Factors Associated With Improvement in Vision Following Femtosecond Astigmatic Keratotomy in Post-Keratoplasty Keratoconus Patients

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• PURPOSE: To evaluate factors associated with improvement in vision following femtosecond astigmatic keratotomy (FSAK) in patients with keratoconus post-keratoplasty.

• DESIGN: Retrospective, interventional case series.

• METHODS: The study took place in an institutional setting. This was a retrospective study that included patients with keratoconus who underwent FSAK for astigmatism following penetrating (PKP) or deep anterior lamellar keratoplasty (DALK). Success was defined as improvement in 3 Early Treatment Diabetic Retinopathy Study lines (doubling of the visual angle) of uncorrected distance visual acuity (UDVA) or best spectacle-corrected visual acuity (BSCVA).

• RESULTS: A total of 56 eyes in 56 patients with keratoconus were included. Following FSAK, there was a significant improvement in UDVA (1.30 ± 0.49 to 0.87 ± 0.58 logarithm of minimal angle of resolution [logMAR]; $P < .001$), BSCVA (0.40 ± 0.26 to 0.27 ± 0.29 logMAR; $P < .001$), and corneal astigmatism (8.69 ± 2.72 to 3.92 ± 2.13 diopter [D]; $P < .001$). Success was achieved in 60.7% (34/56) of cases, and this group had a higher proportion of previous PKP (73.5% vs 45.5%; $P = .03$), worse preoperative UDVA (1.42 ± 0.47 vs 1.11 ± 0.47 logMAR; $P = .03$), and a greater preoperative manifest cylinder (7.56 ± 2.26 vs 5.72 ± 2.12 D; $P = .01$). In multiple regression analysis, PKP (vs DALK) (odds ratio [OR]: 8.52; $P = .009$), worse preoperative UDVA (OR: 9.08, $P = .02$), and greater preoperative cylinder (OR: 1.51; $P = .04$) were independently associated with success, and, when combined, led to a sensitivity and specificity of 84.6% and 93.8%, respectively, in predicting success. The optimal cutoff predicting success with a preoperative cylinder was a cylinder >6.75 D.

• CONCLUSION: Approximately 60% of patients with keratoconus post-keratoplasty experience doubling of the visual angle following FSAK. Patients with previous PKP and a greater cylinder are more likely to benefit from this procedure. Separate nomograms for DALK and PKP patients may be warranted. (Am J Ophthalmol 2020;219:59–65. © 2020 Elsevier Inc. All rights reserved.)

CORNEAL DISEASE IS A LEADING CAUSE OF BLINDness worldwide.[1] Deep anterior lamellar keratoplasty (DALK) and penetrating keratoplasty (PKP) are the 2 main procedures commonly performed that address pathologies involving the corneal stroma.[2] Following these procedures, residual astigmatism may lead to unsatisfactory subjective and objective visual outcomes that may persist following removal of sutures.[3] Smaller amounts of residual astigmatism may be dealt with using less invasive means, such as spectacles and contact lenses; however, often encountered higher levels of astigmatism may require surgical intervention.[4,5]

There are several procedures that may be performed to deal with residual astigmatism following keratoplasty, including photorefractive keratectomy (PRK), toric intraocular lenses (IOLs), and astigmatic keratotomy (AK).[6–8] Toric IOLs preclude the postoperative use of standard gas permeable rigid contact lenses for any residual astigmatism because they neutralize corneal astigmatism, which results in manifest astigmatism from the toric IOL.[9] Ablation techniques (eg, PRK) are limited in the amount of astigmatism they may correct, with adequate results reported for up to 6 diopter (D) of cylinder.[10] Postsurgery haze may also be more prevalent in these patients. As such, AK is often performed as an initial step when managing these patients.[7,8] This can precede a tissue sparing PRK or use of a commercially, readily available toric IOL.

