Int J Ophthalmol, Vol. 8, No. 5, Oct.18, 2015 www. IJO. cn
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·Clinical Research·

Risk factors of regression and undercorrection in photorefractive keratectomy: a case-control study

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Received: 2014-11-17 Accepted: 2015-01-30

Abstract

• **AIM:** To determine risk factors of regression and undercorrection following photorefractive keratectomy (PRK) in myopia or myopic astigmatism.

• **METHODS:** A case-control study was designed in which eyes with an indication for re-treatment (RT) were defined as cases; primary criteria for RT indication, as assessed at least 9mo postoperatively, included an uncorrected distance visual acuity (UDVA) of 20/30 or worse and a stable refraction for more than 3mo. Additional considerations included optical quality symptoms and significant higher order aberrations (HOAs). Controls were chosen from the same cohort of operated eyes which had complete post-operative follow up data beyond 9mo and did not need RT. The cohort included patients who had undergone PRK by the Tissue-Saving (TS) ablation profile of Technolas 217z100 excimer laser (Bausch & Lomb, Rochester, NY, USA). Mitomycin C had been used in all of the primary procedures.

• **RESULTS:** We had 70 case eyes and 158 control eyes, and they were comparable in terms of age, sex and follow-up time (*P* values: 0.58, 1.00 and 0.89, respectively). Pre-operative spherical equivalent of more than -5.00 diopter (D), intended optical zone (OZ) diameter of less than 6.00 mm and ocular fixation instability during laser ablation were associated with RT indications (all *P* values <0.001). These factors maintained their significance in the multiple logistic regression model with odd ratios of 6.12, 6.71 and 7.89, respectively.

• **CONCLUSION:** Higher refractive correction (>-5.00 D), smaller OZ (<6.00 mm) and unstable fixation during laser ablation of PRK for myopia and myopic astigmatism were found to be strong predictors of undercorrection and regression.

• **KEYWORDS:** photorefractive keratectomy; re-treatment; undercorrection; regression

DOI:10.3980/j.issn.2222-3959.2015.05.14

Mohammadi SF, Nabovati P, Mirzajani A, Ashrafi E, Vakilian B. Risk factors of regression and undercorrection in photorefractive keratectomy: a case-control study. *Int J Ophthalmol* 2015;8(5):933-937

INTRODUCTION

While major advances in the precision of laser delivery, ablation profiles and centration/eye tracking has improved the predictability and stability of results, under/over-correction and refractive regression necessitating re-treatment (RT) are still among the most common complications of excimer laser keratorefractive surgeries. The cause of RT has been shifted from induced irregular astigmatism and decentration to under-correction/regression; hence, the popularity of "enhancement" *vs* "retreatment" designation. Recent estimates indicate that 3.8% to 20.8% of patients require RT after myopic corrections [1-6]. With laser *in situ* keratomileusis (LASIK), current risk factors for RT include small optical zones (OZ) [7,8], thicker flaps [9], high corrections [10,11], significant astigmatism [3,11], suboptimal nomograms[12] and flat keratometry readings[13]. It is generally assumed that refractive stability is less satisfactory with photorefractive keratectomy (PRK) [14], but specific risk factors have not been adequately studied.

It is true that RT, especially with the advent of wave front-guided procedures, is quite successful and safe [15-17], but it is very unwelcomed on the part of the patients, especially in PRK; so, identifying modifiable risk factors can lead to remarkable improvement in patient satisfaction and cost reduction. Identifying unmodifiable risk factors, on the other hand, enriches our pre-operative counseling as we can better address patient expectations and foresee the potential need for enhancement. This study aims at finding the predictors and risk factors of RT for undercorrection and regression after PRK in patients with simple myopia, simple myopic astigmatism and compound myopic astigmatism.

