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Features of corneal reparation and postoperative complications after various types of excimer laser correction of myopia

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Purpose: *To determine the features of corneal reparation and postoperative complications after various types of excimer laser correction (ELC) of myopia.*

Material and Methods: *This was a multicenter, prospective, observational clinical study including 255 patients (510 eyes). They were stratified into three equal groups, based on the particular type of ELC: photorefractive keratectomy (PRK), transepithelial PRK (trans-PRK) and laser-assisted subepithelial keratectomy (LASEK). Corneal re-epithelization rate, epithelial and stromal thicknesses (as assessed by anterior segment spectral domain optical coherence tomography), corneal irregularity measurement (CIM), uncorrected visual acuity (UCVA) and incidence of haze were assessed over 3 months postoperatively. Correlation analysis and Principal Component Analysis clustering were used for assessing relationships.*

Results: *There were statistically significant between-groups differences early after surgery. The trans-PRK group showed the best results in terms of re-epithelialization dynamics (with an incidence of delayed re-epithelialization at day 4-5 of 28% vs 38% PRK), maximum epithelial thickness in the central 5-mm map zone (64 µm vs 74 µm LASEK) and the size of stromal edema (444 µm vs 460 µm PRK). At month 3, UCVA was higher in the trans-PRK group (1.00 vs 0.90 PRK, $p = 0.0059$). Haze strongly correlated with stromal edema ($r = 0.96$, $p < 0.001$) and delayed re-epithelization ($r = 0.93$). Cluster analysis revealed subgroups with shared signs of pathological reparation irrespective of the ELC technique. The percentage of patients with a pathological cluster profile was 16.5% in the PRK group, 14.7% in the LASEK group, and 10.6% in the trans-PRK group, which confirmed independent morphometric patterns of complicated healing.*

Conclusion: *Among the three types of ELC, trans-PRK was the best in terms of the dynamics of corneal reparation and visual recovery. Between-groups differences in morphometric and functional parameters almost disappeared at 3 months after surgery. The PRK and trans-PRK groups had the highest and lowest incidences of haze, respectively. Haze had the strongest correlations with corneal edema and delayed re-epithelialization. Cluster analysis revealed subgroups with pathological healing irrespective of the ELC technique. Morphometric parameters may be considered as predictors of complicated corneal reparation after ELC. When comprehensively assessed, they may be used for predicting the risk of complications and in further research on the new etiological factors of complicated corneal reparation.*

Keywords:

myopia, excimer laser correction, photorefractive keratectomy (PRK), transepithelial PRK (trans-PRK), LASEK, corneal reparation, complications

Introduction

In 2020, an estimated 161 million people worldwide were blind or had moderate to severe vision impairment from uncorrected refractive error. Myopia is a major cause of low vision globally. More than 2 billion people worldwide have a degree of myopia, 15% of whom have high myopia [1].

Ametropia can be corrected today with optical means or refractive surgery. Three types of excimer laser correction (ELC) procedures, which differ in the way the epithelium layer is handled, are currently used: photorefractive keratectomy (PRK), laser-assisted subepithelial keratectomy (LASEK) and transepithelial PRK (trans-PRK). Recently, new technologies along with improved understanding of refractive errors, high-order aberrations, and biomechanics and morphology of corneal recovery, have contributed to a reduction in the severity and rate of refractive surgery complications. However, in spite of significant technological advances, complications after PRK and derivative techniques are still clinically

important. Biological determinants of wound healing response are believed to be the major factor limiting the predictability and effectiveness of refractive surgery in some patients [2, 3, 4, 5].

The quality of vision may be affected by complications like subepithelial corneal haze, epithelial hypertrophy, and refractive regression. Subepithelial corneal haze is the most unwanted complication of ELC, with its incidence after surface ablation with mitomycin-C (MMC) ranging from 2% to 7.9% [3, 6, 7]. Other adverse effects include postoperative pain, abnormal corneal nerve regeneration, and night vision symptoms like halos and glare [6].

There have been several reports indicating a potential role of latent viral infections in morphological changes in the cornea. Even subclinical cytomegalovirus (CMV) infection may affect the corneal tissue and mostly the state and function of endothelial cells via tropism for endothelial cell receptors. Subclinical CMV-associated corneal endotheliitis, with no to minimal clinical signs of the disease, has been described in several studies [8-13]. Taking this into account, we may hypothesize that such endothelial changes are likely to trigger secondary abnormalities in other corneal layers, causing changed corneal reparation following surface ablation and, consequently, the above complications. Therefore, given increasing evidence that it is the morphology of corneal healing that determines late functional results after ELC, this study is believed to be important for comparing clinical, morphological and morphometric signs of corneal reparation following PRK, trans-PRK or LASEK, in an attempt to identify the pathological forms of corneal reparation, and in future to reduce the risk of ELC complications.

The purpose of the study was to determine the features of corneal reparation and postoperative complications after various types of ELC for myopia.