Manual AK (MAK) has been performed for decades. Recently, femtosecond assisted keratotomy (FSAK) has been shown to be safe and effective with superior visual outcomes compared with MAK.[11] However, conflicting results from clinical studies have indicated that FSAK may be less predictable than previously reported.[12–14] It is also less available compared with manual techniques. A paucity of data exists regarding factors associated with successful outcomes following FSAK in patients post-keratoplasty. Therefore, the purpose of the present study was to identify factors associated with those patients with notable

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improvement in vision following FSAK in patients with keratoconus post-keratoplasty (PKP or DALK).

METHODS

THIS RETROSPECTIVE STUDY RECEIVED RESEARCH ETHICS Board approval from the University of Toronto and was conducted in compliance with the tenets of the Declaration of Helsinki.

• **STUDY PARTICIPANTS:** This retrospective study included patients with keratoconus who underwent FSAK for the treatment of high astigmatism (≥3.00 D) following primary PKP or DALK at the TLC Laser Center (Toronto, ON, Canada), between 2013 and 2017. All procedures were performed by 2 experienced surgeons (D.S.R and C.C.C). For the sake of homogeneity, patients who underwent DALK or PKP for the treatment of keratoconus were included, and patients with ocular comorbidities that could affect visual acuity (eg, glaucoma, macular edema, and clinically significant cataract) were excluded. In addition, FSAK is not routinely performed in our institute in cases with no definable steep meridian as seen with patients with significant irregular astigmatism.

• **DATA COLLECTION:** Data collected included baseline demographics, laser parameters, subsequent procedures, uncorrected visual acuity (UCVA), best spectacle-corrected visual acuity (BSCVA), corneal topography with corneal astigmatism (OPD Scan II ARK 10000, NIDEK, Tokyo, Japan), manifest sphere and cylinder, and intraoperative and postoperative complications.

• **SURGICAL TECHNIQUE:** The FSAK technique in patients post-keratoplasty applied in our institution was previously described in detail.[7] Briefly, refractive stability following removal of all sutures was documented with the steep meridian determined by corneal topography. FSAK was performed using the iFS IntraLase systems (Johnson and Johnson Vision, Jacksonville, FL) under topical anesthesia. Patients were marked preoperatively using the round light projected by the Visx laser (Johnson and Johnson Vision). The paired incisions were positioned 0.5 mm anterior to the graft-host junction (within the graft tissue) with the incision depth set at 80%-90% of the thinnest measured thickness. The length of the incisions was adjusted according to the amount of astigmatism: 40°-65° for <10 D, 70°-75° for 10-15 D, and 90° for >15 D.

• **MAIN OUTCOME MEASURE:** The main outcome measures were improvement in UDVA and BSCVA at 3-6 months. Specifically, success was defined as a 3-line (>0.30 logarithm of minimal angle of resolution [logMAR]) improvement (doubling of the visual angle) in UDVA or BSCVA following FSAK. Secondary outcomes were safety index, efficacy index, and vector analysis. The safety index was calculated as postoperative BSCVA divided by preoperative BSCVA, whereas the efficacy index was calculated as postoperative UDVA divided by preoperative BSCVA. Vector analysis corneal astigmatism was performed with the Alpins vector analysis,[15–17] and 3 outcomes were calculated: 1) index of success (ideally zero); 2) correction index (ideally 1 with a value >1 indicating overcorrection and a value <1 indicating under correction); and 3) the flattening index (ideally 1 but cannot be >100% of the correction index). The target-induced astigmatism was defined as that which would result from full correction and no residual astigmatism.[18] Standard graphs for reporting outcomes for astigmatism correction[19] were produced using the online Alpins Statistical System for Ophthalmic Refractive Surgery Techniques group analysis calculator.[20]