SUBJECTS AND METHODS

Study Design and Settings Study protocol was approved by the Institutional Review Board of Farabi Eye Hospital, Tehran University of Medical Sciences and was conducted according to the tenets of Declaration of Helsinki 2008. In this case-control study, conducted at Farabi Eye Hospital, Tehran, we reviewed the surgical records of all patients who underwent PRK for myopia or myopic astigmatism by one surgeon (Mohammadi SF) from May 2009 to May 2012. For all patients, the Technolas 217z100 (Bausch & Lomb, Rochester, NY, USA) excimer laser was used to apply conventional (PlanoScan: PS), Tissue-Saving (TS) or Advanced Personalized Treatment (APT) ablation profiles. Indications for RT were mostly seen in the TS cohort, which became the focus of this study (Figure 1).

Cases were defined as eyes, which had indication for RT due to regression or under-correction. Primary criteria for RT indication, as assessed at least 9mo postoperatively, included an uncorrected distance visual acuity (UDVA) of 20/30 or worse and a stable refraction [generally more than 0.5 diopter (D) of residual spherical equivalent correctable with subjective refraction] for more than 3mo (we had no residual mixed refractive error and/or induced cylinder indication for RT; likewise we did not come across with an indication for RT due to overcorrection). Post-operative optical quality symptoms and significant higher order aberrations [HOAs; a HOA root mean square (RMS) of 0.6 μm or higher over a 6.0 mm pupil diameter] were additional considerations. The differentiation between regression and under-correction was made through comparing 3-month *vs* 9-month (or beyond) UDVA and subjective refractions. Regression was defined as UDVA of 20/20 at month 3 but UDVA loss of ≥2 lines correctable with residual refraction at month 9 (or beyond) post-operatively. Under-correction was defined as stable UDVA of ≤20/30 correctable with residual manifest refraction at both times. There was no indication for RT due to stromal haze.

In addition to the cases, 192 eyes had definite refractive data at least 9mo post-operatively; of these, 26 eyes lacked relevant pre-operative data; 3 patients (6 eyes) had pre-operative allergic conjunctivitis or multiple sclerosis or were mentally handicapped; and 2 eyes had transient corneal haze. These eyes were excluded. The remaining 158 eyes served as controls (Figure 1).

Surgical Procedure A TS PRK had been performed. After exposure to 20% alcohol for 15s, the central 8.0-9.0 mm surface epithelium was scraped with a blunt spatula. With the target set for emmetropia (based on subjective refraction and duochrome refinement), photoablation was followed by the application of mitomycin C (MMC) 0.02% for 15s to 30s and irrigation with 30 mL of balanced salt solution. Finally, a bandage contact lens was inserted which was removed 5d later. The post-operative regimen included topical betamethasone every 8h for one month and topical fluorometholone tapered off over a course of 8wk.

Statistical Analysis and Variables Definition Only refractive data of the final follow-up examination was used in the statistical analysis. Based on the calculated means, we categorized eyes as high myopia *vs* low to moderate myopia using a cutoff point of -5.00 D of pre-operative manifest refraction spherical equivalent (MRSE), as well as moderate to high astigmatism *vs* low astigmatism using a cutoff point of -1.00 D of pre-operative cylinder error. Eyes were also divided by the nominal/intended OZ diameters; OZ ≥6 *vs* <6 (range: 5.5 to 7) mm.

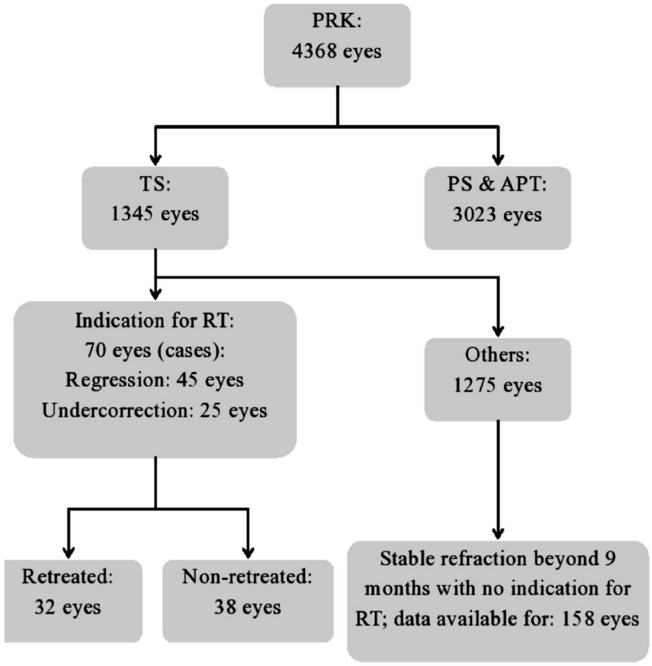

Figure 1 Flow chart illustrating the process for selection of cases and controls PRK: Photorefractive keratectomy; TS: Tissue-Saving; PS: PlanoScan; APT: Advanced personalized treatment; RT: Re-treatment.

