative visit, mean spherical error, cylindrical error, and SEQ were −0.25 D, −4.2 D, and −2.3 D, respectively. At the final follow-up, mean values were −0.19 D, −4.4 D, and −2.4 D, respectively. K central and keratometric astigmatism at preoperative visit were 45.1 ± 0.5 D and 5.9 ± 0.8 D, respectively, and at the final follow-up 44.8 ± 1 D and 5.5 ± 1.4 D, respectively. Owing to the low number of eyes with regression, useful statistical analysis is not possible. Of the 3 that had repeat surface ablation, the regression was successfully treated in 2 eyes, and regression recurred in the third eye. Owing to the missing data, no time point for maximum regression could be calculated; however, it was observed that regression was occurring more than one-year post–TG-PRK (at 24, 30, 48, and 48 months, respectively) in 4 of the 8 eyes. There was a significant correlation between last refractive manifest astigmatism and last keratometric astigmatism values (Pearson correlation coefficient, r = 0.86, *P* = 0.003). A significant regression equation was found ($F_{(1,6)}$ = 17.234, *P* = 0.006), with an R^2 of 0.74 and an adjusted R^2 of 0.70. The linear regression model was able to predict 70.0% of the variation in the refractive manifest astigmatism (ie, dependent variable): refractive manifest astigmatism = 1.0 + 0.62* keratometric astigmatism. Finally, for each 1 D increase in keratometric astigmatism, refractive manifest astigmatism increases by 0.62 D (Fig. 4).

Graft Failure

In total, 4 patients developed graft failure–related corneal decompensation. One of these may have been precipitated by pars plana vitrectomy surgery for ERM removal. The other 3 are believed to be related to the time-related loss of endothelial cells, which is expected with longer follow-up.

Loss of UDVA

Three (5.5%) of 54 eyes had worsened UDVA at the final follow-up. All 3 eyes were PKP eyes and were found to have lost one line of UDVA. One eye lost vision because of progressive astigmatism related to regression and required repeat PKP. Another eye underwent PTK, followed by repeat PKP because of unstable vision. The third eye lost vision because of graft failure and persistent irregular astigmatism and also required a repeat PKP. The final UDVA was recorded for all of these patients before further intervention to avoid bias in reporting of visual outcomes.

Four eyes had unknown UDVA at the final follow-up, but they all had a recorded final follow-up CDVA. The first eye had an improvement in CDVA from 20/30 to 20/20 and had improvement in UDVA from 20/100 preoperatively to 20/30 at the intermediate follow-up. The second eye had an improvement of CDVA from 20/25 to 20/20 at the final follow-up, with no recorded post-op UDVA. The third eye had no change in CDVA (20/20 before and at the final follow-up), and UDVA worsened from 20/40 preoperatively to 20/50 at the intermediate follow-up. Preoperative SEQ was 1.125 D and −2 D at the intermediate follow-up, and this patient required a retreatment because of the initial overtreatment. The fourth eye's CDVA declined from 20/25 to 20/40 at the last post-op visit,

TABLE 2. Summary of Preoperative and Postoperative Visual, Refractive, and Topographic Measurements for Eyes That Underwent Repeat Surface Ablation

	Preoperative (Mean ± SEM)	Final Follow-up (Mean ± SEM)	*P* (paired *t* test)
UDVA (LogMAR)	0.9 ± 0.19	0.65 ± 0.14	0.11
CDVA (LogMAR)	0.62 ± 0.14	0.31 ± 0.08	0.038
RA (D)	4.2 ± 0.6	2.4 ± 0.5	0.009
SEQ (D)	−2.0 ± 0.8	1.4 ± 0.3	0.43
K Central (D)	45.6 ± 1.0	44.5 ± 1.1	0.33
KA (D)	5.3 ± 1.1	2.7 ± 0.6	0.05