• **STATISTICAL ANALYSIS:** Data were analyzed with the Minitab Software, version 17 (Minitab Inc, State College, PA). Student's *t*-test was used for analysis of continuous data. The χ^2 test was used for analysis of categorical variables, and when applicable, odds ratios (ORs) were calculated. Binary logistic regression (stepwise) was performed, looking for factors associated with success following FSAK. For this purpose, only independent variables that were significant or close to significant ($P < .30$) in the univariate analysis were included. Based on the binary logistic regression, the area under the receiver-operating characteristic (ROC) curve (AUC) was determined to evaluate the discriminatory ability according to assessed parameters. The point with the larger Youden index, equal to sensitivity + specificity − 1, was defined as the optimal cut-off point. The Youden index measures the effectiveness of a diagnostic marker and enables the selection of an optimal threshold (balancing between sensitivity and specificity). In all analyses, a 2-sided P value <.05 was considered statistically significant. All data are as presented means ± SDs.

RESULTS

A TOTAL OF 56 EYES IN 56 PATIENTS WERE INCLUDED IN THIS study; patients were a mean age of 44.9 ± 15.5 years, and 62.5% (n = 35) were men. In all cases, this was the first keratoplasty performed and none had undergone previous corneal crosslinking. Following FSAK, there was a significant improvement in UDVA (1.30 ± 0.49 to 0.87 ± 0.58 logMAR; $P < .001$), BSCVA (0.40 ± 0.26 to 0.27 ± 0.29 logMAR; $P < .001$), and corneal astigmatism (8.69 ± 2.72 to 3.92 ± 2.13 D; $P < .001$). There were 5 cases (8.9%) that underwent suturing of the incisions due to overcorrection, 1 case of graft rejection (1.8%), and 1

TABLE 1. A Comparison of Preoperative Parameters Between Eyes With and Without Three-Line Improvement in UDVA and/or BSCVA Following FSAK

Parameter	Success (n = 34)	Non-Success (n=22)	Odds Ratio (95% CI)	*P* Value
Age (y)	46.4 ± 15.7	42.5 ± 15.1	1.02 (0.98-1.05)	.35
Sex, male (%)	64.7	59.1	1.27 (0.42-3.83)	.67
PKP (%)	73.5	45.5	3.33 (1.07-10.35)	.03
UDVA (logMAR)	1.42 ± 0.47	1.11 ± 0.47	4.09 (1.13-14.80)	.03
Manifest sphere (D)	−0.40 ± 3.85	0.42 ± 4.55	0.95 (0.81-1.11)	.55
Manifest cylinder (D)	7.56 ± 2.26	5.72 ± 2.12	1.49 (1.06-2.08)	.01
BSCVA (logMAR)	0.43 ± 0.27	0.35 ± 0.24	3.70 (0.37-37.59)	.26
Ksteep (D)	51.51 ± 2.81	50.95 ± 3.84	1.06 (0.89-1.25)	.56
Kflat (D)	42.47 ± 3.37	42.67 ± 3.07	0.98 (0.82-1.16)	.81
Minimal corneal thickness (μm)	585.9 ± 65.6	568.2 ± 58.3	1.005 (1.00-1.01)	.29
Corneal cylinder (D)	9.05 ± 2.61	8.28 ± 2.81	1.12 (0.91-1.39)	.31
Average K (D)	47.19 ± 2.85	46.74 ± 3.33	1.05 (0.87-1.28)	.63
Incision diameter[a] (mm)	6.62 ± 0.63	6.55 ± 0.65	1.20 (0.50-2.85)	.69

BSCVA = best-spectacle corrected visual acuity; CI = confidence interval; D = diopter; FSAK = femtosecond astigmatic keratotomy; K = keratometry; logMar = logarithm of minimal angle of resolution; PKP = penetrating keratoplasty; UDVA = uncorrected distance visual acuity.

[a]The distance in mm between the opposed FSAK incisions as a surrogate of an effective optical zone.

case of infectious keratitis (1.8%). The graft rejection and infectious keratitis completely resolved with topical therapy within 1 week. There were no cases of perforation.