Stability of the fixation during the procedure had been rated by the surgeon (Mohammadi SF) as "good", "fair" or "poor". Rating the stability of fixation was subjective and had been done based on the observation of eye movements/fixation losses during surgery and comparing it to the average amount routinely seen in a routine case. We also retrieved Sim K readings to represent keratometry readings, pre-operative pachymetry at the thinnest point, angle Kappa and pupil diameter (under low mesopic lighting condition with ambient luminance of 0.4 lx) from the Orbscan IIz (Bausch & Lomb-Orbtek Inc. Salt Lake City, UT, USA) topographer.

Statistical analysis was performed with SPSS version 20 (SPSS Inc., Chicago, IL, USA). Univariate analyses were done with Mann-Whitney *U* test for age, follow-up time, pre-operative keratometry, pachymetry, angle Kappa and pupil diameter; and Chi-square for sex, pre-operative MRSE, pre-operative astigmatism, OZ diameter, and fixation stability during surgery. Based on an alpha level of less than 0.2, variables showing significant association with RT risk were entered into a multiple logistic regression model. Post-operative HOA-RMS at 6 mm exit pupil (Zywave, Bausch & Lomb, Rochester, NY, USA) was analyzed against fixation stability in retreated eyes (Student's *t*-test). A *P* value of less than 0.05 was considered statistically significant.

RESULTS

We identified 70 cases (eyes) with an indication for RT; 45 eyes with a diagnosis of regression and 25 due to under-correction. No case was included in the case group

Table 1 Risk factors and associations of retreatment in PRK in 70 cases and 158 controls

Variables	Cases (%)	Controls (%)	OR (95% CI)	*P*
Sex				
Female	44 (63)	98 (62)	1.03 (0.57 to 1.85)	1.00
Male	26 (37)	60 (38)		
Pre-op MRSE				
High	51 (73)	54 (35)	4.81 (2.60 to 8.89)	<0.001
Low	19 (27)	104 (65)		
Pre-op astigmatism				
High	19 (28)	57 (37)	0.66 (0.35 to 1.22)	0.22
Low	51 (72)	101 (63)		
Optical zone diameter				
Smaller	25 (36)	16 (10)	4.93 (2.42 to 10.04)	<0.001
Larger	45 (64)	142 (90)		
Ocular fixation				
Unstable: “fair” or “poor”	19 (28)	7 (4)	8.03 (3.19 to 20.22)	<0.001
Stable: “good”	51 (72)	151 (96)		

Pre-op: Pre-operative; MRSE: Manifest refraction spherical equivalent; OR: Adjusted odds ratio; CI: Confidence interval.

Table 1 Risk factors and associations of retreatment in PRK in 70 cases and 158 controls (continued)

Variables	$\bar{x} \pm s$		Mean Diff (95% CI)	*P*
	Cases	Controls		
Age (a)	26.72±5.27	26.34±4.59	0.38 (-0.98 to 1.74)	0.58
Follow-up time (mo)	10.15±4.59	10.06±4.57	0.08 (-1.20 to 1.38)	0.89
Pre-op keratometry (D)	43.91±1.49	44.12±1.34	-0.21 (-0.60 to 0.18)	0.18
Pre-op pachymetry (μm)	534.32±37.58	531.18±40.98	3.1 (-8.17 to 14.44)	0.58
Angle Kappa (degree)	4.42±1.39	4.65±1.34	-0.23 (-0.64 to 0.18)	0.28
Mesopic pupil diameter (mm)	4.19±0.84	4.33±0.99	-0.13 (-0.40 to 0.13)	0.32

Pre-op: Pre-operative; Mean Diff: Mean difference; CI: Confidence interval.

solely based on the presence of additional criteria (optical quality symptoms and significant HOAs). All the eyes in case group met the primary criteria for RT. RT had been performed on 32 eyes (of 70). The frequency of RT was estimated at about 0.060 (95% CI: 0.047-0.073).

