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14. ABSTRACT

Despite the proven safety and efficacy of laser refractive surgery in improving uncorrected vision, several important issues require further analysis in the armed forces. Visual performance under low light illumination, cockpit performance in military aviators, ability to meet accession and retention standards, and resistance to trauma are among some of the unique considerations of the active duty military. The current study comprises a comprehensive evaluation of safety, efficacy and visual performance after laser refractive surgery. Initial studies cover surgical procedures and pre- and post-operative assessment of visual performance, refractive error and stability, and ocular integrity. Subsequent phases address military operational factors, including occupation-specific visual requirements and effects of various operational environments. Additional militarily relevant investigations will address emerging technologies, both military and medical, as they apply to refractive surgery in the US service men and women. To date, we have enrolled and treated over 500 subjects in one of 16 approved protocols (9 ongoing and 7 completed). We have published 15 peer-reviewed papers, and presented 8 papers and 22 abstracts at national or international meetings. We have research collaborations with a number of DoD and civilian academic institutions including the US Army Night Vision Laboratory and Electronic Sensor Directorate, the US Army Aviation Research Laboratory, the Naval Medical Center San Diego, Stanford Research Institute, the US Army Center for Health Promotion and Preventative Medicine, the Schepens Eye Research Institute, Harvard Medical School, University of Virginia, James Madison University, and Eastern Virginia Medical School. This report will cover the accomplishments of the program to date and outline future directions and goals for the program.

15. SUBJECT TERMS
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INTRODUCTION

Approximately one-third of the 1 million active duty Army service men and women, reservists and national guardsmen require corrective lenses. Because of the unique operational demands placed on military service members, there are distinct disadvantages to the soldier wearing corrective lenses. Recognizing the tremendous potential for refractive surgery to enhance military readiness, the Army now supports the surgery under the Warfighter Refractive Eye Surgery Program (WRESP). To date over 45,000 soldiers have been treated in the Army WRESP. The WRESP has provided excellent outcomes, enhanced overall readiness, and has been enthusiastically received by soldiers and their commanders. Clinically successful outcomes appear to translate into improved job performance as reported on the post-deployment surveys, consistent with anecdotal reports from patients and unit commanders praising the program and its benefits. Nevertheless, several concerns of particular importance to the military, notably night vision, aviation, susceptibility to trauma, and harsh environmental conditions among others, merit further investigation to determine the impact on military operations. The purpose of this research program is to investigate matters of military importance regarding refractive surgery in the Army. This report will detail efforts and progress to date and outline areas of interest for future research.

BODY

This is the first "annual" report for this project, which has been ongoing since the opening of the Walter Reed Army Medical Center (WRAMC) Center for Refractive Surgery in 2001. It will outline the research protocols opened to date and summarize the research accomplishments of each. In total, there are 16 protocols approved through the WRAMC Department of Clinical Investigation. Of these, 9 are completed/closed while 7 remain open to recruitment and or data collection and analysis. Over 500 Army soldiers have been treated in one of these protocols, which are described below. Along with a brief description of the protocol are included pertinent abstracts detailing results. A separate bibliography is listed under REPORTABLE OUTCOMES section of this report, and PDF files of the published papers will be included in the APPENDIX.

A. Initial Evaluation of Excimer Laser Keratorefractive Surgery in US Army Personnel. PI: Bower KS. (WU # 2335-99) MASTER PROTOCOL (OPEN)

The primary objective of this study is to determine the safety and efficacy of excimer laser keratorefractive surgery in U.S. Army personnel. This study serves as the Master (parent) protocol covering the primary objectives, indications, inclusion/exclusion criteria, refractive surgical procedures, risks, surgical technique, post-operative care, follow-up schedule and core clinical examination measurements. The patient population will include U.S. Army service members. An FDA approved laser system will be utilized in a prospective design to evaluate photorefractive keratectomy (PRK) and laser in-situ keratomileusis (LASIK) for treatment of low to moderate myopia (near-sightedness), including myopia with astigmatism, astigmatism, and hyperopia (far-sightedness). The study will be conducted in phases, with this Master Protocol covering surgical procedures and pre- and post-operative assessment of visual performance, refractive error and stability, and ocular integrity. Subsequent phases, subject to

additional review, will address military operational factors, including occupation-specific visual requirements and effects of combat and environmental stressors.

Objectives of the overall study are to:

1. Determine the safety of PRK and LASIK for maintenance of optimal visual performance and ocular integrity. Initial evaluations will focus on maintenance of best-corrected vision (before and after surgery) as measured with clinical tests of visual acuity and contrast sensitivity, and clinical assessment of corneal integrity and clarity.
2. Determine the efficacy of PRK and LASIK by assessing the improvement in uncorrected vision for target detection, discrimination and recognition. This will be assessed prospectively with clinical measures of visual acuity and contrast sensitivity under normal and low light levels, and in subsequent studies with tasks tailored to assess occupation-specific visual requirements.
3. Determine the efficacy of PRK and LASIK by evaluating the extent to which the refractive outcome agrees with the desired result, and the stability of the refractive error over time.

The study, in separate sub-protocols will attempt to quantify the efficacy of PRK and LASIK for military operations under reduced visibility including unaided night vision, image intensifying systems (e.g., various generation night vision goggles), and helmet-mounted displays (e.g., Apache Integrated Helmet and Display Sighting System; prototypes available for Comanche). Issues regarding specific displays or combat stressors will be assessed in future sub-studies with discrete numbers of subjects necessary to achieve statistical power for the issue under investigation. Sub-studies will be submitted for review and approval prior to initiating.

Abstracts/presentations stemming directly or indirectly form this master protocol are listed below.

(1) Abstract: Rabin J, Bower KS, Chun D. A new approach for measuring disability glare in refractive surgery. Poster presentation at the American Academy of Optometry Annual Meeting, Philadelphia, December 2001.

Purpose: Despite the efficacy of excimer laser surgery for correction of refractive error, many patients complain of glare, particularly at night. Quantification of these symptoms is problematic, since conventional glare testing often yields a paradoxical improvement in performance, by constricting the pupil, and decreasing the effects of peripheral aberrations. We describe theory and methodology of a new approach to quantify disability glare, which overcomes this problem, by combining a mesopic, contrast-modulated stimulus with diffuse glare. We report findings in patients treated successfully with PRK one year ago. **Methods:** Small letter contrast sensitivity (CS), comprised of letters of constant, small size (20/25), which vary in contrast in 0.1 log steps per row (0.01 per letter), was presented under reduced luminance (3 cd/m2), with and without diffuse surrounding glare (300 cd/m2). Pupil size was monitored with an infrared pupillometer. **Results:** Compared to photopic CS, small letter CS was significantly decreased under mesopic conditions (mean decrease 7.7 lines), with the addition of glare causing a further decrement in CS (mean 2.9 lines). Mean pupil size was significantly larger under mesopic conditions (4.52 mm) compared to photopic (3.03 mm), with the mesopic + glare condition midway between these values (3.74 mm). Mesopic CS, both with and without glare, was inversely proportional to pupil size, suggesting that the decrement in CS was due, in part, to peripheral aberrations. **Conclusions:** Mesopic small letter CS (with/without surrounding glare) provides an effective means to quantify disability glare in refractive surgery patients. By maintaining a low stimulus luminance, pupillary constriction is minimized, and CS is consistently reduced in the presence of glare. Further testing is underway to determine if decrements in

refractive surgery fall within normal limits, and how these decrements relate to ocular aberrations.

(2) <u>Abstract:</u> Rabin J, Bower KS, Chun D. Quantitative assessment of disability glare. Association for Research in Vision and Ophthalmology Annual Meeting, Program/Poster #B112, May 2002.

<u>Introduction:</u> Excimer laser surgery (LASIK and PRK) is effective for correction of refractive error, but many patients complain of glare, particularly at night. Since conventional glare testing often improves performance in refractive surgery patients (by constricting the pupil and decreasing the effects of peripheral aberrations), quantification of these symptoms is lacking. **<u>Purpose:</u>** We describe theory and application of a new approach to quantify disability glare, which overcomes problems of current techniques, by combining low luminance, small target contrast sensitivity (CS) with diffuse glare. We report findings for controls subjects and patients treated successfully with PRK at least one year ago. **<u>Methods:</u>** Small letter CS comprised of letters of constant, small size (20/25), which vary in contrast (0.1 log steps per row; 0.01 per letter), was presented at low luminance (3 cd/m^2), with and without diffuse surrounding glare (315 cd/m^2), and under standard photopic conditions (150 cd/m^2). Pupil size was monitored with infrared pupillometry, and higher order ocular aberrations were assessed (WaveFront Sciences COAS). **<u>Results:</u>** In contrast to results with conventional glare tests, CS was significantly decreased in PRK subjects in the presence of glare (mean decrease 2.9 lines), which caused minimal decrease in pupil size (<1mm). While performance in this sample of PRK subjects was not significantly different from normal (p=0.2), there was an inverse relation between CS and pupil size (p<0.01), and individuals with pronounced disability glare showed specific increases in higher order aberrations (coma in PRK; trefoil and spherical aberration in controls). **<u>Conclusions:</u>** Disability glare can be quantified in refractive surgery as well as normal eyes by assessment of low luminance, small target CS, with and without surrounding glare. Pupillary constriction is minimized, and CS is consistently reduced in the presence of glare. Performance decrements can be linked to specific higher order ocular aberrations.