KA, keratometric astigmatism; LogMAR, logarithm of the minimum angle of resolution; RA, refractive astigmatism; SEM, standard error of mean.
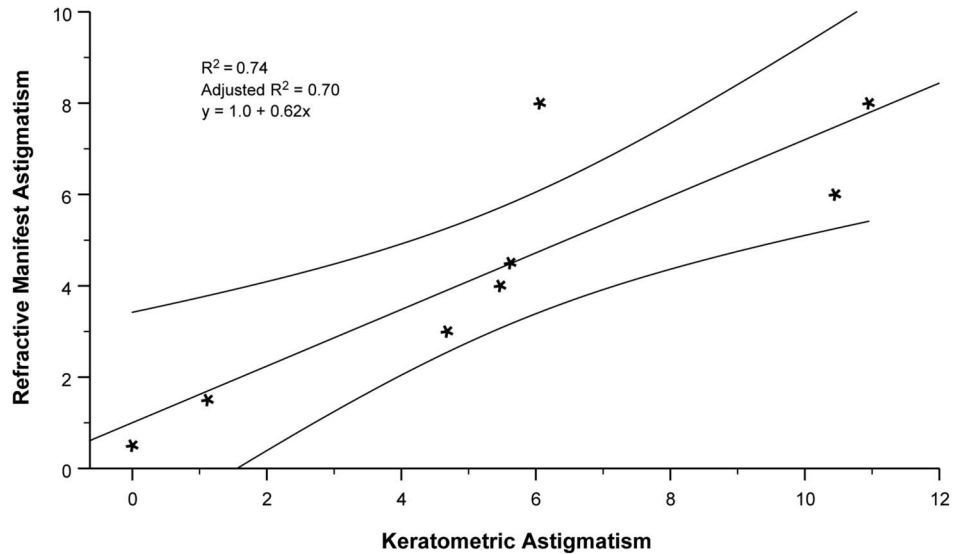
FIGURE 4. Linear regression model displaying relationship between refractive astigmatism and keratometric astigmatism.

and the UDVA decreased from 20/60 preoperatively to 20/200 at the intermediate follow-up. Vision decreased because of post–TG-PRK regression, and the eye had preexisting advanced glaucoma. The mean K central changed from 42.79D to 41.5D and the keratometric astigmatism from 5.61D to 6D at the final follow-up. The final refraction was not known but changed from SEQ of −0.625 D and astigmatism of −2.25 D preoperatively to SEQ of −1.125 D and astigmatism of −4.25 D at 6 months postoperatively.

Loss of CDVA

Seven (13%) of 54 eyes had a reduction of 2 or more lines of CDVA. The reason for loss of CDVA is detailed in Table 3.

Eight eyes lost one line of CDVA. In 4 of these 8 eyes, no clear cause was found and was believed to be because of variable refraction. In fact, 3 of these 4 eyes had improved UDVA (3 or more lines in all eyes), and 1 eye had unchanged UDVA. In the other 4 eyes in which a cause was found, causes were cataract development in the first eye, glaucoma with astigmatism regression in the second eye, epiretinal membrane formation in the third eye, and regression with ectasia in the fourth eye.

DISCUSSION

Our retrospective interventional case series of TG-PRK for post-PK astigmatism is the largest (54 eyes) presented to date, and with the most long-term follow-up (average 31 months), as far as we know. The variability of magnitude and pattern of astigmatism treated in postkeratoplasty eyes, as compared to normal eyes, means that a larger number of eyes is needed to more accurately assess treatment outcomes. Secondly, longer follow-ups would enable a wider time frame for the detection of post–TG-PRK regression. We report a significant improvement in UDVA, astigmatism, SEQ, keratometric astigmatism, and K central readings ($P < 0.0001$, $P < 0.0001$, $P = 0.045$, $P < 0.0001$, and $P < 0.0001$, respectively) between preoperative and final postoperative visits.

This technique is performed in postkeratoplasty eyes with refractive errors which have had removal of all corneal graft sutures and in which treatment would not leave an RSB of less than 300 μm. Our study did not include postkeratoplasty eyes that underwent other invasive interventions (eg, astigmatic keratotomy) for astigmatism correction before TG-PRK. Therefore, our study findings are not applicable to this subgroup of eyes, although our clinical experience (unpublished) suggests efficacy of TG-PRK even in this subgroup.

