A Randomized Prospective Clinical Trial Comparing Laser Subepithelial Keratomileusis and Photorefractive Keratectomy

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**Objective:** To compare laser subepithelial keratomileusis (LASEK) and photorefractive keratectomy (PRK) in different eyes of the same subjects for subjective pain level, visual acuity, and corneal epithelial healing.

**Design:** Prospective, randomized, double-masked study.

**Setting:** David Grant US Air Force Medical Center, Travis Air Force Base, Calif.

**Participants:** A convenience sample of 30 active-duty military members with mild to moderate myopia.

**Methods:** All patients had LASEK performed in one eye and PRK performed in the contralateral eye; the order of surgical procedures (ie, right eye first or left eye first) and the choice of procedures (ie, PRK in the right eye and LASEK in the left eye or LASEK in the right eye and PRK in the left eye) were determined in advance using a block randomization table.

**Main Outcome Measures:** The primary outcome measures were subjective pain level and the rate of corneal epithelial defect recovery. Postoperatively, subjects were evaluated for their subjective pain level, visual acuity, and corneal healing (ie, epithelial defect size) during the first week and up to 30 days after undergoing the surgical procedures.

**Results:** There were no significant differences in subjective pain levels between the LASEK- and PRK-treated eyes on postoperative days 1, 2, or 3 (P > .05) or in visual acuity on postoperative days 3, 7, or 30 (P > .05). There was a statistically significant (P < .001) smaller median epithelial defect in the LASEK-treated group (1.0 mm²) compared with the PRK-treated group (16.0 mm²) on postoperative day 1. However, by postoperative day 3, the PRK-treated group (0.0 mm²) showed significantly (P < .001) smaller epithelial defects compared with the LASEK-treated group (4.0 mm²). By postoperative day 7, epithelial defects were undetectable in any subjects in either group.

**Conclusions:** Laser subepithelial keratomileusis and PRK have similar postoperative pain thresholds and visual acuity recordings. However, the epithelial healing pattern for LASEK and PRK differs. No additional clinical benefit is seen from the LASEK procedure relative to the PRK procedure.

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Laser subepithelial keratomileusis (LASEK) is a newly advocated laser refractive procedure for patients with myopia in whom photorefractive keratectomy (PRK) or laser in situ keratomileusis may not be ideal because of their drawbacks. These drawbacks may include subepithelial haze, postoperative discomfort, and prolonged visual recovery for patients who undergo PRK and who have flap complications and/or diffuse lamellar keratitis, and epithelial ingrowth for patients who undergo laser in situ keratomileusis. Laser in situ keratomileusis and PRK also may be unsuitable refractive choices for certain patients who have corneal thinning or for patients who have higher potential risk for corneal injuries. In these groups of patients, LASEK has been proposed to be a superior alternative refractive procedure.

In LASEK, a corneal epithelial flap is created using diluted alcohol (18%-20%) placed on the cornea for 30 to 40 seconds. Thereafter, the same excimer laser used typically for PRK or laser in situ keratomileusis is used to ablate the corneal stroma. The epithelial flap is reflected back on the cornea at the end of the LASEK procedure. Recent studies have shown a reduction in pain, faster visual rehabilitation, better visual acuity, and decreased corneal haze in LASEK-treated patients compared with PRK-treated patients; thus, LASEK has
been proposed to be a superior refractive procedure compared with PRK. Another study\textsuperscript{10} has also shown the vitality of corneal epithelial cells after exposure to the diluted alcohol. Photorefractive keratectomy, on the other hand, has been well established for the past decade to be the standard traditional method of treating myopia, hypermetropia, and certain types of astigmatism.\textsuperscript{13} In the past 2 years, several publications have used comparative control samples in their study design of the LASEK procedure\textsuperscript{14-16}; however, these studies either lacked randomization, double masking, or were not prospective. In this study, we attempt to answer the question of whether LASEK is truly a better refractive option compared with PRK by comparing these procedures performed consecutively in the different eyes of the same subjects. In this study, specific variables such as pain assessment, visual acuity, and corneal epithelial healing recovery period were measured. To date, we are unaware of any randomized double-masked study in the literature comparing the subjective pain level, visual acuity, and the corneal epithelial healing period of LASEK and PRK consecutively performed in different eyes of the same patients at the same treatment sitting.