(3) <u>Abstract:</u> Weichel E, Morgan ER, Bower KS, Rabin J. Visual performance in photorefractive keratectomy: One year and beyond. Association for Research in Vision and Ophthalmology Annual Meeting, Program/Poster #B118, May 2002.

<u>Purpose:</u> The efficacy of refractive surgery typically is based on the level of high contrast visual acuity (VA) achieved and the degree of post-operative, residual refractive error. While decrements in contrast sensitivity (CS) and other measures of visual performance have been demonstrated, these effects are often transient, and not consistently related to visual symptoms. Moreover, information about long-term effects on visual function is lacking. We describe comprehensive measures of visual performance in photorefractive keratectomy (PRK) one year or more after surgery. **<u>Methods:</u>** Subjects were active duty Army soldiers treated for myopia (-1 to -5D) with a VISX Star excimer laser (6 mm ablation zone) at least one year ago. VA versus contrast (1.25% to 100%) and small letter CS were measured at photopic and mesopic light levels. Glare disability was assessed for mesopic VA (2.5 and 5% contrast) and mesopic small letter CS. Complete spatial and temporal sine-wave CS functions were obtained at photopic and mesopic levels, using a computer-controlled, 2-alternative forced choice system. **<u>Results:</u>** At 12-18 months after PRK, uncorrected VA for a range of contrasts (2.5%, 10% and 100%) was not significantly different from pre-operative VA with best correction (p>0.1), despite correction for post-operative magnification effects. Whereas small target CS, and spatial and temporal CS were largely within normal limits, there was considerable inter-subject variability (>0.2 log units), with some subjects falling below normal levels. In some cases performance decrements were related to higher order aberrations. **<u>Conclusions:</u>** Comprehensive visual assessment, including target detection and recognition with static and dynamic displays, at normal and reduced luminance, is necessary to fully characterize visual performance in refractive surgery. Further testing is underway to determine how higher order aberrations, pupil size and other factors account for decrements in visual performance detected with this methodology.

B. Evaluation of Alcon LADARVision conventional photorefractive keratectomy (PRK) in U.S. Army personnel. PI: Bower KS. AI: Stutzman RD, VanRoekel RC, Burka JM, Kuzmowych CP. (WU #01-2335-99d) SUB-PROTOCOL (OPEN)

The purpose of this sub-protocol is to develop a control group, which will evaluate the safety and efficacy of conventional PRK in U.S. Army personnel who have naturally occurring myopia with or without astigmatism. The data from this control group will be compared to study groups undergoing wavefront guided PRK as well as other technical modifications and emerging technologies. This study is a twelve-month prospective non-randomized investigation. The study will evaluate the safety and efficacy of conventional PRK. The subjects will be evaluated before and after the same PRK procedure that is performed on all non-research patients. These evaluations will include the best spectacle-corrected visual acuity (BSCVA), uncorrected visual acuity (UCVA), psychometric questionnaire, pupil size, biomicroscopic examination, manifest refraction, wavefront measurements, and other tests that are performed on all non-subjects who receive PRK at Walter Reed's Center for refractive Surgery. No investigational drugs or devices will be used in this study. To date, all 150 subjects have been enrolled and treated. Data analysis will be completed after 12-month post-operative data is available. No adverse events have been reported. No abstracts, presentations, or papers have resulted as of this report.

C. Night Vision Goggle and Night Firing Range Performance After Myopic Excimer Laser Keratorefractive Surgery in U.S. Army Personnel. PI: Bower KS. AI: Rabin JC. Collaborating personnel: O'Kane B (Night Vision Laboratory and Electronic Sensor Directorate, Ft. Belvoir, Virginia). (WU #01-2335-99a) SUB-PROTOCOL (CLOSED)

Military operations often take place at night or under conditions with reduced contrast; therefore, any further degradation of vision under these conditions after refractive surgery could compromise operational performance and safety. In addition, limitations inherent in night vision devices have been well documented in the literature. The combination of low contrast, low luminance, and isochromatic viewing conditions pose significant challenges for object detection, discrimination and recognition. While much work has been done regarding the quality of vision after laser refractive surgery, the true incidence, cause, nature, and optimal treatment of night vision difficulties, as well as the effect on NVG performance, remain areas of concern to the military.

This study is one component of a larger study designed to determine the safety and efficacy of excimer laser keratorefractive surgery in U.S. Army personnel. This is the first of the sub-studies designed to evaluate issues regarding specific displays or combat stressors and the effects of various operational environments including, but not limited to, combat, urban, tropical, desert, and cold weather. It is a one-year, prospective, non-randomized investigation of night vision goggle and night firing performance using a two-group (PRK surgical treatment, LASIK surgical treatment) longitudinal design with measurements taken at four points in time (initial or month 0, and months 1, 3, and 9 after the initial measures). The initial, baseline measures (obtained pre-operative as part of the master protocol for the surgically-treated subjects and abstracted from the master protocol database, and at the initial data collection for control subjects) will consist of a one time only measure of the key variables. The subsequent measures will consist of 3 evaluations made at 1, 3, and 9 months following the surgical procedure or, for the control group, following the baseline measures. The NVG measures specific to this protocol will be made at

baseline and at 1, 3 and 9 months post- baseline. All baseline pre-operative evaluation and all study follow-up evaluations will be conducted at Walter Reed, except for NVG acuity and night firing to be conducted at the Night Vision Laboratory, Fort Belvoir. The overall goal of this NVG sub-study is to evaluate the effect of two types of refractive surgery on performance with night vision goggles and the M-16 on the night firing range over time as compared to no surgical intervention.

Specific objectives of this sub-protocol are to:

1. Evaluate visual performance in Night Vision Goggles (NVG) before and after excimer laser refractive surgery. Performance measurements will include high and low contrast targets viewed with and without optical correction.
2. Determine the safety of LASIK and PRK in terms of maintenance of best-corrected NVG visual resolution of both high and low contrast targets under a full range of night sky conditions. The magnitude and duration of any transient post-operative changes in best-corrected NVG performance will be evaluated.
3. Evaluate the efficacy of PRK and LASIK by assessing improvement of uncorrected NVG visual performance.
4. Evaluate whether any measured post-operative NVG performance changes affect the ability to perform a specific task, as determined by performance testing on the night firing range before and after excimer laser refractive surgery.
5. Evaluate subjective responses to the surgery to determine satisfaction and complaints with respect to glare, night vision, and halos.

The following abstracts/papers resulted from this sub-protocol:

(1) Abstract: O'Kane B, Stefanik R, Stevens R, Subramanian P, Rabin J, Bower KS. Night vision performance and contrast sensitivity after photorefractive keratectomy. Vision Science and Its Applications 2001 Topical Meeting /2nd International Congress of Wavefront Sensing and Aberration-Free Refractive Correction, Monterrey, California, February 2001.

Purpose: To evaluate visual performance and resolution through night vision goggles (NVG) before and after photorefractive keratectomy (PRK). **Methods:** Nineteen patients (38 eyes), active-duty US Army Special Forces soldiers, were treated with PRK for myopia and astigmatism. Photopic contrast sensitivity with best optical correction was measured pre- and postoperatively (3 months) using low-contrast visual acuity charts (100%, 10%, 2.5%, 1.25%). Preoperative and postoperative (3 month) uncorrected and best-corrected visual resolution through NVG were assessed using a tri-bar chart presented at four light levels simulating a range of night sky conditions (10^{-5}, 10^{-4}, 10^{-3}, 10^{-2} foot Lamberts). Subjects were trained prior to testing. **Results:** Uncorrected visual acuity at the 3-month post-operative assessment was greater than or equal to 20/20 in 33 of 38 (86.8%) eyes. No eyes lost 2 or more lines of best spectacle-corrected visual acuity. Pre- and 3 month postoperative best-corrected photopic contrast sensitivity measurements showed no significant differences at all levels of resolution. Preoperative visual resolution through NVG decreased systematically with night sky conditions. Visual acuities prior to PRK were reduced without optical correction. Postoperative visual performance with NVG (without optical correction) equaled or exceeded performance preoperatively with optical correction. **Conclusions:** This prospective case series provides data on the safety and efficacy of PRK with respect to visual performance under night-sky conditions using NVG. There was no significant loss of contrast sensitivity at 3 months postoperatively. There was no change in best-corrected NVG visual resolution post-operatively, while uncorrected visual resolution was significantly enhanced compared to preoperative levels. This improvement may translate into better

function for soldiers who are unable to or choose not to use optical correction in an operational environment.