In our experience, most patients with postkeratoplasty irregular astigmatism, and refractive error are likely to be

TABLE 3. Reasons for Loss of Two or More Lines of CDVA Following TG-PRK

Patient Number	Lines of CDVA Lost	Reason for CDVA Loss
Patient #1	4	Regression with ectasia development, eye had to undergo penetrating keratoplasty.
Patient #2	2	No clear cause for CDVA decrease from 20/20 to 20/30. UDVA improved from 20/200 to 20/50
Patient #3	3	Unstable vision despite improvement in astigmatism irregularity. Reduced vision thought to be related to very endothelial low cell count (pre-existing before TG-PRK) leading to subclinical corneal decompensation.
Patient #4	3	SEQ improved from −5.4D to −2.6D. Worsened vision due to Epiretinal membrane peel surgery followed by cornea decompensation.
Patient #5	6	Astigmatism down to 0 D 1 year post op, then regressed to −8D.
Patient #6	3	Cornea decompensation due to graft failure.
Patient #7	5	Developed cornea decompensation which was treated successfully with endothelial keratoplasty. Final vision reduced due to significant cataract formation.

candidates for the TG-PRK using a transepithelial technique. High levels of ametropia with astigmatism up to 7 D can be effectively treated with a single ablation. Even a partial treatment can improve the refractive error and irregular astigmatism to the point where patients are able to function well with unaided vision, soft CLs, or spectacles. Our impression is that patients who were most satisfied were those with CL intolerance and more extreme irregular astigmatism. The rapid recovery was also appreciated compared with the recovery after their corneal transplant surgery. As mentioned later in the discussion, regression is a challenge in some patients in the long term.

The most common intervention for the correction of postkeratoplasty astigmatism is arcuate keratotomy (AK).[14,15] It is an effective intervention but has the limitations of poor predictability, operator dependence, need for additional interventions, and risk of vision loss. Furthermore, AKs only treat astigmatism and not spherical error, meaning significantly improved UDVA is often not achieved.[15,16] Previous studies of TG-PRK for postkeratoplasty astigmatism have consistently shown significant improvement in UDVA.[6,7] This finding is supported by our study, in which the improvement in UDVA is both statistically and clinically significant. Good UDVA is particularly beneficial to CL-intolerant patients. The mean number of lines of improvement was 4.4 lines, with 46% achieving UDVA of 20/40 or better (compared with 6% pre-op) at the final follow-up. UDVA of 20/40 enables independence for various activities of daily living. For instance, 20/40 UDVA is the satisfactory visual acuity for driving in most developed countries.[17–19] Thus, the improvement in UDVA is one of the most important treatment outcomes of TG-PRK.

The aim of TG-PRK in our study was to correct both ametropia and high astigmatism, which are 2 principal challenges in postkeratoplasty visual improvement. We conducted refractive TG-PRK, aiming to correct both ametropia and astigmatism in a single-step ablative procedure. There are alternative methods that require multiple interventions, for example, arcuate keratotomy to reduce astigmatism, followed by laser excimer ablation or toric intraocular lens implantation to treat residual astigmatism.[14] Multistep laser refractive surgery has also been proposed.[6,20–22] Sorkin et al[6] used TG-PRK to regularize the corneal surface, followed by refractive PRK. This method has the advantage of allowing refractive correction of TG-PRK–induced refractive error in the second step. There are pros and cons to single-step versus multistep techniques. Our preferred technique of single-step TG-PRK has the advantages of minimizing cost to patients, minimizing the risk of repeat surface ablation (eg haze development), and avoiding barriers to having a second ablation (eg patient wishes and insufficient residual stromal bed). In our study, repeat TG-PRK was therefore only performed when needed and not as a preplanned procedure. We report a 16.7% repeat surface ablation rate. In our subgroup of repeat surface ablation, there was significant improvement in mean CDVA, mean astigmatism, and mean keratometric astigmatism. UDVA improved without reaching statistical significance. Additional surface ablation enhancement is therefore a potential option for eyes with regression or undertreatment. The significant improvement in CDVA indicates better regularity of the corneal surface

after repeat surface ablation. This may therefore be an effective option to explore with patients who still have irregular astigmatism after initial TG-PRK.