Material and Methods

This was a multicenter, prospective, observational clinical study. Approval for the study was obtained from the Bioethics Committee, the Shupik National Healthcare University of Ukraine (Date of approval: 31 May, 2024; Reference number: 5). The procedures followed were in accordance with the ethical standards of the Helsinki Declaration of the World Medical Association, European Convention on Human Rights and Biomedicine (1977), relevant provisions of WHO's Constitution, Council for International Organizations of Medical Science, International Code of Medical Ethics (1983), and Ministry of Health Order No. 690, dated 23 September, 2009. Informed consent was obtained from all participants.

A total of 255 patients (510 eyes) aged 20 to 44 years were under observation. Of these, 120 were males and 135 were females. Patients were prospectively stratified into three groups of 85 each, based on the respective ELC technique: group 1 (PRK), group 2 (trans-PRK) and group 3 (LASEK). Other inclusion criteria included no contraindications to ELC; myopia (≥ -5 to ≤-2D) with corneal astigmatism of less than 1 diopter (D) or without corneal astigmatism; central corneal thickness of ≥ 500 μm; no preoperative signs of keratitis, corneal degeneration or cicatricial changes (local opacities of various etiologies) and no history of chronic conjunctivitis, mild to moderate dry eye, eye surgery, autoimmune disease or immunosuppressive condition. Corneal re-epithelization rate, epithelial and stromal thicknesses, changes in corneal irregularity measurement (CIM) as assessed by corneal topography were determined in patients of various groups throughout the study to understand the effect of these parameters on the functional outcome.

The PRK technique included the mechanical removal of the corneal epithelium followed by excimer laser ablation.

Trans-PRK was performed in two steps: the use of excimer laser PTK as a first step to remove the epithelium followed by stromal laser ablation as a second step. The LASEK technique included applying alcohol solution to the epithelial layer, creating an epithelial flap, ablating the corneal surface with an excimer laser, and repositioning the flap.

Patients were treated with 0.02% MMC for a period of 12 s after the laser ablation. A bandage contact lens was placed at the end of the procedure.

Patients were examined and treated at Laser Plus medical center (Lviv) and Visium medical centers (Kyiv).

The ophthalmological examination was performed preoperatively and at day 4-5, week 1, week 2, month 1, and month 3 after ELC of myopia, and included visual acuity (Snellen uncorrected visual acuity (UCVA)) measurements, corneal topography, biomicroscopy with fluorescein staining for the assessment of epithelial recovery, and corneal optical coherence tomography (OCT). Corneal epithelial and stromal thicknesses were measured using an Anterior Segment Spectral Domain® OCT (AS-OCT) device (REVO SOCT Copernicus, OPTOPOL Technology, Zawiercie, Poland). Longitudinal changes in the maximum epithelial thickness in the central 5-mm map zone were assessed. Changes in average central corneal stromal thickness measurements in the 5-mm zone were also assessed. An increase in corneal thickness exceeding 20 μm was considered evidence of clinically significant corneal edema [14].

Corneal topography measurements were obtained using the Zeiss Atlas 9000 corneal topographer (Carl Zeiss Meditec, Inc. Jena, Germany). The state of the corneal surface was monitored by the assessment of corneal irregularity measurement (CIM), with CIM values ranging from 0.42 to 5.33 μm and classified as normal (0.49-1.68 μm), borderline (1.69-3.01 μm) and abnormal (0–0.42 μm or 3.02–5.33 μm) [15].

Subepithelial corneal haze is the most unwanted complication of excimer laser surface ablation [3, 6], is associated with scarring and directly affects the functional outcome. Postoperative recovery features may have influence on the risk of this complication. Therefore,

we assessed the incidence of haze in groups at late time points and conducted correlation analysis to find the strongest associations of haze with different signs of an abnormal postoperative course. Corneal haze was defined as a clinically significant subepithelial stromal opacity recorded within 3 months after intervention and was assigned a numerical grade according to the Fantes grading scale (range from 0–4) [6].

The duration of the follow-up was 3 months.

Analyses were carried out in Python v. 3.10 using statsmodels, pandas, and scipy, and plots were generated using matplotlib and seaborn. Data are presented as mean and 95% confidence interval (CI). A two-tailed t-test was used for pairwise compari-sons of three independent groups (PRK, trans-PRK, and LASEK). A chi-square test was used for comparing categorical variables (the incidence of complications). One eye for each patient was included in the analysis. Pearson coefficient (r) was used to determine correlations between haze and other morphological characteristics (de-layed re-epithelialization, epithelial hyperplasia, and CIM). A p-value of < 0.05 was considered statistically significant. Principal Component Analysis (PCA) was used to reduce the number of dimensions to 2 and k-means clustering was used to identi-fy reparation patterns. Patients were classified as those having pathological corneal recovery if there were 3 or more signs of pathological healing. Random jitter was used in 2D images to separate values for visual identification. SPSS v.11.0, MedStat and MedCalc v.15.1 (MedCalc Software bvba) were used to perform some analysis phases.

Results

Fig. 1 shows percentage rates of corneal re-elithelialization for PRK, trans-PRK, and LASEK groups of patients at different time points, demonstrating a substantial effect of a particular keratectomy technique on corneal re-epithelialization rate. At day 4-5 after surgery, the PRK group showed the highest incidence of delayed corneal re-elithelialization (~38%), followed by the LASEK group (~34%) and the trans-PRK group (~28%).