(2) <u>**Abstract:**</u> **Bauer R, Bower KS, O'Kane B, Stefanik R, Stevens R, Subramanian P, Rabin J. Physical limits on visual resolution through image intensifiers before and after PRK. Association for Research in Vision and Ophthalmology Annual Meeting, Ft. Lauderdale, Florida, May 2001**

<u>**Purpose:**</u> Photopic visual acuity typically returns to normal levels after photorefractive keratectomy (PRK). Notwithstanding complaints of decreased night vision following PRK, quantitative evaluations of night vision performance are lacking. Our purpose was to evaluate visual resolution through image intensifiers before and after PRK across a range of night sky conditions. <u>**Methods:**</u> Visual resolution through 3rd generation image intensifiers was assessed in 19 Army service members (age 20-41) before and at 3 months after PRK for simple and compound myopia. The minimum resolvable high contrast grating was determined for four simulated night sky conditions (full moon to overcast starlight) spanning a 2 log unit range. Measurements were taken with and without best spectacle correction. <u>**Results:**</u> Pre-surgical resolution without spectacle correction was decreased at all light levels compared to results with best spectacle correction ($p<0.001$). In contrast, post-surgical visual resolution without correction was as good or better than pre- and post-surgical resolution with best correction, underscoring the efficacy of PRK in this study. Under all viewing conditions, visual resolution decreased systematically with night sky level, and the slope of this power law function was the same before and after PRK. <u>**Conclusions:**</u> As has long been known, visual resolution through image intensifiers decreases systematically with night sky level. This study shows that the slope of this relation remains constant before and after PRK, indicating that the decrease in resolution with night sky does not reflect changes in the optical quality of the eye. Rather, for the luminance range tested, the decline in resolution with night sky likely reflects the quantal nature of light, wherein the uncertainty of detection is inversely proportional to the square root of luminance, making acuity targets less visible at low luminance. Research is planned to determine whether physical or optical factors (e.g., ocular aberrations) limit visibility of larger, low contrast targets after refractive surgery.

(3) <u>**Presentation:**</u> **Subramanian PS, O'Kane B, Stefanik R, Stevens J, Rabin J, Bauer RM, and Bower KS. Visual acuity and night vision performance after photorefractive keratectomy for myopia. American Society for Cataract and Refractive Surgery Annual Meeting, San Diego, California, May 2001.**

<u>**Purpose:**</u> To compare visual resolution through night vision goggles (NVG) before and after excimer laser photorefractive keratectomy (PRK). <u>**Methods:**</u> 20 myopic active duty U.S. Army patients of both sexes, 21 years of age or older who met inclusion/exclusion criteria were treated with the VISX Excimer Laser System. Uncorrected visual acuity (UCVA), best spectacle corrected visual acuity (BSCVA), manifest refraction (MR), and photopic contrast sensitivity function (CSF) were assessed at baseline and at 3 months after surgery. In addition, uncorrected and best corrected visual resolution was measured through NVG (PVS-7D) using a tri-bar chart presented at four light levels simulating a range of night sky conditions (10^{-5}, 10^{-4}, 10^{-3}, 10^{-2} foot lamberts). 3-month post-operative NVG results were compared to pre-operative values. <u>**Results:**</u> 40 eyes of 20 patients were treated. The mean pre-operative spherical equivalent (SE) was -2.42D (range -1.0D to -5.50D). Mean pre-op refractive cylinder was 0.7D (range 0 to 2.00D). At 3 months post-op, UVCA was 20/20 or better in 87.2%, 20/40 or better in 100%. The mean post-op SE was -0.03D (range +1.00 to -1.125D). There was no loss of BSCVA. Photopic CSF was unchanged at 3 months post-op. The post-operative uncorrected NVG resolution was significantly enhanced compared to pre-operative levels. There was no change in best-corrected NVG visual resolution at 3 months post-op. <u>**Conclusions:**</u> PRK is a safe and effective treatment for low myopia and myopia with astigmatism. In this study there was no significant loss of photopic contrast sensitivity at 3 months post-operatively. Uncorrected NVG visual resolution post-operatively matched the best-corrected NVG visual resolution. The improvement in unaided NVG resolution may translate to better performance in soldiers who cannot or choose not to wear corrective lenses in the operational environment. Task-performance measures must be developed to further test the above hypothesis.

(4) Paper: Subramanian PS, O'Kane B, Stefanik R, Stevens J, Rabin J, Bauer RM, and Bower KS. Visual acuity and night vision performance after photorefractive keratectomy for myopia. Ophthalmology 2003 Mar;110(3);525-30.

Objective: To evaluate visual performance and resolution through night vision goggles (NVG) before and after photorefractive keratectomy (PRK). **Design:** Non-comparative prospective case series **Participants:** Nineteen patients (38 eyes) of active-duty US Army Special Forces soldiers. **Intervention:** PRK for myopia and astigmatism. **Main Outcome Measures:** Visual acuity with best optical correction was measured pre- and postoperatively (3 months) using acuity charts of various contrast (100%, 10%, 2.5%, 1.25%). Preoperative and postoperative (3 month) uncorrected and best-corrected visual resolution through NVGs was assessed using a high contrast tri-bar chart presented at four light levels (3.44 X 10^{-3}, 1.08 X 10^{-3}, 1.04 X 10^{-4}, 1.09 X 10^{-5} foot Lamberts) simulating a range of night sky conditions. Subjects were trained prior to testing. **Results:** Uncorrected visual acuity at the 3 months post-operative assessment was greater than or equal to 20/20 in 33 of 38 (86.8%) eyes. No eyes lost 2 or more lines of best spectacle-corrected visual acuity. Pre- and 3 month postoperative best-corrected low contrast acuity measurements showed no significant differences at all levels of resolution. Preoperative visual resolution through NVGs decreased systematically with decreasing night sky condition. Visual acuities prior to PRK were reduced without optical correction. Post-operative visual performance with NVGs (without optical correction) equaled or exceeded performance pre-operatively with best correction. **Conclusions:** This prospective case series provides data on the safety and efficacy of PRK with respect to visual performance under night-sky conditions using NVGs. There was no significant loss of visual acuity across a range of contrast levels at 3 months post-operatively. There was no change in best-corrected NVG visual resolution post-operatively, while uncorrected visual resolution was significantly enhanced compared to preoperative levels. This improvement may translate into better function for soldiers who are unable to or choose not to use optical correction in operational environments.

(5) Abstract: Bower KS, Subramanian PS, Stutzman RD, Rabin JC. Prospective evaluation of night vision goggle (NVG) and night firing performance in soldiers treated with LASIK and PRK. Association for Research in Vision and Ophthalmology Annual Meeting, Program/Poster #2634/B473, May 2003.

Introduction: Excimer laser surgery (LASIK and PRK) has proven effective for correction of refractive error, and holds great promise for widespread application in military environments. While service members typically achieve normal post-operative visual acuity and satisfy military retention standards, less is known about performance in operational settings, particularly at night. **Purpose:** Our purpose is to conduct a prospective evaluation of night vision goggle (NVG) and night firing performance in soldiers treated with LASIK and PRK. We report initial (1-month) findings in nine soldiers. **Methods:** 9 subjects underwent surgery for naturally occurring myopia or myopic astigmatism using the ALCON LADARVision laser system. Night Firing Range performance with the M-16A2 was measured preoperatively and at 1 month after surgery under the following conditions (corrected and uncorrected): 1) NVG and aiming light under simulated starlight, and 2) iron sight under low light (simulated dusk). Targets were scored using a standard system. Before and after surgery scores were compared for the iron sight and NVG sight. **Results:** A comparison of post-operative performance without correction to pre-operative performance with correction is the most relevant for military operations. In nine subjects tested thus far, 1-month post-operative night firing score (without optical correction) was not significantly different from pre-operative performance with best correction for either the iron sight or NVGs (p>0.4). Interestingly, mean post-operative firing with NVGs (but without optical correction), was slightly higher than mean pre-operative NVG firing performance (with best correction), and this difference approached significance (p=0.08). **Conclusions:** Despite reports of reduced night vision following laser refractive surgery, performance of one important military task, firing a weapon in low light setting, improved in this study. Initial results indicate that, by 1-month after surgery night firing performance without optical correction is equal to or slightly better than pre-operative performance with best correction. The trend toward improved post-operative firing performance with NVGs may reflect the lack of intervening spectacle correction between NVG and observer, which can impede performance by increasing reflections, distortion, and weight. The finding of

enhanced performance through NVGs is consistent with our previous study of NVG visual acuity (Bauer at al, ARVO 2001 Abstract 3266).