A smaller study by Laíns et al[8] reported not only significant improvements in refractive errors and UDVA at mean of 9.2 months of follow-up but also significant improvements in CDVA. The study only included eyes with a minimum spectacle CDVA of 20/100, which would have resulted in the exclusion of eyes with very high irregular astigmatism. Ward et al reported not only significant improvements in UDVA and refractive errors at 1 year in 20 eyes for postkeratoplasty PRK (non-TG) but also found significant improvements in best spectacle corrected visual acuity. Similarly, Bandeira e Silva et al reported significant improvements in best spectacle corrected VA of 15 postkeratoplasty eyes after TG-PRK.[7] The CDVA for the eyes in our study had been measured with both CL (soft, rigid, or scleral) and spectacles, hence making a difference in CDVA more difficult to appreciate because of better CL correction of irregular astigmatism. Sorkin et al[6] conducted a study of 34 eyes in which TG-PRK was initially used to treat postkeratoplasty astigmatism, followed by additional surface ablation (either TG-PRK, WG-PRK, or WO-PRK) for 21 (62%) of 34 eyes to correct residual refractive error or improve corneal regularity. A nonsignificant improvement in CDVA was noted after initial TG-PRK. Of note, in the initial TG-PRK, a group of patients had topographical regularization of the corneal surface only, with no manifest refraction correction. An analysis was performed for 24 of 34 eyes, in which patients unable or unwilling to undergo second-step ablation were excluded from the VA analysis. In this group, a significant improvement in CDVA was reported from mean LogMAR of 0.22 to 0.14. Therefore, although the results of the aforementioned study are important in determining the value of stepwise PRK, they are no comparable with studies focusing primarily on single-step refractive TG-PRK. Another consideration for both clinicians and patients is the extent of CDVA improvement. In other words, although an overall mean improvement of one line can be statistically significant, it is important to address whether this is clinically significant considering risks and costs of treatment. In our study, the CDVA improvement was not significant even when eyes which developed comorbidities (eg ERM and cataract) were excluded (improvement from 0.22 LogMAR to 0.18 LogMAR). It is likely that the preoperative LogMAR of 0.22 was reasonable, meaning that a significant treatment effect is more difficult to appreciate. Our study included eyes with irregular astigmatism and eyes with high regular astigmatism and ametropia that were non-CL tolerant. The latter group would not be expected to have significant improvements in CDVA because they have less irregular astigmatism and may therefore explain our results. Aforementioned studies have focused on the treatment of irregular astigmatism and a higher improvement in best spectacle corrected visual acuity is therefore expected. It is interesting that when eyes with a CDVA of 20/50 or worse (high irregular astigmatism) in our study were analyzed separately, the mean LogMAR improved significantly from 0.46 LogMAR preoperatively to 0.21 LogMAR at the final follow-up, and 75% of eyes had a final CDVA of 0.2 LogMAR (Snellen 20/32) or

better. This finding, along with the aforementioned studies' findings, suggest an important role for TG-PRK in the correction of irregular astigmatism.