• **COMPARISON OF SUCCESS AND NON-SUCCESS GROUP:** Success was achieved in 60.7% (34/56) cases. Table 1 depicts a comparison between the success and non-success groups. Briefly, the success group had a higher proportion of eyes that underwent PKP versus DALK (73.5% vs 45.5%; $P = .03$), had worse preoperative UDVA (1.42 ± 0.47 vs 1.11 ± 0.47 logMAR; $P = .03$), and had a greater preoperative manifest cylinder (7.56 ± 2.26 vs 5.72 ± 2.12 D; $P = .01$).

• **BINARY LOGISTIC REGRESSION ANALYSIS:** Table 2 depicts the results of the binary logistic regression analysis. Briefly, PKP (vs DALK) (OR: 8.52; $P = .009$), worse preoperative UDVA (OR: 9.08; $P = .02$) and greater preoperative cylinder (OR: 1.51; $P = .04$) were all independently significantly associated with success.

• **ROC CURVE ANALYSIS:** When assessing the preoperative cylinder as a single predictor of success, the optimal Youden cutoff identified for predicting success was a cylinder > 6.75 D, which led to an AUC of 0.70 ($P = .01$) with a sensitivity of 65.4% and a specificity of 81.3% (Figure 1). In ROC curve analysis that incorporated the 3 parameters that were significant in regression analysis (PKP vs DALK, preoperative cylinder and preoperative UDVA), an AUC of 0.89 ($P < .001$) was achieved with a sensitivity of 84.6% and a specificity of 93.8% in predicting success (Figure 2).

TABLE 2. Binary Logistic Regression Analysis of Factors Associated With Three-Line Improvement in UDVA and/or BSCVA Following FSAK

Parameter	R2 (Total = 33.32%)	Odds Ratio (95% CI)	*P* Value
PKP (vs DALK)	12.29%	8.52 (1.47-49.50)	.009
UDVA (logMAR)	12.30%	9.08 (1.08-75.97)	.02
Manifest cylinder (D)	8.65%	1.51 (1.01-2.32)	.04

BSCVA = best-spectacle corrected visual acuity; CI = confidence interval; D = diopter; DALK = deep anterior lamellar keratoplasty; FSAK = femtosecond astigmatic keratotomy; logMar = logarithm of minimal angle of resolution; PKP = penetrating keratoplasty; UDVA = uncorrected distance visual acuity.

• **DALK VERSUS PKP:** At baseline, there was no significant difference in magnitude of corneal astigmatism between the DALK (9.22 ± 3.15D) and PKP (8.46 ± 3.28D) groups ($P = .35$). There was no significant difference in terms of the safety index between the PKP and DALK groups (1.66 ± 1.15 vs 1.45 ± 0.85, respectively; $P = .45$). However, the efficacy index was significantly greater in the PKP group (0.74 ± 0.54 vs 0.33 ± 0.26; $P < .001$). A mean surgically-induced astigmatism (SIA) stratified by procedure (DALK vs PKP) and length of incision (40-60, 70-75, and 90°) was calculated (Table 3). There was a larger SIA in the DALK group compare with the PKP group, which reached significance for the 70°-75° ($P = .009$) and 90° ($P = .02$) incisions. Alpins vector analysis showed a