At week 1, the incidence of delayed corneal re-elithelialization in these groups improved to 16%, ~13% and ~9%, respectively, with a reduction in differences between groups. The duration of re-elithelialization exceeded one week in ~5%, ~4%, and ~2% of patients in the PRK, LASEK and trans-PRK, groups, respectively. Therefore, trans-PRK was the most favorable technique in terms of the rate of re-elithelialization.

Corneal re-elithelialization dynamics is also associated with changes in the maximum epithelial thickness in the central 5-mm map zone. Epithelial maps and maximum epithelial thickness in the central 5-mm map zone were analyzed in an attempt to elucidate the details of epithelial recovery process.

Table 1 shows maximum corneal epithelial thickness in the central 5-mm map zone for the three groups at different time points after surgery. At day 4-5 after surgery, the LASEK group showed the largest maximum epithelial thickness in the central 5-mm map zone (75 μm; 95% CI: 71.2–76.8), followed by the PRK group (71 μm) and the trans-PRK group, with a significant difference between the latter group and other groups.

At week 1 after surgery, the corneal epithelium was still thickened in the three groups, especially in the LASEK group (70 μm), with a significant difference between this group and the trans-PRK group (60 μm; $p = 0.0057$) and between the PRK group (67 μm) and trans-PRK group.

At week 2 after surgery, all the three groups showed reductions in the corneal epithelium thickness compared to the previous time point, and the difference between the trans-PRK group and the LASEK group was still

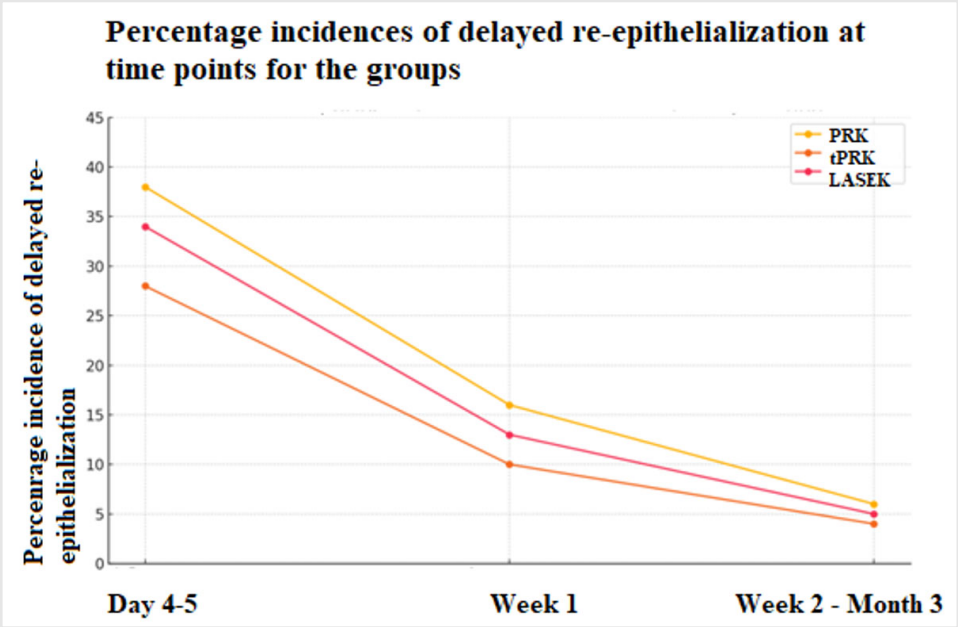

Fig. 1. Corneal re-epithelialization duration

Table 1. Corneal epithelial thicknesses at different time points following three types of excimer laser correction for myopia

Time point	Type of excimer laser correction for myopia			P-value		
	PRK (95% CI)	trans-PRK (95% CI)	LASEK (95% CI)	PRK vs trans-PRK	PRK vs LASEK	trans-PRK vs LASEK
Day 4–5	71 (68.7– 3.3)	64 (62.1–65.9)	74 (71.2–76.8)	< 0.0001	0.1056	< 0.0001
Week 1	67 (64.9–9.1)	60 (58.3–61.7)	70 (67.2–72.8)	< 0.0001	0.0939	< 0.0001
Week 2	63 (60.9–5.1)	58 (56.3–59.7)	66 (63.8–68.2)	0.0003	0.0540	< 0.0001
Month 1	59 (56.9–0.7)	57 (53.5–56.5)	58 (56.1–59.9)	0.1063	0.4662	0.4187
Month 3	57 (55.1–8.9)	55 (52.5–55.5)	56 (54.3–57.7)	0.1063	0.4426	0.3879

Note: Data are presented as mean and 95% confidence interval (CI). The two-tailed t-test for independent samples was used for group comparisons. The sample size in each group was n = 170. A p-value of < 0.05 was considered statistically significant. Abbreviations: LASEK, laser-assisted subepithelial keratectomy; PRK, photorefractive keratectomy; trans-PRK, transepithelial PRK; PRK vs trans-PRK / PRK vs LASEK / trans-PRK vs LASEK, P-values for pairwise comparisons between respective groups

statistically significant ($p = 0.0002$), favoring a more stable corneal thickness profile in the former group.