Table 1 summarizes a comparison between cases and controls; no statistically significant difference was found between them in variables of age, sex, follow-up time or pre-operative astigmatism. However, significant differences were found between cases and controls in pre-operative MRSE (73% *vs* 35% with high myopia), intended OZ diameter (36% *vs* 10% with small OZ diameters) and eye fixation stability (28% *vs* 4% with fair or poor fixation), and thus, these factors were significantly associated with an increased risk of RT (P<0.001).

The four variables with a P value <0.2 were analyzed in a multivariate binary logistic regression model in which the three aforementioned variables (pre-operative MRSE, intended OZ diameter and ocular fixation stability) maintained their significant role in RT risk (Table 2).

Post-operative aberrometry data was available for 31 RT eyes. The means of post-operative HOA-RMS (pre-RT) were 0.44±0.06 μm for eyes with “good” ocular fixation stability (22 eyes) and 0.77±0.08 μm for “fair” or “poor” stability (9 eyes), respectively (P=0.003).

Table 2 Multivariate logistic regression model of independent predictors of retreatment in PRK

Factor	OR	95% CI	*P*
Pre-op MRSE	6.12	2.98 to 12.53	<0.001
Optical zone diameter	6.71	2.87 to 15.69	<0.001
Ocular fixation	7.89	2.66 to 23.37	<0.001
Pre-op keratometry	1.20	0.94 to 1.52	0.13

R square of model: 0.36; PRK: Photorefractive keratectomy; Pre-op: Pre-operative; MRSE: Manifest refraction spherical equivalent; OR: Adjusted odds ratio; CI: Confidence interval.

DISCUSSION

Postoperative residual refractive error constitutes one of the most common complications of keratorefractive surgeries. Our estimate of 6% indication for RT is comparable with or relatively better than that of the other reports and contradicts the general impression of surface ablation having a poorer refractive stability and predictability; however, due to the retrospective nature of the study, this claim should be treated with caution.

We replicated some of the previously reported risk factors for RT; namely, smaller OZ[18] and deep ablations[19]. At the same time, some other plausible factors like pre-operative high astigmatism and keratometry reading were not shown to be risk factors. Age, sex, pachymetry, angle Kappa and pupil diameter were not risk factors either.

Application of standard nomograms tends to lead to overcorrection at lower corrections and under-correction at the upper extremes [20], and we know that the ablation rate is higher in the beginning and declines as the ablation progresses [21]. As average rates are used in nomograms, the mentioned inaccuracy seems inevitable to different extents. Thus, surgeons may consider some adjustments and the industry are recommended to provide different nomograms for different refractive error ranges. Alternatively, it is argued that longer ablation time in deeper ablation contributes to less accuracy[22].

OZ size is most frequently linked to pupil size and optical quality symptoms of glare and halo but its role in refractive stability (refractive status in the long run) is less appreciated. Additionally, smaller OZ (less than 5.5 mm) causes day-to-day vision fluctuation, plausibly through higher amount of induced spherical aberration; its significant role has already been proved for OZ sizes of less than 5.5 mm[23]. In our study, we were able to show the OZ significance in refractive stability in relatively higher OZ sizes (in a quite narrow range).

Surgeons input the OZ size as one of the surgical parameters. This value is in fact "intended/nominal" but "effective" and "functional" OZs are the results of a variety of factors and arrangements of the ocular optical elements. Of these factors, ablation depth and angle Kappa are respectively relevant; the higher the ablation depth, the smaller the effective OZ and the larger the angle Kappa, the smaller the functional OZ[24].