(6) <u>**Paper:**</u> **Bower KS, Burka JM, Subramanian PS, Stutzman RD, Mines MJ, Rabin JC. Night firing range performance following photorefractive keratectomy and laser in situ keratomileusis. Military Medicine 2006 Jun;171(6):468-71.**

<u>Objective:</u> To investigate the effect of laser refractive surgery on night weapons firing. <u>Methods:</u> Firing range performance was measured at baseline and postoperatively following photorefractive keratectomy (PRK) and laser in situ keratomileusis (LASIK). Subjects fired the M-16A2 rifle with night vision goggles (NVG) at starlight, and with iron sight (simulated dusk). Scores, before and after surgery, were compared for both conditions. <u>Results:</u> No subject was able to acquire the target using iron sight without correction before surgery. After surgery, the scores without correction (95.9 +/- 4.7) matched the pre-operative scores with correction (94.3 +/- 4.0; p=0.324). Uncorrected NVG scores after surgery (96.4 +/- 3.1) exceeded the corrected scores before surgery (91.4 +/- 10.2) but this trend was not statistically significant (p=0.063). <u>Conclusion:</u> Night weapon firing with both the iron sight and the NVG sight improved after surgery. This study supports the operational benefits of refractive surgery in the military.

D. Operational Assessment of Refractive Surgery for Rated Army Aviators: A Prospective Evaluation. PI: Bower KS. AI: Rabin JC. Collaborating personnel VandePol C (US Army Aviation Research Laboratory, Ft. Rucker, Alabama). (WU #01-2335-99c) SUB-PROTOCOL (CLOSED)

LASIK and PRK have the potential to improve flight performance in the active aviator population by improving uncorrected vision and reducing interface problems. Despite the use of advanced instrumentation, sensors, warning devices, and automation systems, high velocity/low altitude flight is guided primarily by direct visual input, frequently requiring accurate, time-limited visual discriminations under degraded conditions. While corrective lenses provide clear vision, displacement or loss of optical correction during flight can potentially lead to loss of aircraft control. Moreover, spectacle incompatibility has been a major problem with NVGs and helmet-mounted displays (HMD), such as the Integrated Helmet and Display Sighting System (IHADSS) used on the AH-64 Apache attack helicopter, because the proximity of the optical system of HMDs and the eye does not allow for spectacle wear. Although contact lenses lessen compatibility problems, successful use of contacts in operational flight environments is limited, and considerable tactical support is required. Army aviation combat doctrine often requires night flight operations, frequently using NVGs, and the same concerns over night vision discussed above apply to the aviator.

Moreover, these procedures have the benefit of increasing the applicant pool of aviation trainees, which has decreased from a traditional ratio of 3:1 to a current low level of 1.3 applicants per position. Inability to meet vision standards is the primary cause for flight applicant medical disqualification. Applicants with myopia beyond –0.75 diopters, hyperopia beyond +3.00 diopters, or astigmatism greater than 0.75 diopters are ineligible in accordance with paragraph 4-12b, AR 40-501 (Class 1A Flight Physical standards). Because over 25% of the population has refractive errors that exceed these standards[17], this imposes significant limitations on the applicant pool and excludes individuals who may otherwise be exceptional candidates.

This protocol is a two-year prospective study of the efficacy and safety of keratorefractive surgery in rated Army Aviators. Forty subjects will undergo PRK and forty subjects who will

undergo LASIK. Subjects will be UH-60 pilots who will complete pre- and post-operative visual and detailed flight performance testing at USAARL. At WRAMC, subjects will complete pre-operative and post-operative visual and ocular testing and the keratorefractive procedure. The study will evaluate standard FDA-approved PRK and LASIK procedures to determine whether PRK and/or LASIK are compatible with the Army Aviation environment, and if they are safe and effective for rated Army Aviators.

Based on the proven efficacy and safety of PRK and LASIK in military and non-military studies, we hypothesize that, overall, there will be no significant difference between pre and post-operative flight performance in the Army Aviation environment. However, due to the differences between the Army flight environment and those studied elsewhere, we anticipate both enhancements and decrements in performance under certain conditions. We anticipate slight improvements in certain aspects of flight, particularly those in which the wear of spectacles have been shown to interfere with performance (due to fogging, reflections, interface problems, etc). Alternatively, we foresee slight decrements in performance under specific ambient conditions, such as low luminance and low contrast and it is the extent of these decrements that may or may not be critical in the flight environment, especially at night. It is expected that, overall, the subjective response will be quite favorable, due to the decreased reliance on spectacles and/or contact lenses. This could translate into improved performance in flight. No significant difference is anticipated between PRK and LASIK, although the more rapid visual recovery following LASIK is likely to produce a more favorable subjective response. Additionally, it is conceivable that certain pre-operative visual factors, including pupil size, higher order ocular aberrations, and/or the degree of initial refractive error may prove to be correlated with pre and/or post-operative flight performance.

The specific objectives of the study are as follows:

1. Test the null hypothesis that refractive surgery does not significantly impact visual or flight performance of experienced Active Army Aviators by conducting a prospective evaluation of the military occupational-specific impact of photorefractive keratectomy (PRK) and laser in-situ keratomileusis (LASIK) on both visual and flight performance of experienced Active Army Aviators.
2. Identify vision-related pre-operative factors (e.g., initial refractive error, degree of astigmatism, wave front aberrations, corneal curvature or thickness, pupil size, initial level of visual performance) that may predict performance and/or compromise safety of flight.
3. Make formal recommendations on the efficacy and safety of keratorefractive laser surgery for experienced Army Aviators, to include selection criteria and mode of treatment, which insure optimal flight and visual performance with maximum safety.

The number of subjects enrolled to the study at WRAMC is 14. Because of funding issues, the study was terminated. Summary of the data provides the following observations:

1. PRK subjects experience a greater deficit in the early post-op period due to epithelial healing processes. Once healed, NVG visual performance was essentially equivalent between PRK and LASIK for all conditions except extreme low luminance (starlight).
2. Flight performance in the simulator decreased in the first post-operative week after both PRK and LASIK, returning to baseline at one month post-op for both groups.

3. Mean post-operative flight performance at one and six months after refractive surgery did not change significantly from baseline in the aircraft for either group.
4. While refractive surgery did impact clinical measures of visual performance including contrast sensitivity, the effect on flight maneuvers in this study was only transient. Flight performance in trained aviators may be resilient against minor visual changes and other factors may contribute to maintenance of flight performance, such as improved field of view without spectacles.

The following abstracts/papers resulted from this sub-protocol:

(1) **Abstract: Bower KS, VandePol C, McLean WE, Greig JL. Night Vision Goggle Visual Performance after Refractive Surgery in Army Aviators. Association for Research in Vision and Ophthalmology Annual Meeting, Program/Poster #2824/B459, April 2004.**

Purpose: The Army is considering PRK and LASIK for their aviation population. However, there are concerns about the quality of vision and the visual recovery after refractive surgery, especially under night vision goggle (NVG) conditions. This study was designed to prospectively evaluate current pilots to determine the level of impact on NVG performance. **Methods:** Twenty current Black Hawk pilots were tested pre-operatively and 1 week, 1 month and 6 months after randomization to PRK or LASIK surgery. High contrast acuity and contrast sensitivity at 1, 2, 4, 8 and 16 c/deg under quarter moon (0.1 cd/m^2) and overcast starlight (0.001 cd/m^2) conditions was measured using computer-generated stimuli (PowerPoint® and Vision Works™ for Windows) set for the wavelength sensitivity range of standard Aviator Night Vision System (ANVIS OMNI IV) goggles. The goggle output was 4 cd/m^2 at quarter moon and 0.3 cd/ m^2 at starlight. **Results:** PRK subjects experienced a greater decrease in NVG visual acuity at one week than LASIK subjects under quarter moon conditions (0.2 logMAR versus 0.05 logMAR; p<0.01). Loss of acuity under starlight conditions was not significant at one week. By one month post-op both groups trended towards improved visual acuity under both luminance conditions (0.05 logMAR). At one week post-op PRK subjects had a greater decrease in contrast sensitivity under both luminance conditions than LASIK subjects. Under quarter moon conditions the loss was in the low spatial frequency range and under the starlight conditions it was uniform across the CSF. By 6 months post-op both groups had improved sensitivity across the CSF for the quarter moon condition, however performance under starlight conditions remained depressed at mid-frequencies for the LASIK group. **Conclusions:** The transient recovery of visual performance with night vision goggles is in keeping with previous studies of low luminance visual performance after refractive surgery. PRK subjects experience a greater deficit in the early post-op period due to epithelial healing processes. Once healed, NVG visual performance was essentially equivalent between PRK and LASIK for all conditions except extreme low luminance (starlight). The residual decrease in mid-frequencies for LASIK warrants further investigation.