By months 1 and 3, all the three groups showed gradual normalization of the corneal epithelium thickness, indicating completion of the fundamental stage of the reparative process, but the differences between groups were not statistically significant ($p > 0.07$ each).

Longitudinal changes in stromal pachymetry are well illustrative of postoperative restorative processes. Over the three months of the study, the three groups exhibited a gradual reduction in stromal thickness, likely reflecting the activity of inflammatory processes throughout postoperative recovery, which in turn is likely to be indirectly associated with a transient postoperative reduction in the pumping function of the endothelium. Differences in stromal thickness between groups were most substantial early after surgery, and subsequently tended to completely disappear.

At day 4-5 after surgery, the PRK group showed the largest corneal stromal thickness, and the differences between this group and other groups and between the trans-PRK group and LASEK group were statistically significant (Table 2), indicating a potential influence of the way the epithelium is removed on the early postoperative period.

At week 1, all the groups showed a reduction in the corneal stromal thickness, with the differences between the PRK group and other groups, but not between the trans-PRK group and the LASEK group, being statistically significant.

At later time points, all the differences between groups in the corneal stromal thickness were not statistically significant ($p > 0.1$ each). At month 1 and month 3, the magnitudes of reductions in the corneal stromal thickness in groups were insubstantial, likely due to a reduced inflammatory response, completion of principal reparative processes and gradually normalized hydration.

Topographic CIM was used for assessing irregularity of the anterior corneal surface following ELC procedures, which was helpful for elucidating the details of postoperative recovery of the superficial cornea. Table 3 shows CIM values in the three groups and P-values for differences between these groups at the time intervals studied.

At day 4-5 after surgery, the largest CIM values were seen in the PRK group, and the differences between this group and other groups were statistically significant. Additionally, the smallest CIM values were seen in the trans-PRK group, and the differences between this group and other groups were statistically significant.

At week 1, all the groups showed a reduction in CIM values, the lowest CIM value still found in the trans-PRK group, and the difference between this group and the PRK group (but not the LASEK group) was statistically significant.

At week 2 and month 1, there was a further reduction in CIM values in all the groups, with a further reduction in the magnitude of differences between them. At month 1, a significant difference was found only between the PRK group and the trans-PRK group.

At month 3, all the groups showed relatively low CIM values (0.81–0.84), with no significant difference between groups, which was consistent with other examined features at late time points after surgery.

Because the primary aim of refractive surgery is to improve UCVA, assessing this parameter was important in this study. All the three groups showed a progressive improvement in UCVA over the 3-month follow-up. There

Table 2. Stromal pachymetry at different time points following three types of excimer laser correction for myopia

Time point	Type of excimer laser correction for myopia			P-value		
	PRK (95% CI)	trans-PRK (95% CI)	LASEK (95% CI)	PRK vs trans-PRK	PRK vs LASEK	trans-PRK vs LASEK
Day 4-5	460.0 (454.9–65.1)	444.0 (438.5–449.5)	452.0 (444.9–59.1)	< 0.0001	0.0246	0.0389
Week 1	448.0 (442.3–53.7)	437.0 (430.8–443.2)	440.0 (434.7–45.3)	0.0109	0.0447	0.4715
Week 2	434.0 (428.9–39.1)	429.0 (423.3–434.7)	432.0 (426.1–37.9)	0.2010	0.6155	0.4740
Month 1	428.0 (423.3–32.7)	424.0 (418.9–429.1)	426.0 (421.5–30.5)	0.2591	0.5473	0.5648
Month 3	425.0 (420.5–29.5)	423.0 (418.1–427.9)	424.0 (419.7–28.3)	0.5561	0.7530	0.7639

Note: Data are presented as mean and 95% confidence interval (CI). The two-tailed t-test for independent samples was used for group comparisons. The sample size in each group was n = 170. A p-value of < 0.05 was considered statistically significant. Abbreviations: LASEK, laser-assisted subepithelial keratectomy; PRK, photorefractive keratectomy; trans-PRK, transepithelial PRK; PRK vs trans-PRK / PRK vs LASEK / trans-PRK vs LASEK, P-values for pairwise comparisons between respective groups

Table 3. Topographic corneal irregularity measurement (CIM) at different time points following three types of excimer laser correction for myopia

Time point	Type of excimer laser correction for myopia			P-value		
	PRK (95% CI)	trans-PRK (95% CI)	LASEK (95% CI)	PRK vs trans-PRK	PRK vs LASEK	trans-PRK vs LASEK
Day 4–5	1.72 (1.67–1.77)	1.55 (1.50–1.60)	1.67 (1.62–1.72)	0.0006	0.2124	0.0266
Week 1	1.52 (1.47–1.57)	1.39 (1.34–1.44)	1.47 (1.42–1.52)	0.0002	0.0695	0.0597
Week 2	1.23 (1.18–1.28)	1.18 (1.13–1.23)	1.20 (1.15–1.25)	0.0796	0.3248	0.3746
Month 1	1.03 (0.98–1.08)	0.91 (0.86–0.96)	0.98 (0.93–1.03)	0.0235	0.2269	0.2914
Month 3	0.83 (0.78–0.88)	0.81 (0.76–0.86)	0.84 (0.79–0.89)	0.1375	0.5853	0.3314

Note: Data are presented as mean and 95% confidence interval (CI). The two-tailed t-test for independent samples was used for group comparisons. The sample size in each group was n = 170. A p-value of < 0.05 was considered statistically significant. Abbreviations: LASEK, laser-assisted subepithelial keratectomy; PRK, photorefractive keratectomy; trans-PRK, transepithelial PRK; PRK vs trans-PRK / PRK vs LASEK / trans-PRK vs LASEK, P-values for pairwise comparisons between respective groups

was, however, substantial variation among them in terms of the amount and rate of UCVA recovery at early time points.