In order to ensure stability of the anterior corneal surface reshaping by excimer laser, a transitional zone is incorporated into ablation profiles to the periphery of the OZ. Recent ablation profiles have made changes to this blending area to save tissue. For instance, in Technolas 217z100, treatment zones for correcting -4.00 D of sphere and a -1.00 D of cylinder with PS and TS profiles set for an OZ of 6.0 mm would be 9.0 by 12.5 mm and 8.5 by 9.5 mm, respectively; so, tissue efficient ablation profiles may have a less stable outcome.

It is noteworthy that we also found a significant relationship between RT and fixation stability during laser ablation. This finding is quite logical, but to our knowledge, has not already been studied clinically. We compared the amount of induced HOAs in such eyes with the eyes which had a steady fixation during laser ablation and found an almost 75% higher amount of induced HOAs. In animal studies it had been shown that higher induction of HOA is accompanied by undercorrection[25].

During the procedures, the eye tracking system was constantly engaged. The Technolas 217z100 eye tracking system is defined as a 4-dimensional eye tracker (*i.e.* X, Y, Z, rotation) of ACE Technology. It registers XY plane movements and rotation with a digital camera and a sampling rate of 240 Hz international. Its overall detection and response time has been stated as 6.6 ms[26]. On the other hand the platform repetition rate in TS mode is 100 Hz. So theoretically, the tracking system can catch up with the eye movements in the XY plane. Practically speaking though, "response time" determines the effectiveness of eye tracking process and laser beam re-adjustment. It should be emphasized that other factors like Z-axis inaccuracies and laser beam parallax[27] also affect ablation fidelity.

It should be noted that some studies achieved comparable outcomes in terms of centration and refractive outcomes with and without eye tracking technology [28] but on the other hand there is a consensus on the application of eye tracking systems for the improvement of visual outcomes. Such treated eyes have shown to have less induced coma and spherical aberration[29]. In another study by Ghosh *et al*[30], the use of iris recognition system in excimer laser refractive surgery was associated with better visual and refractive outcomes, especially in patients with a significant amount of myopic astigmatism.

We conclude that eye tracking systems are useful but they do not guarantee perfect fidelity. Surgeons should take measures like turning off the background light during laser ablation in order to make identification of the fixation light easier. Simulation devices should be helpful for fixation exercises and studying fixation stability before surgery.

We could not show a relationship between RT and the pre-operative astigmatism. This finding is in contrast with Randleman *et al*'s [3] in which an astigmatism of higher than 1.00 D was shown to be a risk factor for RT. It is noted that we treated astigmatisms higher than of 2.50-3.00 D with the APT module of the platform. This limited the cylindrical range which essentiality lowers the likelihood of astigmatism to emerge as a risk factor.

Age remains to be a controversial factor. Some studies reported older age as a risk factor of regression. Oral contraceptives, sunlight exposure and ocular surface diseases, like allergic conjunctivitis were reported as risk factors of myopic regression after PRK [31,32]. Baseline keratometry, tear film status, biomechanics of the cornea and wound healing (MMC use) are additional factors, which may contribute to RT risk.

It should be mentioned that in our series there was no indication for RT due to overcorrection or stromal haze and in fact we are reporting risk factors for undercorrection and regression. As we applied MMC to all of the eyes, MMC role in RT cannot be assessed too.

Our data were retrospective and the patients were not compliant with the recommended regular follow-ups in a consistent manner; we cannot claim that all indications for RT were included. Despite finding important risk factors, our study is not strong enough to exclude other variables from the list of potential risk factors.

In conclusion, we showed that an OZ smaller than 6.0 mm, an ablation for a spherical equivalent myopia of more than -5.00 D and unsteady fixation during laser ablation increase the need for RT after PRK for myopia and myopic astigmatism for undercorrection and regression. In the light of our findings, an intended optical zone of less than 6.0 mm is not recommended; surgeons may consider adjusting their nomograms for the treatment of high myopia in order to achieve emmetropia; and they should take measures to improve ocular fixation stability during laser ablation.

ACKNOWLEDGEMENTS

It is noteworthy that the subject has been presented as a free paper in the 5th annual meeting of Iranian Research Association for Vision and Ophthalmology 2015.

Conflicts of Interest: Mohammadi SF, None; **Nabovati P**, None; **Mirzajani A**, None; **Ashrafi E**, None; **Vakilian B**, None.

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