(2) **Abstract: VandePol C, Greig JL, Bower KS. Helicopter Night Flight Operations following Refractive Surgery, Association for Research in Vision and Ophthalmology Annual Meeting, Program/Poster #2823/B458, April 2004.**

Purpose: Refractive surgery, while reducing the need for spectacles or contact lenses, has been shown to impact night vision performance. U.S. Army helicopter pilots fly a large percentage of missions at night, often without the benefit of night vision goggles (NVGs). The purpose of this study was to prospectively evaluate the impact of PRK and LASIK on the visual and flight performance of rated and current Army Black Hawk pilots. **Methods:** Twenty pilots were tested before and after being randomized to PRK or LASIK surgery. The pilots flew a visually demanding flight profile under day, night unaided and NVG conditions in a research-instrumented Black Hawk flight simulator and in a research-instrumented Black Hawk aircraft. **Results:** Only the night unaided flight results are included in this report. Flight performance in the simulator decreased in the first post-operative week for the combined group (pre-op mean = 59.8; post-op mean = 58.0; p=0.02). A higher ratio of LASIK than PRK subjects experienced a decrease in performance from baseline (7/9 versus 7/11), however only the LASIK group had a mean change from

baseline that approached significance at one week (p=0.06). Night flight performance in the simulator returned to baseline at one month post-op for both groups, although more than half of the subjects had a residual deficit in performance at 6 months. Subjects were not flown in the aircraft at one week. Mean post-operative flight performance at one and six months after refractive surgery did not change significantly from baseline in the aircraft for either group. **Conclusions:** Helicopter flight involves a complicated set of skills, relying on excellent visual capability. While refractive surgery did impact clinical measures of visual performance including contrast sensitivity, the effect on flight maneuvers in this study was only transient. Flight performance in trained aviators may be resilient against minor visual changes and other factors may contribute to maintenance of flight performance, such as improved field of view without spectacles.

(3) **Paper: VandePol C, Greig JL, Estrada A, Bissette GM, Bower KS. Visual and flight performance recovery after PRK and LASIK in helicopter pilots. Aviation, Space, and Environmental Medicine. In press.**

Introduction: Refractive surgery, both photorefractive keratectomy (PRK) and laser in-situ keratomileusis (LASIK) are becoming more acceptable in the military environment. Aviation is one of those environments where acceptance comes only after extensive scrutiny. **Methods:** A prospective evaluation of 20 Black Hawk pilots pre-surgically and at 1 week, 1 month, and 6 months post surgery was conducted to compare both PRK and LASIK visual and flight performance outcomes to expedite the return of aviators to duty following surgery. **Results**: Nineteen of 20 pilots in this study returned to flight status at 1 month after surgery; only one PRK subject was delayed due to corneal haze and subjective visual symptoms. Improvements were seen under night and night vision goggle flight conditions in the simulator after LASIK, but not PRK; no significant changes in flight performance were measured in the aircraft. Results indicated a significantly faster recovery of all visual performance outcomes one week after LASIK versus PRK patients, with no difference between procedures at 1 and 6 months post-surgical. Low contrast acuity and contrast sensitivity correlated to flight performance in the early post-operative period; however, correlations were not strong. **Discussion:** The flight performance tasks assessed in this study after PRK and LASIK were stable or improved from baseline, indicating a resilience of performance despite measured decrements in visual performance, especially in PRK. More visually demanding flight tasks are expected to be impacted by subtle changes in visual performance, as measured with contrast tests. These tests were more sensitive to the effects of refractive surgical intervention and may prove to be a better indicator of visual recovery for return to flight status.

E. Brimonidine Tartrate Ophthalmic Solution 0.15% on pupil diameter in normal eyes. PI: Thordsen J. AI: Bower KS, Stutzman RD, Warren BB. (WU #03-23004) (CLOSED)

The purpose of this study is to evaluate the effect of brimonidine tartrate ophthalmic solution 0.15% (Alphagan P) on pupil diameter under different luminance conditions. We hypothesize that the 0.15% solution of brimonidine tartrate possesses similar miotic properties as has been previously published for the 0.2% solution of brimonidine tartrate. Significance: If brimonidine tartrate 0.15% is shown to have similar miotic effects on pupil diameter as the 0.2% solution, then the drug could be used to decrease night-vision difficulties such as haloes, glare, and monocular diplopia in postoperative refractive patients, but at a lower drug concentration. A large number of our active duty population have under gone refractive surgery and if troubled by glare, haloes, or diplopia may be put at a disadvantage during night –time operations. Brimonidine tartrate may provide a simple and effective treatment for post refractive night vision disturbances in our war fighting soldier population. Fifteen eyes of 15 volunteers were enrolled and tested, resulting in the following abstract/paper:

(1) <u>Abstract:</u> **Thordsen JE, Warren BB, Stutzman, RD, Subramanian P, Bower KS. Effect of brimonidine tartrate ophthalmic solution 0.15% on pupil diameter in normal eyes. Association for Research in Vision and Ophthalmology Annual Meeting, Program/Poster #792/B767, May 2003.**

<u>Purpose:</u> To evaluate the effect of brimonidine tartrate ophthalmic solution 0.15% (Alphagan P) on pupil diameter under different luminance conditions, and see if the 0.15% solution of brominidine tartrate possesses similar miotic properties as has been previously published for the 0.2% solution of brimonidine tartrate. <u>Methods:</u> Using the Colvard pupillometer, the pupil diameter in 15 eyes of 15 participants was measured under 3 different luminance conditions (scotopic, mesopic, photopic) while the participants fixated on a distant target 20 feet away. The luminance of the room was measured using the Minolta LS-110 Luminance Meter. One drop of 0.15% brimonidine tartrate ophthalmic solution was administered to each patient. Pupil diameter was measured using the same technique as stated above 30 minutes, 4 hours, and 6 hours after drop administration. <u>Results:</u> Under scoptopic conditions (luminance 0.0 cd/m^2), 15 of 15 pupils (100%) and 13 of 15 pupils (86.7%) showed a decrease in diameter equal to or greater than 1 mm at 30 minutes and 4 hours, respectively (P<0.005). At 6 hours, the miotic effect of at least 1 mm or greater was still present in 9 of 15 participants (60%). Under mesopic conditions (luminance 0.18 cd/m^2), 14 of 15 pupils (93.3%) and 11 of 15 pupils (73.3%) showed a decrease in pupil diameter greater than or equal to1 mm (P<0.005). By 6 hours, 6 of 15 pupils (40%) showed a decrease in diameter of at least 1mm or greater. Under photopic conditions (luminance 150.2 cd/m^2), 11 of 15 pupils (73.3 %) and 13 of 15 pupils (86.7 %) showed a decrease in diameter equal to or greater than 1 mm at 30 minutes and 4 hours, respectively (P<0.005). By 6 hours, 10 of 15 eyes (66.7 %) still showed a decrease in pupil diameter of at least 1 mm or greater. <u>Conclusions:</u> Brimonidine tartrate 0.15 % ophthalmic solution showed a significant effect in decreasing pupil diameter under both scotopic and low light (mesopic) conditions which may be of use to postoperative refractive patients with night vision difficulties (halos, glare, etc). When compared to previous studies which used the 0.2% solution of brimonidine, the weaker 0.15 % concentration of brimonidine tartrate showed an equavalent ability to constrict the pupil. Also, the 0.15 % bromonidine tartrate ophthalmic solution showed a significant decrease in the pupil diameter under photopic conditions; a finding which was not observed in a prior study with 0.2% brimonidine tartrate ophthalmic solution.