Table 4 shows UCVA values for PRK, trans-PRK, and LASEK groups at different time points. At day 4-5 after surgery, the lowest UCVA values were seen in the PRK group, and the differences between this group and other groups were statistically significant (Table 4). Additionally, the trans-PRK group had better UCVA than the LASEK group, but the difference was not statistically significant. At week 1, all groups improved in UCVA, with the trans-PRK group showing the best UCVA, directly followed by the PRK group and the LASEK group; however, only the difference between the trans-PRK group and the PRK group was significant. At week 2, again the trans-PRK group showed the best UCVA, and only the difference between the trans-PRK group and the PRK group was significant. At month 1, all groups had high UCVA, and the UCVA in the trans-PRK group was equal to that in the LASEK group. At month 3, almost all patients obtained maximum UCVA. Mean UCVA in groups was 0.90 or better, and the trans-PRK group showed the best UCVA (1.00), with the difference between this group and the PRK group being statistically significant.

Table 4. Uncorrected visual acuity (UCVA) at different time points following three types of excimer laser correction for myopia

Time point	Type of excimer laser correction for myopia			P-value		
	PRK (95% CI)	trans-PRK (95% CI)	LASEK (95% CI)	PRK vs trans-PRK	PRK vs LASEK	trans-PRK vs LASEK
Day 4–5	0.30 (0.20–0.40)	0.50 (0.40–0.65)	0.50 (0.35–0.60)	0.0148	0.0148	1.0000
Week 1	0.50 (0.45–0.55)	0.70 (0.50–0.85)	0.60 (0.45–0.75)	0.0320	0.2160	0.3957
Week 2	0.65 (0.60–0.70)	0.75 (0.70–0.80)	0.70 (0.60–0.85)	0.0059	0.4672	0.4672
Month 1	0.80 (0.75–0.85)	0.90 (0.80–1.00)	0.90 (0.80–0.95)	0.0805	0.0304	1.0000
Month 3	0.90 (0.85–0.95)	1.00 (0.95–1.05)	0.95 (0.90–1.00)	0.0059	0.1667	0.1667

Note: Data are presented as mean and 95% confidence interval (CI). The two-tailed t-test for independent samples was used for group comparisons. The sample size in each group was n = 170. A p-value of < 0.05 was considered statistically significant. Abbreviations: LASEK, laser-assisted subepithelial keratectomy; PRK, photorefractive keratectomy; trans-PRK, transepithelial PRK; PRK vs trans-PRK / PRK vs LASEK / trans-PRK vs LASEK, P-values for pairwise comparisons between respective groups

Table 5. Percentage incidence of major postoperative complications following three types of excimer laser correction for myopia

Parameter	Type of excimer laser correction for myopia			P-value		
	PRK %	trans-PRK %	LASEK %	PRK vs trans-PRK	PRK vs LASEK	trans-PRK vs LASEK
Visual acuity < 0.8 (at 3 months)	22	11	17	0.067	0.496	0.3239
Delayed re-epithelialization (≥ 1 week)	16	10	13	0.3076	0.6978	0.6658
Stromal edema (> 20 μm)	28	14	19	0.0321	0.2087	0.4637
Epithelial hyperplasia (> 20 μm)	14	12	23	0.8383	0.1636	0.0743
Pathological CIM	22	15	20	0.2961	0.8691	0.4753

Note: Complication incidences are presented as percentage of patients in each study group. A chi-square test was used for comparing the incidence between groups. The sample size in each group was n = 170. A p-value of < 0.05 was considered statistically significant. Abbreviations: LASEK, laser-assisted subepithelial keratectomy; PRK, photorefractive keratectomy; trans-PRK, transepithelial PRK; PRK vs trans-PRK / PRK vs LASEK / trans-PRK vs LASEK, P-values for pairwise comparisons between respective groups

These results may indicate that corneal recovery is longer in myopic eyes treated with PRK and partially illustrate the association between PRK and haze.

We compared the groups for the incidences of major complications throughout fol-low-up in an attempt to generalize the reviewed post-ELC changes. Table 5 shows the percentage incidences of major complications throughout follow-up for the groups.

The PRK group had the highest incidences for most complications; e.g., it had a higher incidence of stromal edema exceeding 20 μm (28%) than the trans-PRK group (14%; $p = 0.0321$) and the LASEK group (19%; $p = 0.1284$). Delayed re-epithelialization (≥ 1 week) was seen in 16 %, 10 % and 13% of the patients in the PRK, tPRK and LASEK groups, respectively, but the differences were not statistically significant.