METHODS

DESIGN

This was a prospective, randomized, double-masked, comparative clinical trial performed in the Refractive Laser Center, David Grant US Air Force Center, Travis Air Force Base, Calif. Subjects signed an informed consent document to undergo a clinical trial comparing LASEK with PRK procedures, which was reviewed and approved by the facility institutional review board. All surgical procedures conformed to the tenets of the Declaration of Helsinki. The voluntary, fully informed consent of the subjects used in this research was obtained as required by 32 CFR §219 and AFI 40-402, Protection of Human Subjects in Biomedical and Behavioral Research.

This convenience sample initially included 32 (11 female and 21 male) healthy subjects with myopia (−1.00 to −8.75 spherical equivalent) between the ages of 21 and 46 years. At this center, all patients with refractive conditions who were previously treated or who were being treated had similar age distribution and preoperative refractive error of −1.00 to −8.50 spherical equivalent. However, at the end, these data were analyzed and measured for 30 patients. One subject’s visual acuity was not collected on postoperative day 3 because the patient was unable to keep the appointment. The second subject was dropped from the analysis because of his or her failure to simply record his or her daily subjective pain scores for all 3 postoperative days. All subjects were active-duty military members. Each subject had a bilateral consecutive laser treatment consisting of LASEK performed in one eye and PRK performed in the contralateral eye following the first laser treatment at the same sitting. All surgical procedures were done by the same surgeon (A.P.). The order of the surgical procedures (ie, right eye first or left eye first) and the choice of procedures (ie, PRK in the right eye and LASEK in the left eye or LASEK in the right eye and PRK in the left eye) was determined in advance using a block randomization table. The first eye was randomized to either PRK or LASEK and the contralateral eye was automatically given the other laser procedure. This method of assignment to groups was used to help control for the possible confounding effects of surgery order and eye order on the main outcome measures. In addition, subjects were not told which procedure would be performed on each eye, thus making this study a double-masked clinical trial. Ametropia was targeted for both eyes in all patients.

LASEK PROCEDURE

Tetracaine hydrochloride eyedrops were used for topical anesthesia preoperatively. Twenty percent alcohol was applied to the center of the cornea for 45 seconds using a corneal wipe. It was then thoroughly rinsed with a balanced salt solution. An 8.5-mm epithelial trephine (Shahinian LASEK trephine; Katena Products Inc, Demsville, NJ) was used to create a 270° epithelial hinge. The epithelial flap was reflected back from the cornea with an epithelial peeler (Sloane LASEK Micro Hoe; Katena Products Inc). Excimer laser treatment (VISX Star 3; VISX Inc, Santa Clara, Calif) was performed using the same normogram as that used for the PRK procedure by the same surgeon (A.P.). The epithelial flap was rinsed with a balanced salt solution before being repositioned with the edges overlapping the original intact epithelium. One minute was allowed for the readherence of the epithelium to the underlying stromal tissue before a bandage contact lens was placed in the eye. Lubricating eyedrops were immediately initiated and instillation continued every hour at minimum for the first 3 days until epithelial healing was complete. An ophthalmic solution of 0.3% ofloxacin (Ocuflox; Allergan Inc, Irvine, Calif) eyedrops were started immediately after the completion of the surgical procedure and instillation continued 4 times daily for 3 days. A sterile ophthalmic solution of 0.5% ketorolac tromethamine (Acular; Allergan Inc), 4 times daily, was given for the first 24-hour postoperative period. After bandage contact lens removal, fluorometholone was administered 4 times daily and continued for 1 month if the preoperative refractive error was greater than −3.00. If the refractive error was less than −3.00, fluorometholone therapy was tapered by 1 eyepod per week.