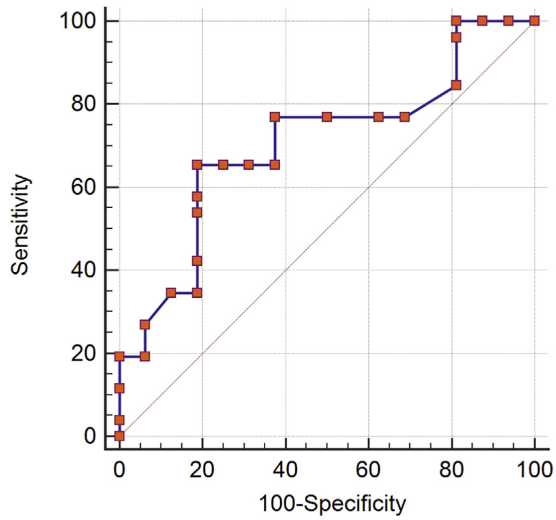

FIGURE 1. A ROC curve analysis with preoperative cylinder. A receiver-operating characteristic (ROC) curve analysis with preoperative cylinder as a single predictor of success. The optimal Youden cutoff identified for predicting success was a cylinder >6.75 D, which led to an area under the curve of 0.70 (P = .01) with a sensitivity of 65.4% and a specificity of 81.3%. In ROC curve analysis that incorporated the 3 parameters that were significant in regression analysis (penetrating keratoplasty vs deep anterior lamellar keratoplasty, preoperative cylinder, and preoperative uncorrected distance visual acuity) an area under the curve of 0.89 (P < .001) was achieved with a sensitivity of 84.6% and a specificity of 93.8% in predicting success (Figure 2).

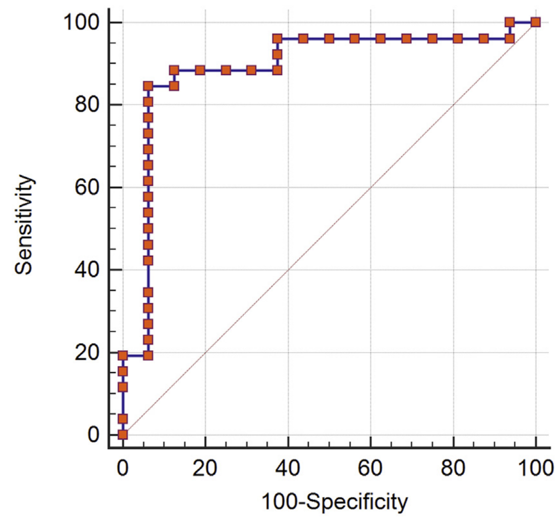

FIGURE 2. A ROC curve analysis incorporating the three parameters. A receiver-operating characteristic (ROC) curve analysis incorporating the 3 parameters that were significant in regression analysis (penetrating keratoplasty vs deep anterior lamellar keratoplasty, preoperative cylinder, and preoperative uncorrected distance visual acuity). An area under the curve of 0.89 (P < .001) was achieved with a sensitivity of 84.6% and a specificity of 93.8% in predicting success.

trend toward a lower index of success (better outcome) in the PKP group (0.47 ± 0.22 vs 0.56 ± 0.34; *P* = .27). A comparison of the correction index indicated a significant difference between groups, with overcorrection in the DALK group (1.23 ± 0.76) and under correction in the PKP group (0.76 ± 0.35) (*P* = .001). Similarly, there was a significant difference in the flattening index between the PKP and DALK groups (0.72 ± 0.36 vs 1.16 ± 0.43) (*P* < .001). All other comparisons between PKP and DALK are depicted in Table 4. Suturing of the incisions due to overcorrection occurred more often in the DALK group (23.8% vs 0.0%; *P* = .002). Standard single-angle polar plots for the entire cohort and the PKP and DALK groups are provided in Figure 3.

TABLE 3. SIA Stratified by Procedure (DALK or PKP) and Length of Incision

Length	DALK	PKP	*P* Value[a]
40°-60°	7.83 ± 3.85	5.49 ± 3.06	.60
70°-75°	14.92 ± 6.47	8.18 ± 3.75	.009
90°	22.32 ± 2.79	8.82 ± 1.85	.02

DALK = deep anterior lamellar keratoplasty; PKP = penetrating keratoplasty; SI = surgically-induced astigmatism.

[a]General linear model with Bonferroni adjustment for multiple comparisons.