UCVA reduced to < 0.8 was seen in 22 %, 11 % and 17% of the patients in the PRK, trans-PRK and LASEK groups, respectively, but the differences were not statistically significant. Epithelial hyperplasia was most common in the LASEK group (23%), but the differences were also not statistically significant.

Pathological CIM was most common in the PRK group (22%), followed by the LASEK and trans-PRK groups (20% and 15%, respectively). Although the differences between groups were not statistically significant, the results may indicate a potential role of corneal epithelial hyperplasia in corneal surface irregularity and reduced visual acuity.

Figure 2 shows the incidence of haze in the PRK, trans-PRK and LASEK groups at 1 and 3 months after surgery.

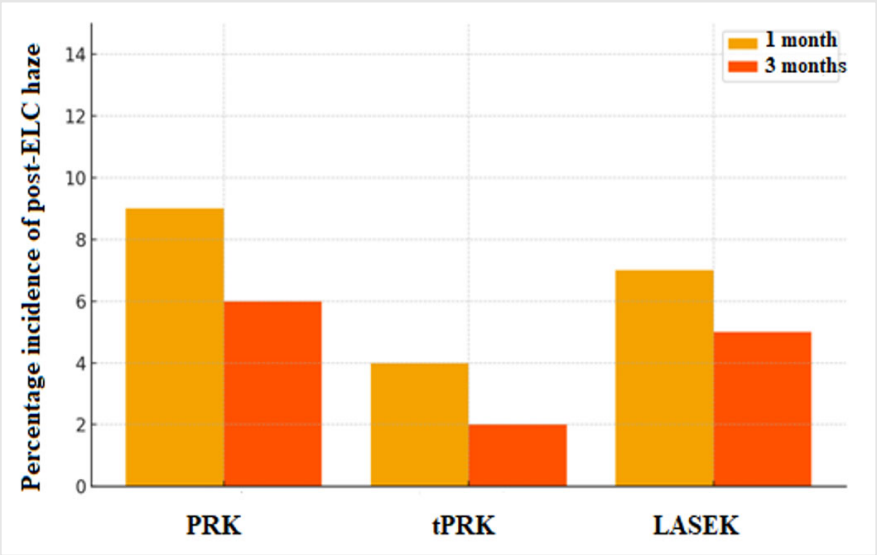

Fig. 2. Percentage incidences of haze at 1 month and 3 months following excimer laser correction (ELC) for the groups

The PRK and trans-PRK groups had the highest and the lowest incidences of haze at 1 and 3 months after surgery (Fig. 2). Of note, in all groups of patients, the incidence of haze at 1 month was higher than that at 3 months; this indicated that early haze was more common, suggesting that the course of corneal recovery was mostly favorable.

Table 6 shows the results of the analysis of correlation between the studied parameters and the incidence of haze.

Haze was very strongly positively correlated with stromal edema and the delay in re-epithelialization (Table 6). A moderate correlation of haze with epithelial hyperplasia and CIM might indicate some relationship between the irregularity of the anterior corneal surface and increased risk of haze. These features, however, are likely to indirectly illustrate the epithelial changes associated with haze through the relationship between the epithelial defect and the activity and duration of inflammation.

Our study found that, irrespective of the technique used, there were subgroups of patients with an increased risk of complications. PCA plots illustrate clear discrimination between clusters, indicating the presence of subgroups with a very favorable course of reparation among patients treated with different excimer laser ablation procedures.

The results of PCA clustering for the three types of ELC are shown in Fig. 3.

Our cluster analysis demonstrated that the PRK group had the highest proportion of patients with a pathological cluster profile (16.5%) – which is consistent with the highest incidence of early postoperative complications registered for this group – followed by the LASEK group (14.7%) and the trans-PRK group (14.7%).

The visual distribution of clusters in the PCA space revealed clear separation of pathological cases, providing an indication of significant morphology-associated patterns.

Table 6. Analysis of correlations between study parameters and the incidence of haze

Parameters	Coefficient of correlation (r)
Stromal edema > 20 μm	0.96
Delayed re-epithelialization (≥ 1 week)	0.93
Pathological values of CIM	0.67
Epithelial hyperplasia > 20 μm	0.77

Notes: Pearson's linear correlation coefficients (r) were used to assess the relationship between morphometric parameters and the incidence of haze. Pearson's correlation coefficients of > 0.7 were considered strong, 0.5-0.7 were considered moderate, and < 0.5 were considered weak. Pearson's correlation coefficients were calculated based on the fixed sample size (n = 510) in the three groups (PRK, trans-PRK and LASEK).

Subgroups with ≥3 signs of complications formed a dense cluster in the PCA space, whereas most other cases were seen outside this cluster and within the norm.