PRK PROCEDURE

Tetracaine hydrochloride eyedrops were used for topical anesthesia as in the LASEK procedure. The epithelium was removed using an automatic epithelial scrubber (Amonlis; Advance Vision Technology Co Ltd, Bangkok, Thailand). The laser treatment was performed using an excimer laser (VISX Star 3; VISX Inc) by the same surgeon (A.P.). The eye was washed, thereafter, using a balanced salt solution. A bandage contact lens was placed in the eye. Treatment with 0.3% ofloxacin (Ocuflox; Allergan Inc) eyedrops was started immediately after the completion of the surgical procedure and continued 4 times daily for 3 days. A sterile ophthalmic solution of 0.5% ketorolac tromethamine (Acular; Allergan Inc), 4 times daily, was given for the first 24-hour postoperative period. After bandage contact lens removal, fluorometholone was administered 4 times daily and continued for 1 month if the preoperative refractive error was greater than −3.00. If the refractive error was less than −3.00, fluorometholone therapy was tapered by 1 drop per week.

MAIN OUTCOME MEASURES

An optometrist (S.N.) evaluated all measurements; each (the optometrist and the patient) was unaware of the surgical procedure performed in each eye. For the subjective pain scores, patients were given the Faces Pain Scale and asked to rate the pain level in each of their eyes on a scale from 1 (least painful) to 10 (most painful) on postoperative days 1 through 3. Patients were asked to return the scale by the end of their first postoperative week visit. Visual acuity was evaluated on postoperative days 1, 3, 7, and 30 using Snellen visual acuity charts. To evaluate change in spherical equivalent, measurements were taken both preop-
RESULTS

Statistical significance for all analyses was set at $P<.05$. Most data were not normally distributed; for this reason, medians and percentiles were used to describe these data; non-parametric techniques (Mann-Whitney test, 2-tailed) were used to compare the surgical groups (PRK vs LASEK) at each of the different time points. The change in spherical equivalent data was normally distributed; therefore, a $t$ test was used to determine any difference between the surgical groups, and 95% confidence intervals are reported.

SUBJECTIVE PAIN LEVEL SCORES

The results of the Mann-Whitney test indicated that there was no difference in pain scale scores between patients with PRK-treated eyes and patients with LASEK-treated eyes on days 1 ($z$ score $=-0.29, P=.77$), 2 ($z$ score $=-1.37, P=.17$), or 3 ($z$ score $=-0.05, P=.96$). The results are summarized in Table 1.

VISUAL ACUITY

The results of the Mann-Whitney test indicated that there was no difference in uncorrected visual acuity between patients with PRK-treated eyes and patients with LASEK-treated eyes on days 3 ($z$ score $=-0.48, P=.63$), 7 ($z$ score $=-0.17, P=.86$), or 30 ($z$ score $=-0.49, P=.62$). The uncorrected visual acuity is reported as the denominator of the Snellen visual acuity chart in Table 2.

VISUAL ACUITY: CHANGE IN SPHERICAL EQUIVALENT

To calculate change in spherical equivalent, preoperative measurements of refractive error were subtracted from postoperative measurements; a positive change value thus indicates an improvement in spherical equivalent and vice versa (Table 3). Results of a $t$ test indicated no difference in the change in spherical equivalent between the PRK-treated eyes and the LASEK-treated eyes ($t=−0.38, P=.71$). In addition, all spherical equivalent change scores were positive in both surgical groups, meaning that no patients exhibited worsened spherical equivalent postoperatively.

EPITHELIAL DEFECT SIZE

The area of epithelial defect (in square millimeters) was computed by multiplying the horizontal (in millimeters) and vertical (in millimeters) diameter of the epithelial defects (Table 4). On postoperative day 1 the results of the Mann-Whitney test indicated that patients with LASEK-treated eyes had a significantly smaller area of epithelial defect compared with patients with PRK-treated eyes ($z$ score $=−4.91, P<.001$). On postoperative day 3 the results of the Mann-Whitney test indicated that patients with
PRK-treated eyes had a significantly smaller area of epithelial defect compared with patients with LASEK-treated eyes (z-score = −4.10, P < .001). On postoperative day 7 statistical techniques were not used for these data because all patients had an epithelial defect measurement of 0 regardless of surgical group.