(2) <u>Paper:</u> **Thordsen JE, Bower KS, Warren BB, Stutzman RD. Miotic effect of brimonidine tartrate ophthalmic solution 0.15% in normal eyes. J Cataract Refract Surg 2004 Aug;30(8):1702-6.**

<u>Purpose:</u> To evaluate the effect of brimonidine tartrate ophthalmic solution 0.15% (Alphagan P) on pupil diameter of healthy adults under different luminance conditions. <u>Setting:</u> Center for Refractive Surgery, Ophthalmology Service, Department of Surgery, Walter Reed Army Medical Center, Washington, DC. <u>Methods:</u> Using the Colvard pupillometer, the pupil diameter was measured in 15 eyes of 15 patients under 3 different luminance conditions (scotopic, mesopic, photopic). The luminance of the room was measured using the Minolta LS-110 Luminance Meter. Pupil diameter was re-measured using the same technique 30 minutes, 4 hours, and 6 hours after administration of one drop of 0.15% brimonidine tartrate ophthalmic solution. <u>Results:</u> Under scoptopic conditions (luminance 0.0 cd/m^2), 100%, 86.7%, and 60% of pupils showed a descrease in diameter of at least 1mm or greater at 30 minutes, 4 hours and 6 hours respectively (P<0.005). Under mesopic conditions (luminance 0.18 cd/m^2), 93.3%, 73.3%, and 40 % of pupils showed a decrease of at least 1mm or greater at 30 minutes, 4 hours, and 6 hours, respectively (P<0.005). Under photopic conditions (luminance 150.2 cd/m^2), 73.3%, 86.7%, and 66.7% of pupils showed a decrease in diameter of least 1mm or greater at 30 minutes, 4 hours, and 6 hours, respectively (P<0.005). <u>Conclusions:</u> Brimonidine tartrate 0.15 % ophthalmic solution showed a significant miotic effect under all three luminance conditions. The reproducible miotic effect under scotopic and mesopic conditions may be of use to postoperative refractive patients complaing of night vision difficulties related to a large pupil.

F. Effect of brimonidine tartrate ophthalmic solution 0.15% on patients experiencing night vision difficulties after laser refractive surgery. PI: Stutzman RD. AI: Bower KS, Riddle JA, Burka JM, VanRoekel RC, Kuzmowych CP, Psolka M. (WU #04-23008) (OPEN)

A relatively common and sometimes significant patient complaint following refractive surgery is difficulty with night vision. Such difficulties include reduced contrast sensitivity, glare disability, and visual aberrations such as starburst and haloes. The incidence of night vision disturbances is highest immediately after both PRK and LASIK, and gradually improves such that by 3 months postoperatively most night vision complaints have returned to preoperative baselines. In some patients, however, night vision difficulties can be significantly bothersome and permanent.

The purpose of this study, which builds on the experience of the previous Alphagan results, is to evaluate the safety and efficacy of brimonidine tartrate ophthalmic solution 0.15% (Alphagan-P) in U.S. Army personnel who have complaints of significant night vision difficulties following laser refractive surgery. This study is a six-month prospective non-randomized investigation. The study will evaluate the safety and efficacy of Alphagan-P in the treatment of postoperative glare, halos and starbursts. Initial evaluations will include subjective and objective tests, which will focus on evaluation and correction of any additional possible causes of aberrations. After those subjects are excluded, subsequent evaluations will be performed before and after treatment with Alphagan-P eye drops. These evaluations will include the best spectacle-corrected visual acuity (BSCVA), uncorrected visual acuity (UCVA), effects of glare, subjective difficulties such as ghost images, which may occur with changes in pupil size and subjective changes with treatment, and complications. We have had a notable difficulty enrolling subjects, which seems to indicate a low incidence of significant night vision difficulty in our patient population using current technology and practice standards. Nevertheless, 6 subjects enrolled and completed the testing protocol, and the results are described in the abstract below. We are keeping the protocol open in order to continue to evaluate those soldiers who present with significant complaints.

(1) <u>Abstract:</u> **Stutzman RD, Burka JM, Bower KS, VanRoekel RC, Kuzmowych CP, Riddle JA, Psolka M. Alphagan-P improves night vision difficulty and contrast testing after refractive surgery. Association for Research in Vision and Ophthalmology Annual Meeting, Program/Poster #3462/B995, April-May 2006.**

<u>Purpose:</u> To evaluate the efficacy of brimonidine tartrate ophthalmic solution 0.15% (Alphagan-P®, Allergan, Inc., Irvine, CA,) in patients with night vision difficulties following laser refractive surgery. <u>Methods:</u> 6 patients with significant night vision complaints following refractive surgery were enrolled in this study after excluding other treatable causes of night vision difficulty such as residual refractive error and dry eye. Low contrast visual acuity (LCVA) over a range of contrasts (1.25% to 25%) and small letter contrast sensitivity (CS) were tested at photopic (100 cd/m^2) and mesopic luminance levels (1 cd/m^2), with and without a standard glare source. Testing was performed before and 1 hour after using Alphagan-P®, and was repeated after subjects used Alphagan-P® nightly for 1 month. <u>Results:</u> 1 hour after using Alphagan-P® subjects demonstrated significant improvement in LCVA and CS **(Table 1)**. After 1 month of treatment all 6 patients reported subjective improvement in their night vision with Alphagan-P® use, and there was a significant difference in performance at the mesopic LCVA at 1.25% (p=0.028), 2.5% (p=0.030), and 5% (p=0.042). One patient reported tachyphylaxis after 6 months. <u>Conclusions:</u> Alphagan-P® improves contrast sensitivity and acuity and decreases night vision difficulty in patients with significant complaints following refractive surgery.

G. Comparison of the effect of 4th generation fluoroquinolones, gatifloxacin and moxifloxacin, on epithelial healing following photorefractive keratectomy (PRK). PI: Bower KS. AI: Stutzman RD, Burka JM, VanRoekel RC, Kuzmowych CP. (WU #01-2335-99e) SUB-PROTOCOL (CLOSED)

Topical antibiotics are frequently used for prophylaxis following laser keratorefractive surgery. Selection of the most appropriate antibiotic is often based on considerations such as spectrum of coverage, bioavailability, ocular tolerance, and cost. When there is no clear evidence to support the superiority of one drug over another in these regards, additional factors may be considered. In the case of the fourth generation fluoroquinolones, subtle differences in the mechanism of action, concentration, vehicle, pH, solubility, and preservative of each compound may lead to a potential difference in their effect on epithelial healing. Such a difference would have important implications on the selection of antibiotic prophylaxis for photorefractive keratectomy (PRK). Faster epithelial healing speeds visual recovery, allows patients to return to work and other daily activities sooner, and decreases the risk of adverse events. In this prospective, double-blinded, randomized clinical trial we performed a prospective within-subject comparison of the rate of epithelial healing between two fourth-generation fluoroquinolones approved for ophthalmic use in the US, gatifloxacin 0.3% ophthalmic solution (Zymar®, Allergan, Inc, Irvine, California) and moxifloxacin 0.5% topical ophthalmic solution (Vigamox®, Alcon Laboratories, Fort Worth, Texas), Patients were randomized to one of two groups: Group A will use moxifloxacin in the right eye and gatifloxacin in the left eye. Group B will use gatifloxacin in the right eye and moxifloxacin in the left eye. Neither the patient nor the examiner will know which antibiotic is used in which eye. The primary outcome measure was time to complete epithelial healing. Secondary outcome measures assessed ocular tolerance, early post-op visual recovery, visual outcome, complications, and safety. Thirty-five subjects were enrolled, treated, and completed the protocol. The results are covered in the following abstracts and papers. An unanticipated outcome from the study was the development of a technique to measure surface area of ocular processes using simple technology. This was published in additional abstract/paper, also listed below.

(1) Abstract: Burka JM, Bower KS, VanRoekel RC, Stutzman RD, Kuzmowych CP. Comparison of the effect of 4th generation fluoroquinolones, gatifloxacin and moxifloxacin, on epithelial healing following photorefractive keratectomy (PRK). Association for Research in Vision and Ophthalmology Annual Meeting, Program/Poster #4879/B82, May 2005.

Purpose: To compare the rate of epithelial healing following photorefractive keratectomy (PRK) after the use of two commercially available 4th generation fluoroquinolones, moxifloxacin (Vigamox®, Alcon Laboratories, Fort Worth, Texas) and gatifloxacin (Zymar ®, Allergan, Inc, Irvine, California). **Methods:** 35 subjects were included in this double-blinded, randomized, prospective trial. Patients were randomly assigned to one of two groups. Group A received Vigamox in the right eye and Zymar in the left. Group B received Zymar in the right eye and Vigamox in the left. PRK was performed on all subjects after creating a 9.0mm epithelial defect using 20% alcohol for 25 seconds after which a therapeutic bandage contact lens was applied to the ablated surface for all patients. Patients were examined daily after surgery until the epithelium had healed completely in both eyes. Beginning on post-op day 3, photos were taken and used to confirm epithelial healing or measure the area of residual epithelial defects. Healing times and defect sizes were compared using the Wilcoxon signed ranks test. **Results:** While median healing time for both groups was 4 days (Vigamox range: 3 to 7 days, Zymar range: 3 to 9 days), only 69% of Zymar-treated eyes had healed by day 4 compared to 80% of the Vigamox-treated eyes (P=0.01). Successful removal of the

bandage contact lens was accomplished earlier (P=0.042) in the Vigamox group (median: 3, range: 3 to 7) than the Zymar group (median: 4, range 3 to 9). Both eyes healed on the same day in 18 of the 35 subjects (51.4%). In 13/35 (37.1%) subjects the Vigamox-treated eye healed first, compared to only 4/35 (11.4%) whose Zymar-treated eye healed first. Moreover, all 6 of the eyes that took 2 days longer than their fellow eye to heal were Zymar-treated eyes. Overall, on each postoperative day, defect sizes were greater for the Zymar-treated eyes. This difference was statistically significant on day 4 (P=0.027) and a similar trend was seen on day 5 (P=0.055). One Zymar treated eye developed peripheral corneal infiltrates on postop day #4 that resolved after removal of the bandage contact lens. There were no significant adverse effects reported in the Vigamox-treated eyes. **Conclusions:** Eyes treated with Vigamox healed faster and had smaller defects compared to those treated with Zymar. This provides another factor to consider in selecting antibiotic prophylaxis for corneal refractive surgery.