Discussion

We took into account the published features of corneal tissue recovery after ELC of myopia, and focused our attention on postoperative corneal morphological changes [2-4, 6, 7]. Corneal epithelial injury (e.g. that occurring during ELC) triggers a cascade of cytokine-mediated responses which determine the subsequent course of reparation. Healing occurs through stages regulated by growth factors and intercellular signaling. Epithelial growth factor (EGF), hepatocyte growth factor (HGF), keratinocyte growth factor (KGF), and especially transforming growth factor (TGF)-β play a key role in

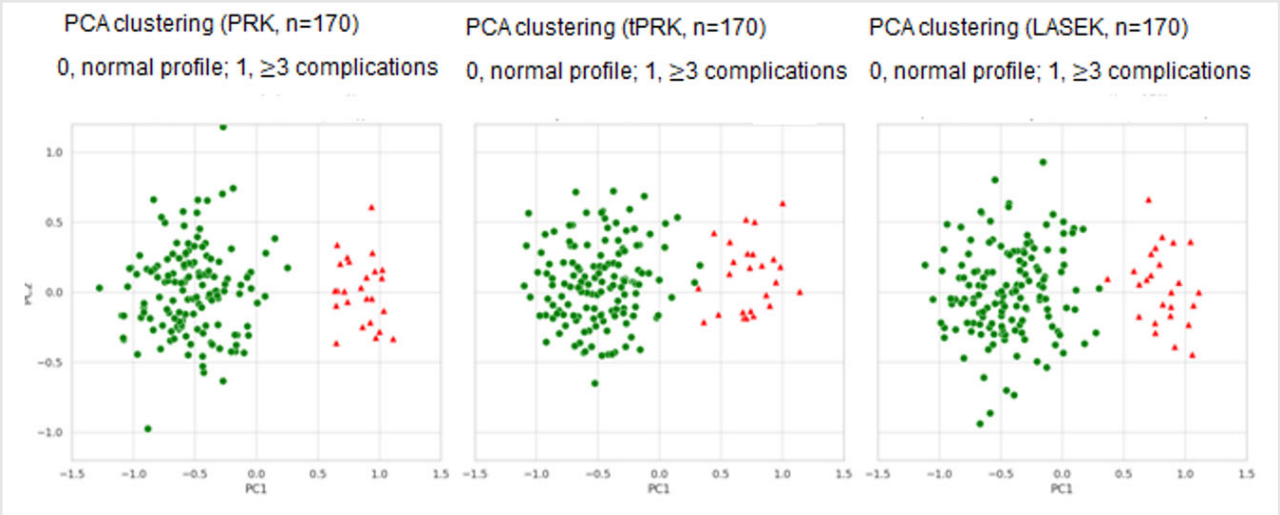

Fig. 3. Visualization of the results of PCA clustering for PRK, trans-PRK and LASEK

this process; the latter factor not only stimulates epithelial cell proliferation, but also is involved in the modulation of stromal response. These cytokines stimulate epithelial cell proliferation due to their mytogenic properties. IL-1 and Fas/Fas signaling pathways integrate epithelial and stromal responses and are also involved in process regulation [16-18]. The cascade of inflammatory responses to corneal surface disruption and corneal microstuctural changes in low-grade CMV infection are likely to cause a postoperative corneal reparative process of different features and rates. Low-grade CMV infection may affect the state and function of endothelial cells. Other factors capable of modulating post-ELC corneal reparative processes include reactivated herpes virus infections, dry eye disease, corneal dystrophy, diabetes mellitus, vitamin D deficiency, ultraviolet radiation, etc. This indicates a multifactorial nature of atypical corneal healing, which requires further research [6, 19, 20, 21]. With this in mind, we determined a number of corneal morphological parameters and their effects on the functional outcome of ELC.

In this study, we found that the type of ELC had some influence on the rate and features of post-ELC corneal recovery. We found the PRK technique to be more commonly associated with early signs of abnormal postoperative corneal recovery than two other types of ELC. The trans-PRK technique, however, demonstrated the most favorable dynamics of epithelial and stromal recovery, with the lowest proportion of patients with secondary changes and subepithelial haze. Such clinical features are consistent with reports on studies assessing microstructural changes in the corneal tissue. Transepithelial ablation has been reported to be advantageous to mechanical or chemical (e.g., alcohol-assisted) epithelial removal, causing reduced cytokine-mediated activity of stromal keratocytes, and is associated with a reduced risk of haze [4, 5, 22, 23, 24, 25].

Epithelial recovery process also reflects changes in corneal epithelial thickness maps. Over the first two weeks after surgery, our patients exhibited a marked in-crease in corneal epithelial thickness, which is consistent with the active regenera-tion phase. Subsequently, all the groups exhibited gradual normalization of the epi-thelial layer, with certain differences in the rate and severity of hyperplasia among them. Early after surgery, patients in the LASEK group showed the most severe hy-perplasia, likely as a response to the preservation of the epithelial flap [26-28]. Pa-tients in the trans-PRK group showed the lowest corneal epithelial thickness values throughout the follow-up, providing indication of more uniform and better regulated reparation. This is in agreement with the reports that laser epitelialectomy allows for the regular surface, resulting in faster and more uniform re-epithelialization [4, 5].

The CIM values derived from corneal topography were helpful for elucidating the details of postoperative recovery of the corneal surface layer and were consistent with longitudinal changes in epithelial thickness maps and UCVA in our groups of patients. Additionally, longitudinal changes in UCVA throughout the follow-up correlated with changes in major morphometric parameters in groups.

In this context, it should be noted that, at late time points, there were no statistically significant difference in any of the signs examined between the groups.