WG-PRK is an alternative to TG-PRK and takes into account the optical aberrations of the whole eye, rather than the corneal topography only. One of the main limitations of good vision postkeratoplasty is irregular astigmatism. TG-PRK should theoretically enable better visual correction than WG-PRK because topography-guided treatment can more specifically target maximum irregular astigmatism correction. A comparison between the effectiveness of WG-PRK with TG-PRK for postkeratoplasty astigmatism is not possible to the small number of studies on the former, which have a small number of eyes and short follow-up durations. In one study of 18 postkeratoplasty eyes undergoing simultaneous WG-PRK and phototherapeutic keratectomy (PTK), CDVA improved significantly, but UDVA improvement did not reach statistical significance.[23] The efficacy of WG-PRK is not clear because eyes also underwent PTK, and the mean follow-up was only 7 months. In another study of 13 postkeratoplasty eyes with an astigmatism range between 3 and 5 D, UDVA improved significantly, but CDVA did not.[24] As the authors note, the eyes treated had a small component of irregular astigmatism as evidenced by the good preoperative CDVA (LogMAR 0.05 ± 0.08, Snellen equivalent ∼ 20/22). Larger studies with longer follow-up are needed to better define the role of WG-PRK in postkeratoplasty astigmatism correction.

In our case series, regression occurred in 8 eyes. In normal nonkeratoplasty eyes undergoing PRK, regression has been reported to plateau by 1 year post-PRK,[25] but this was not the case in our study. There was ongoing regression in 4 eyes at 2 to 4 years post-PRK. There was a high preoperative cylindrical error in our subgroup of regressed eyes, mean cylindrical error: −4.2 D, and mean spherical error: −0.25 D. High astigmatism, particularly keratometric astigmatism and corneal irregularity are known to be associated with refractive error regression.[26,27] It would be useful to analyze the correlation of factors such as gender, age and preoperative CCT with incidence of regression. This could be performed with a statistical regression analysis; however, because of the small number of data points, we are unable to draw meaningful conclusions. It is noteworthy, however, that we detected a significant correlation between keratometric astigmatism and refractive astigmatism at the final follow-up. This is evidence that the astigmatic regression observed in the treated eyes is related to keratometric (corneal) regression. The indication for PKP was keratoconus in 7 of the 8 eyes. Thinning at the corneal periphery (residual host corneal rim) was noted in 3 eyes. It may be that progressive ectatic disease in the residual peripheral host cornea is contributing to the observed regression, but we do not have the evidence to support this hypothesis. However, our clinical experience is that regression seems to recur more frequently where there is thinning of the residual peripheral host cornea and in cases of pellucid marginal degeneration.

A question posed by our study is the value of corneal collagen cross-linking in minimizing or preventing postre-

fractive surgery regression in postkeratoplasty eyes with known corneal ectasia (eg, keratoconus). Another theory is that part of the laser ablation may affect the donor host junction resulting in thinning. Although most eyes undergo treatment inside the rim (ie, graft only), some eyes may have laser ablation on the wound in the presence of high off set. This can result in corneal haze/scar development in the peripheral furrows after treating higher cylinders, which may lead to suboptimal refractive outcomes and regression.

Although only 1 eye underwent deep anterior lamellar keratoplasty (DALK) and all the other eyes in our study underwent PKP, it was decided not to exclude the DALK eye for 2 reasons. First, to avoid patient selection bias. Second, no convincing difference in response to TG-PRK has been detected in the past.[6]

In conclusion, this is the largest study, to date, of TG-PRK for postkeratoplasty refractive error and has the longest follow-up results. In line with previous studies, our study gives strong evidence for the role of TG-PRK in improving refraction, topographic keratometry measurements, and visual acuity. An important finding in this study is that most eyes do not required more than 1 TG-PRK treatment. In addition, regression observed after the first year of treatment means that future studies on refractive laser correction postkeratoplasty should ideally have a minimum of 2 to 3 years of follow-up. The main weaknesses of this study are the absence of a control group, the retrospective nature, and missing aberrometery data. A prospective study is warranted to further investigate the benefit of this procedure, explore patent satisfaction rates, and compare it with other techniques for postkeratoplasty astigmatism and ametropia correction. Other measures of visual function, such as contrast sensitivity, would help in evaluating the efficacy of TG-PRK in highly aberrated postkeratoplasty eyes. We also suggest that a preset definition of irregular astigmatism is used in any prospective study, particularly for studies focusing on the improvement of corneal regularity.

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