(2) <u>Paper:</u> Burka JM, Bower KS, VanRoekel RC, Stutzman RD, Kuzmowych CP, Howard RH. The effect of 4th generation fluoroquinolones gatifloxacin and moxifloxacin on epithelial healing following photorefractive keratectomy. Am J Ophthalmol 2005 July;140(1):84-7.

<u>Purpose:</u> To compare the rate of epithelial healing following photorefractive keratectomy (PRK) with two commercially available 4th generation fluoroquinolones, moxifloxacin (Vigamox®, Alcon Laboratories, Fort Worth, Texas) and gatifloxacin (Zymar ®, Allergan, Inc, Irvine, California). **<u>Design:</u>** Double-blinded, randomized, prospective trial. **<u>Methods:</u>** 35 subjects received Vigamox® in one eye and Zymar® in the fellow eye following PRK with a 9.0 mm epithelial defect. Patients were examined daily after surgery until the epithelium had healed completely in both eyes. Beginning on post-op day 3, photos were taken and used to confirm epithelial healing or measure the area of residual epithelial defects. Healing times and defect sizes were compared using the Wilcoxon signed ranks test. **<u>Results:</u>** Both eyes healed on the same day in 18 of the 35 subjects (51.4%). In 13/35 (37.1%) subjects the Vigamox®-treated eye healed first, compared to only 4/35 (11.4%) subject whose Zymar®-treated eye healed first. All 6 of the eyes that took 2 days longer than their fellow eye to heal were Zymar®-treated eyes. Median healing time for both groups was 4 days (Vigamox® range: 3 to 7 days, Zymar® range: 3 to 9 days) (P=0.01) but only 69% of Zymar®-treated eyes had healed by day 4 compared to 80% of the Vigamox®-treated eyes. Overall, on each postoperative day, defect sizes were greater for the Zymar®-treated eyes. This difference was statistically significant on day 4 (P=0.027). **<u>Conclusions:</u>** Eyes treated with Vigamox® healed faster and had smaller defects compared to those treated with Zymar®. This provides another factor to consider in selecting antibiotic prophylaxis for corneal refractive surgery.

(3) <u>Paper:</u> Burka JM, Bower KS, VanRoekel RC, Stutzman RD, Kuzmowych CP. The effect of moxifloxacin and gatifloxacin on long term visual outcomes following PRK. J Refract Surg. In press.

<u>Purpose:</u> To compare the effect of gatifloxacin and moxifloxacin on visual outcomes after photorefractive keratectomy (PRK). **<u>Methods:</u>** 35 PRK patients were treated post-operatively with gatifloxacin (Zymar ®, Allergan, Inc, Irvine, California) in one eye and moxifloxacin (Vigamox®, Alcon Laboratories, Fort Worth, Texas) in the fellow eye. Post-operative regimens were otherwise identical. In the initial phase of this study we evaluated epithelial healing. In this second phase of the study, uncorrected visual acuity (UCVA), best spectacle corrected visual acuity (BSCVA), manifest spherical equivalent (MSE), and corneal haze at 6 months post-operatively were compared using the Wilcoxon signed ranks test. **<u>Results:</u>** There was no statistically significant difference between Zymar® and Vigamox® eyes in terms of UCVA, BSCVA, MSE or corneal haze at 6 months post-op. 2 Vigamox® eyes (6%) vs. no Zymar® eyes lost 1 line of BSCVA from pre-op. Median UCVA and MSE were equivalent for both groups. **<u>Conclusions:</u>** In the initial phase of the study, Vigamox® eyes healed faster than eyes treated with Zymar®. Long term results, however, suggest no significant difference in outcomes with either antibiotic.

(4) <u>Abstract:</u> VanRoekel RC, Bower KS, Burka JM, Tarbett AK, Howard RS. Anterior segment measurements using digital photography: A simple technique. Association for Research in Vision and Ophthalmology Annual Meeting, Program/Poster #1342/B338, April-May 2006.

<u>Purpose:</u> To describe a simple method of measuring anterior segment lesions from digital slit lamp images, and confirm reliability of the technique. <u>Methods:</u> All images where taken with a Sony DKC-5000 digital photo camera on a Haag-Streit BQ 900 slit lamp, imported into a Macintosh G3 computer running Adobe Photoshop 5.0. For system calibration, 10 reference photos were taken of a standard PD ruler at 16x magnification, refocusing on the ruler for each photo. Using Adobe Photoshop© the number of pixels per mm^2 (area) and one mm (linear) were recorded for each photo. Descriptive statistics in MS Excel were used to calculate mean, standard deviation, and confidence interval from the reference data. An Excel spreadsheet was set up to convert pixels to mm and mm^2. Interrater reliability was determined by two observers who independently calculated the area of 69 epithelial defects. A Bland and Altman plot was used to demonstrate the agreement between the two doctors. <u>Results:</u> From the reference photos the pixel mean per mm was 138 +/- 0.5. (The 95% confidence interval was 1.002 to 0.998 mm). The pixel mean per mm^2 was 19,588 +/- 579 pixels (The 95% confidence interval was 1.02 to 0.98 mm^2). Interrater reliability was excellent as measured by an intraclass correlation coefficient ICC(2,1) = 0.99. From the Bland and Altman plot it was determined that the values calculated by Provider 2 will fall between 27% below and 20% above that of Provider 1. <u>Conclusions:</u> This simple method, which allows accurate measurements from digital images using common off-the-shelf software, is a valuable tool for clinical documentation as well as research purposes.

(5) <u>Paper:</u> VanRoekel RC, Bower KS, Burka JM, Howard RS. Anterior segment measurements using digital photography: A simple technique. Optom Vis Sci. 2006 Jun;83(6):391-5.

<u>Purpose:</u> To describe a simple method of measuring anterior segment lesions from digital slit lamp images, and confirm reliability of the technique. <u>Methods:</u> Ten reference photos were taken of a PD ruler, refocusing on the ruler for each photo. Using Adobe Photoshop© the number of pixels per mm^2 (area) and one mm (linear) were recorded for each photo. An Excel spreadsheet was set up to convert pixels to mm and mm^2. Interrater reliability was determined by two doctors who independently calculated the area of 69 epithelial defects. A Bland and Altman plot was used to demonstrate the agreement between the two doctors. <u>Results:</u> Interrater reliability was excellent as measured by an intraclass correlation coefficient ICC(2,1) = 0.99. From the Bland and Altman plot it was determined that t the values calculated by Provider 2 will fall between 27% below and 20% above that of Provider 1. <u>Conclusions:</u> This simple method, which allows accurate measurements from digital images using common off-the-shelf software, is a valuable tool for clinical documentation as well as research purposes.