DISCUSSION

THIS STUDY IDENTIFIED FACTORS ASSOCIATED WITH improvement in vision following FSAK in patients with keratoconus post-keratoplasty. The present study focused on patients with keratoconus because they were less likely to have ocular comorbidities that would affect BCVA and/or UCVA. Patients with keratoconus who were post-PKP were more likely to benefit from FSAK compared with patients who were post-DALK (OR: 8.52; *P* = .009). In addition, an ideal cutoff point of >6-7 D of cylinder was identified. To the best of our knowledge, this was the first study to identify these factors as associated with better outcomes for post-keratoplasty patients who underwent FSAK.

In the present study, there was a significant mean improvement in both UDVA and BSCVA as well as corneal astigmatism. This finding was supported by several previous studies that reported improvement in both parameters following FSAK in post-keratoplasty patients. Elzarga et al.[21] reported that UCVA and BSCVA improved following FSAK in a prospective study of 17 post-keratoplasty eyes. They also reported that the predictability of astigmatism correction was

TABLE 4. A Comparison of Outcomes Between the DALK and PKP Groups

Length	DALK	PKP	*P* Value[a]
Visual outcomes (mean ± SD)			
Safety index	1.45 ± 0.85	1.66 ± 1.15	.45
Efficacy index	0.33 ± 0.26	0.74 ± 0.54	<.001
Vector analysis[b] (mean ± SD)			
Target induced astigmatism	9.22 ± 3.15	8.46 ± 2.38	.35
Surgically induced astigmatism	11.91 ± 6.79	6.45 ± 3.42	.002
Magnitude of error	2.69 ± 4.68	−2.01 ± 2.91	<.001
Angle of error	2.13 ± 9.31	−0.30 ± 10.20	.36
Difference vector	5.18 ± 4.01	3.89 ± 1.81	.18
Correction index	1.23 ± 0.49	0.76 ± 0.35	.001
Index of success	0.56 ± 0.34	0.47±0.22	.27
Complications (%)			
Suturing of incisions (reduce overcorrection)	23.8	0.0	.002
Perforations	0.0	0.0	1.00
Graft rejection	4.8	0.0	.38
Infectious keratitis	0.0	2.9	1.00

DALK = deep anterior lamellar keratoplasty; PKP = penetrating keratoplasty.
[a]Student t-test was used for continuous variables and chi square was used for categorical variables.
[b]Arithmetic means.

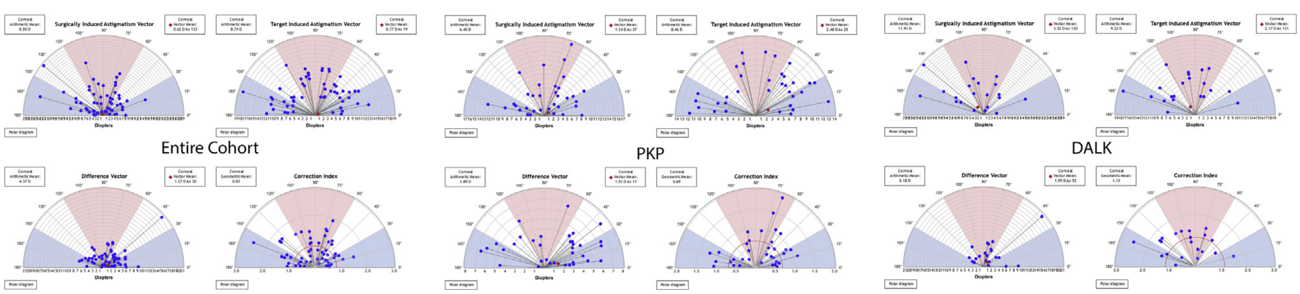

FIGURE 3. Standard graphs for reporting outcomes for astigmatism correction. Standard graphs for reporting outcomes for astigmatism correction, based on the Alpins method for the entire cohort (left), penetrating keratoplasty (PKP) (middle), and deep anterior lamellar keratoplasty (DALK) (right) groups. Single-angle polar plots for the target -induced astigmatism vector (TIA), surgically-induced astigmatism vector (SIA), difference vector (DV), and correction index (CI). The vector means are plotted as a red diamond (calculated in double-angle vector space).