VISION QUALITY

Immediately after the completion of the consecutive bilateral procedure, patients were asked to point to the eye with better visual acuity. All patients pointed to the PRK-treated eye. These data were recorded on the patients’ medical records.

At the end of 30 days, patients were asked the same question once again. Fifteen patients selected the PRK-treated eye and the other 15 selected the LASEK-treated eye. These data were recorded on the patients’ medical records.

PROCEDURAL PREFERENCE

Immediately after the completion of the procedure patients were asked to point to the eye which they favored the laser treatment on. 15 patients pointed to their PRK-treatment eyes and the other 15 patients pointed to their LASEK-treatment eyes. These data were recorded on the patients’ medical records.

As reported in the medical literature, Camellin and Cimberle17 were among the first authors to describe and perform the LASEK procedure. Azar et al3 described a similar but differently named surgical procedure about the same time. The popularity of LASEK has recently been gaining momentum among refractive ophthalmologists after a few clinical series showed that LASEK might have significant clinical advantages over PRK.3 Reported advantages included the reduced level of pain, faster visual recovery, and possible decreased risk for corneal haze formation.2,5,7

Although previous studies have shown faster visual recovery and decreased pain levels in patients with LASEK-treated eyes5,7 none of the studies have attempted to compare these factors within the same subject receiving different procedures in each eye in a double-masked format. To our knowledge, our randomized prospective clinical trial is the first study of this kind which attempted to quantify the reported advantages of the LASEK procedure by comparing it with the PRK procedure in the same subjects in a double-masked technique.

In the review of the published literature, we noted that Camellin and Cimberle17 reported a series of 249 LASEK-treated cases with wide variability in the ease of making epithelial flaps. More than half of their patients in the study felt no pain after the first day. In their prospective comparative trial of 50 eyes with a follow-up of 1 month in which the results of LASEK and PRK were analyzed, Litwak et al14 reported less discomfort and better visual acuity in the PRK-treated eyes during the early postoperative period. Lee et al10 reported in their prospective study of 84 bilateral consecutive LASEK-treated eyes for a moderate myopia with a 6-month follow-up that LASEK is an effective and safe refractive procedure with a mean epithelial healing time of 3.68 days. In another study, Lee et al15 prospectively compared the results of LASEK in 1 eye vs PRK in the other eye of 27 patients (54 eyes) with myopia (−3.00 to –6.50 spherical equivalent) performed 2 weeks apart and reported lower postoperative pain and corneal haze scores in the LASEK-treated eyes at 1 month with more than half (63%) of the participants preferring the LASEK procedure. This study, although designed to be randomized, was not masked and the laser treatments were not done consecutively in a simultaneous fashion. Shahinian10 reported in his prospective 12-month study of 146 consecutive LASEK-treated eyes that LASEK was safe and effective in treating myopia and astigmatism with varying degrees of pain and blurry vision for several days. Claridge-bold10 reported in his retrospective noncomparative interventional case series of 222 consecutive LASEK-treated myopic eyes no loss of best-corrected Snellen visual acuity and no serious complications. Shah et al5 in their prospective, nonrandomized, comparative-paired eye trial of 72 moderate myopic eyes (36 patients) with a mean 1-year follow-up reported no statistically significant difference between the 2 groups in their postoperative mean change in spherical equivalent. The corneal haze was also less in the LASEK-treated group. However, this trial neither evaluated the patient’s pain level nor the epithelial healing rate.