The next phase of our study was to identify the most clinically significant sign of the abnormal postoperative corneal healing. We conducted correlation analysis to find the signs of abnormal postoperative reparation showing the strongest associations with postoperative haze, the complication directly associated with low functional outcome. Stromal edema and delayed re-epithelialization were found to have the strongest correlations with haze. Of note that, although stromal edema was found to have the strongest correlation with haze, attention should be

paid to the association of the latter with the features of the technique. In the current study, the incidences of haze and stromal edema were higher among myopes treated with PRK than among those treated with trans-PRK or LASEK; this does not allow excluding the influence of the method itself on the nature of these changes. Although the delayed re-epithelialization also had the strong correlation with haze, it is more multifactorial and is likely to indicate extracellular dysregulation in the presence of more active and prolonged inflammation, including possible subclinical CMV-induced endothelial dysfunction. It is important also to take into account the fact that the epithelium, in turn, has a role in maintaining normal stromal hydration. Injuries or ischemia of the epithelium commonly cause edema of the underlying stroma owing to the loss of the epithelial barrier function that allows unchecked water passage into the stroma from the tears that overcomes the pumping function of the endothelium until epithelial integrity is restored [2]. This explains our finding that abnormal corneal reparation following ELC for myopia featured not only prolonged re-epithelialization, but also stromal edema. Clinical and experimental studies on corneal wound healing confirmed the association between prolonged re-epithelialization and corneal cicatricial changes [2-4, 6, 7].

Although we found a significant difference in the features of corneal healing between the major excimer laser ablation procedures (PRK, trans-PRK and LASEK), a portion of patients in each group exhibited an abnormal postoperative corneal recovery. This was confirmed by our cluster analysis which demonstrated that, in each group, there was a clear separation of an abnormal postoperative corneal recovery from normal postoperative corneal recovery. The PRK group was found to include a larger portion of patients with an abnormal postoperative corneal recovery relative to other two groups, which agrees with the results of other calculations and analysis within the framework of this study. Other two groups, however, were found to include patients with a combination of several signs of a complicated postoperative recovery, which provided an indication of significant morphology-associated patterns. Subgroups with ≥3 signs of complications formed a dense cluster in the PCA space, whereas most other cases were seen outside this cluster and within the norm. This finding suggests that there is a factor that has not been yet studied but may have some influence on the process of corneal reparation following ELC of myopia. The cluster model developed may be subsequently integrated within a prognostic model for assessing complication risks following excimer laser surface ablation and within the framework of further research on the influence of low-grade CMV infection on the corneal reparative process.

Therefore, the results of the current study confirmed that morphological changes in, and the features of corneal reparation following various types of excimer laser surface ablation are directly associated with the risk of late postoperative complications and have influence on the functional outcome. The morphometric approach to the analysis of corneal healing allows identifying the forms of pathological reparation, and may lay the ground for further research of etiological factors of postoperative complications.

Conclusion

We found statistically significant differences between groups in terms of the incidence of delayed re-epithelialization, corneal epithelial thickness, corneal stromal thickness, CIM and BCVA at early time points after surgery. The trans-PRK group was found to have the most favorable recovery profile.

Between-group differences in morphometric and functional parameters almost disappeared and were not significant at 3 months after surgery.

The PRK group had the highest incidence of visual acuity worse than 0.8 (22%), followed by the LASEK group (17%) and trans-PRK group (11%). Pathological CIM was most common in the PRK group (22%), followed by the LASEK and trans-PRK groups (20% and 15%, respectively). Epithelial hyperplasia was most common in the LASEK group (23%).

The highest and the lowest incidences of early haze were seen in the PRK group and trans-PRK group, respectively. The proportion of patients with haze decreased in all groups at month 3 compared to month 1, providing an indication that early haze was more common than late, with beneficial changes in corneal reparation.

Haze strongly correlated with stromal edema ($r = 0.96$, $p < 0.001$) and delayed re-epithelization ($r = 0.93$), confirming the prognostic significance of early corneal changes for complicated postoperative recovery and reduction in vision.

PCA clustering allowed identifying subgroups with a pathological reparative profile within each group.

The PRK group had the highest incidence of a pathological reparative profile (16.5%), followed by the LASEK group (14.7%) and trans-PRK group (10.6%). The visual distribution of clusters in the PCA space supported the value of multidimensional stratification.

Morphometric parameters (epithelial thickness, stromal pachymetry, CIM, and the rate of re-epithelialization) may be considered as independent predictors of complicated corneal reparation after ELC. When comprehensively assessed, they may be used for predicting the risk of complications and in further research on the new etiological factors of complicated corneal reparation.

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Consent for publication*: This manuscript contains no personal data in any form (including any individual details, medical record numbers or images).*

Abbreviations: *AS-OCT, Anterior Segment Spectral Domain-OCT; CIM, Corneal Irregularity Measurement; CMV, cytomegalovirus; LASEK, laser-assisted subepithelial keratectomy; MMC, mitomycin C; PCA, Principal Component Analysis; PRK, photorefractive keratectomy; trans-PRK, transepithelial PRK; UCVA, uncorrected visual acuity.*