variable in reducing astigmatism. Two additional retrospective studies reported improvement in visual outcomes following FSAK with up to 28 months of follow-up.[12,13] However, Hoffart et al. reported improvement in UCVA only without an improvement in BSCVA.[14] Differences in study populations, ocular comorbidities, surgical technique, and nomograms might all explain the somewhat conflicting results among studies that reported on results of FSAK following keratoplasty.

Interestingly, the PKP group had a higher success rate in univariate analysis and remained associated with success in the multiple regression analysis. Similarly, the PKP group had an overall greater efficacy index compared with the DALK group. There were reports of overcorrection with DALK that were attributed to the wound-healing attributes of DALK contributing to an exaggerated healing response.[22] In the present study, overcorrection was noted in the DALK group, whereas undercorrection was noted in the PKP group. This was further supported by higher mean SIA values at different ranges of incision lengths for the DALK group compared with the PKP group. These findings seemed to contradict those of a recent study by anNakhli et al.,[23] who reported that FSAK was more effective for DALK than for patient who underwent PKP based on vector analysis. However, it is worth pointing out that nearly all of the DALK eyes in the aforementioned study were treated for keratoconus (n = 14/15), whereas the PKP group had more diverse indications.[23] In addition, they performed FSAK for irregular astigmatism,[23] whereas we avoid using FSAK in cases in whom the steep meridian is based on corneal topography and is not discernible. As such, examining separate nomograms for post-DALK and post-PKP patients who underwent FSAK might be of interest, and more standardized protocols may be considered. The higher success rate in the PKP group might also partially be explained by better BCVA outcomes in patients with PKP compared with patients with DALK. In a recent meta-analysis, Liu et al. reported that patients who underwent DALK had a poorer BCVA compared with PKP with a higher proportion of patients reaching 6/6 or 6/12 in the PKP group.[24]

In the present study, a cylinder in the 6-7 D range (6.75 D) was identified as the ideal cutoff point for predicting success for FSAK. The ideal treatment for residual astigmatism following PKP or DALK depends on the amount of astigmatism. This study supports the notion that a stepwise approach, starting with FSAK, should be considered in patients with high astigmatism (>6 D) following keratoplasty. The FSAK may then be safely followed up with either a toric IOL,[7] LASIK,[25] or PRK.[26,27] An initial wedge resection may be considered for astigmatism that may not be amenable to FSAK (>15-20 D).[28] For cases with a substantial component of irregular corneal astigmatism topo-guided PRK may also serve as excellent treatment modality.[29]

This study had some limitations. The first was its retrospective nature. Second, its findings applied patients with keratoconus, although it was probable that these findings could be extrapolated to other populations as well. Third, preoperative surface irregularities were not assessed as predictors of success following FSAK or compared between patients with PKP and patients with DALK. Large prospective studies that evaluate outcomes and potential predictive factors of FSAK (eg, surface irregularity indexes) may be of interest.

In conclusion, 60.7% of post-PKP or -DALK patients with keratoconus experience doubling of the visual angle following FSAK. Patients with previous PKP and a greater cylinder are more likely to benefit from this procedure. Patients following DALK trend toward overcorrection, whereas patients following PKP trend toward under correction, which indicates that separate nomograms for each group may be useful to improve outcomes.

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Author contributions: All authors contributed to design of the work, acquisition and analysis∖interpretation of data.Michael Mimouni, Mohammad Kreimei and Nir Sorkin drafted the work. Tanya Trinh, Gisella Santaella, Eyal Cohen, Clara C. Chan and David S. Rootman critically revised the work.All authors provided final approval of the version to be published.

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