In our study, we did not observe the differences reported in the literature between LASEK- and PRK-treated eyes. There was no statistically significant difference in postoperative visual acuity between the PRK- and the LASEK-treated eyes, nor was there a difference in the subjective pain level between these 2 groups. In addition, none of the eyes in either the PRK- or the LASEK-treated group lost any lines of visual acuity compared with their best-corrected preoperative visual acuity (ie, all spherical equivalent change scores were positive). However, the epithelial healing pattern was somewhat different between PRK and LASEK. On postoperative day 1, the median area of the epithelial defect...
in LASEK-treated eyes (1.0 mm²) was significantly smaller compared with the PRK-treated eyes (16.0 mm²). However, by postoperative day 3, the median area of epithelial defect in the LASEK-treated eyes (4.0 mm²) was significantly larger relative to the PRK-treated eyes (0.0 mm²). Indeed, while the median size of the epithelial defect decreased from postoperative days 1 to 3 in the PRK-treated eyes (16.0-0.0 mm²), it increased in the LASEK-treated eyes between days 1 and 3 (1.0-4.0 mm²). We would like to call this phenomenon of nonadherence and natural breakdown of the epithelium the early onset postoperative LASEK–epithelial degradation. It is possible that epithelial flaps exposed to alcohol during the LASEK procedure lose their cellular integrity, thus, are unable to adhere and recover in the same fashion as the newly deposited and formed epithelium could do in the PRK-treated eyes. Nevertheless, the total days needed for the complete recovery of the cornea was similar by postoperative day 7 for both procedures. No epithelial defects were detectable in either group of eyes. Furthermore, no corneal haze was observed for either of the treatment groups as was expected owing naturally to the short follow-up time of this study. The corneal haze in PRK and LASEK procedures typically occur 3 to 4 months afterward. No intraoperative or postoperative flap complications, any other complications, or bad outcomes occurred in any of our patients in the interval of this study.

About half of our patients preferred PRK over LASEK because of its quicker procedural completion time; the PRK treatments took an average of 4 minutes to complete vs an average of 11 minutes for the LASEK procedure. On the other hand, the other half of patients preferred LASEK because they did not like the use of the epithelial scrubber on their eyes during the PRK procedure. However, overall the patients’ satisfaction with their final postoperative visual acuity was equal between the PRK and LASEK treatment after 30 days (data collected via self-report).

Another interesting observation was that, in general, the PRK-treated eyes demonstrated better visual acuity and patients naturally preferred the PRK-treated eyes immediately after the completion of the procedure, compared with the LASEK-treated eyes, most likely because of the presence of epithelial edema (data collected via self-report). Patients nowadays have been told and have come to expect that their visual acuity would be outstanding immediately after undergoing a refractive procedure. As a result, this immediate postoperative visual blurring could be disconcerting and disappointing for patients who have come to expect to have a perfect immediate postoperative visual outcome.

In our study, we also noted intersubject variability and unpredictability in the ease of making epithelial flaps in the LASEK-treated eyes. Typically we noted that it was significantly more difficult to complete the epithelial flap in younger patients compared with older patients (aged >30 years).

After completing this study and comparing LASEK with PRK in an objective manner, we do not share the same enthusiasm expressed by our colleagues for the superiority of LASEK over PRK. The LASEK procedure typically takes an average of twice as long for a surgeon to perform compared with the PRK procedure. Patients’ anxiety may increase with increased surgical time. In addition, in the market-driven refractive practices of today, the longer time necessary to perform the LASEK procedure, without its significant benefits, would adversely affect busy refractive surgical centers.

From our standpoint, additional studies are warranted to create epithelial flaps with different concentrations of alcohol or with different automated machines. Research on the long-term stability of visual acuity in a large LASEK series could also provide additional information about the stability and efficacy of this procedure. One-year follow-up results of the visual acuity, refractive error, and corneal findings for both our PRK- and the LASEK-treated patients will be presented in the near future.

**CONCLUSIONS**

The previously described advantages of LASEK compared with PRK, such as faster epithelial healing, shorter visual rehabilitation, and decreased postoperative pain compared with PRK were not observed in this study. Based on our data, we see no additional benefits from the LASEK procedure compared with the PRK procedure in low to moderately myopic eyes.

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