H. Incidence, treatment, pathogenesis and outcomes of infectious keratitis following PRK. PI: Bower KS. Collaborating personnel: Wroblewski KJ (Kimbrough ACH, Ft. Meade, Maryland). (WU #05-23003EX) (CLOSED)

This project is a retrospective review of all cases of infectious keratitis following photorefractive keratectomy (PRK), either culture proven or clinically presumed, in patients treated at the WRAMC Center for Refractive Surgery. The PI will collaborate with LTC Keith Wroblewski, Chief, Ophthalmology Service, Kimbrough Army Community Hospital, Ft. Meade, Maryland. This study will establish the incidence, treatment, pathogenesis and outcomes of infectious keratitis following PRK. Data will be collected from records of patients who have been treated at the WRAMC Center for Refractive Surgery between January 2002 and September 2004. All patients are active duty personnel aged 21 or over and gave informed consent to undergo the procedure. Electronic database with results from all refractive surgery patients treated at the WRAMC Center for Refractive Surgery since its inception will be reviewed for pertinent data. Any patient with a diagnosis of infectious keratitis, corneal ulcer, microbial keratitis, or corneal

infiltrate, either suspected clinically or confirmed by culture, will be selected for review. All data used in this analysis will come from information that was collected in routine clinical post-operative evaluation of refractive surgery patients. Patients who are enrolled as subjects in other research activities within the Center for Refractive Surgery will be excluded from this analysis. Records for patients who were treated at the Center for Refractive Surgery between January 2002 and September 2004 will be reviewed. All records will have existed prior to initiating data collection. The data will be presented and analyzed as a group. No individual patient data or identifiers will be presented in the analysis. Indirect identifiers will be removed immediately following data collection. Date of treatment, age at time of treatment, post-operative date and examination findings, microbiology studies and results, treatment rendered, follow-up course including final uncorrected, best-corrected visual acuity, and presence and degree of corneal scarring. Data were pooled with results from seven other Army and Navy laser centers, and the results are published in the following paper:

(1) Paper: Wroblewski KJ, Pasternak J, Bower KS, MD Schallhorn SC, Hubickey WJ, Harrison CE, MD Torres MF, Barnes SD. Infectious keratitis following PRK in the United States Army and Navy. Ophthalmology 2006 Apr;113(4):520-5.

Purpose: To review the incidence, culture results, clinical course, management, and visual outcomes of infectious keratitis after photorefractive keratectomy (PRK) at six Army and Navy refractive surgery centers. **Design:** Retrospective study. **Participants:** Twelve thousand, six hundred and sixty eight Navy and Army sailors and service members. **Methods:** Army and Navy refractive surgery data banks were searched for cases of infectious keratitis. A retrospective chart review and query of the surgeons involved in the care of those patients thus identified provided data regarding pre-operative prep, perioperative medications, treatment, culture results, clinical course, and final visual acuity. **Results:** Between January 1995 and May 2004, we performed a total of 25,337 PRK procedures at the six institutions. Culture proven or clinically suspected infectious keratitis developed in 5 eyes of 5 patients. All patients received topical antibiotics perioperatively. All cases presented two to seven days postoperatively. Cultures from four cases grew *Staphylococcus*, including 2 methicillin-resistant *Staphylococcus aureus* (MRSA). One case of presumed infectious keratitis was culture negative. There were no reported cases of mycobacterial or fungal keratitis. In addition, we identified 26 eyes with corneal infiltrates in the first post-operative week that were felt to be sterile, and which resolved upon removal of the bandage contact lens and increasing antibiotic coverage. **Conclusions:** Infectious keratitis is a rare, but potentially vision-threatening complication following PRK. It is often caused by gram-positive organisms, including MRSA. Early diagnosis, appropriate laboratory testing, and aggressive antimicrobial therapy can result in good outcomes.

I. A prospective evaluation of contrast sensitivity and disability glare in refractive surgery. PI: Bower KS. AI: Stutzman RD, Burka JM, VanRoekel RC, Betts AM. Collaborating personnel: Rabin JC (USAF School of Aerospace Medicine, Brooks City Base, San Antonio, Texas). (WU #01-2335-99f) SUB-PROTOCOL (OPEN)

The purpose of this study is to conduct a prospective assessment of small target contrast sensitivity and disability glare in refractive surgery. This study is a prospective, non-randomized, clinical investigation. After extensive counseling subjects will undergo the treatment of their choice, photorefractive keratectomy (PRK) or laser-assisted in situ keratomileusis (LASIK). Patients were evaluated before and after treatment. These evaluations included the best spectacle-corrected visual acuity, uncorrected visual acuity, psychometric questionnaire, pupil size, biomicroscopic examination, manifest refraction, wavefront measurements, and low contrast acuity, and contrast sensitivity at normal and at low luminance with and without disability glare. Fifty subjects enrolled and were treated, with the results in the abstract below.

(1) <u>Abstract:</u> **Bower KS, Rabin JC, Burka JM, Stutzman RD, VanRoekel RC, Betts AM. A prospective evaluation of a new test of contrast sensitivity and disability glare for use in refractive surgery. Association for Research in Vision and Ophthalmology Annual Meeting, Program/Poster #520/B288, April-May 2006.**

<u>Purpose:</u> Contrast sensitivity (CS) can reveal decrements in vision despite normal high contrast visual acuity (VA). We used a commercially available letter CS test to assess visual performance in refractive surgery. <u>Methods:</u> In this prospective, non-randomized, clinical investigation, 50 subjects underwent either photorefractive keratectomy (PRK) or laser-assisted in situ keratomileusis (LASIK). Best spectacle-corrected high and low contrast VA and small letter CS (20/50 letter size, PrecisionVision®) was assessed at normal and low luminance with and without glare. <u>Results:</u> At 1-week post-operative, CS was decreased in PRK (mean decrease = 0.35 log CS, p<0.001) and in LASIK (0.32 log CS, p<0.001), with the decrease greater in PRK at low luminance and with glare. At 1-month post-op CS was improved in PRK and LASIK, but remained below baseline (p<0.05). From 1 to 6 months CS continued to improve in PRK eventually reaching baseline, but in LASIK CS stabilized below baseline performance (p<0.05; see figure). A similar effect prevailed for low contrast VA. The results are consistent with a greater impact of higher order aberrations in LASIK vs. PRK, the impact of which becomes evident with low contrast testing. <u>Conclusions:</u> This CS test provides enhanced sensitivity for detecting subtle decrements in vision undisclosed by high contrast VA. It holds promise for quantifying improved vision anticipated after correction of higher order aberrations.

J. Evaluation of Alcon LADARVision wavefront-guided PRK. PI: Bower KS. AI: Stutzman RD, VanRoekel RC, Burka JM, Kuzmowych CP. Collaborating personnel: Schallhorn SC (Naval Medical Center, San Diego, California). (WU #04-23006) (CLOSED)

Wavefront-guided LASIK (laser in-situ keratomileusis) is a refractive surgery technique that can correct not only sphere and cylinder (i.e. the prescription for glasses) but also naturally occurring higher order aberrations, such as coma and spherical aberration. The result of correcting these higher order aberrations may be an improvement in visual outcome over conventional LASIK, which only corrects sphere and cylinder. The FDA recently approved wavefront-guided LASIK for the treatment of naturally occurring low to moderate myopia using the LADARVision®4000 Excimer Laser System (PMA# P970043/S010). Preliminary results show the procedure is very effective with an excellent visual outcome. No published study has compared the visual outcome of wavefront-guided PRK (photorefractive keratectomy) and LASIK treatments using the LADARVision®4000 Excimer Laser System. Previous studies comparing conventional (non-wavefront-guided) PRK to conventional LASIK have shown similar outcomes. LASIK and PRK procedures differ in many areas. The surgical techniques induce distinctly different healing and biomechanical responses. Both of these factors may affect the accuracy of ablations designed to neutralize subtle wavefront errors. In particular, the microkeratome used to create the corneal flap in LASIK can induce optical aberrations. It is possible that a wavefront-guided ablation may be more successful with PRK than LASIK. In addition, many military members are ineligible to undergo LASIK either because of medical contraindications, such as a cornea that is too thin, or warfare restrictions, such as aviation. In these cases, PRK is generally the procedure of choice. This project was a two-site, prospective, randomized 12-month comparison of two surgical techniques, wavefront-guided PRK and wavefront-guided LASIK. Three hundred seventy-five (375) subjects will be randomized into two treatment groups (250 for PRK and 125 for LASIK). Outcome measures were based on the safety (complications), efficacy (acuity and refraction), and visual performance (contrast sensitivity, night driving visual performance, higher order aberrations, and psychometric evaluation) of the procedure.

The IDE was approved as a nomogram adjustment study initially and limited to two institutions and 75 subjects (50 PRK and 25 LASIK). Because neither WFG PRK nor WFG LASIK was yet approved for treatment of myopic astigmatism, only one eye of each subject received WFG treatment, pending analysis of the initial cohort; fellow eyes were treated were sphero-cylindrical ("standard") ablations.

The purpose of the Nomogram Adjustment Group ("Nomogram Group") was to treat a small cohort of patients and evaluate the outcomes to assess the potential need for an adjustment. Seventy-five subjects were enrolled. At NMCSD, subjects were randomized to a treatment group (PRK or LASIK); at WRAMC, all subjects received PRK. All subjects were treated with WFG ablations in the Primary Eye (all but one had the proper nomogram adjustment) and a standard unadjusted treatment in the Fellow Eye. Ultimately, 150 eyes (100 PRK and 50 LASIK) were treated in the Nomogram Group. Upon review of the nomogram group, it was noted that several eyes demonstrated an unusual healing pattern and delayed recovery. An Unanticipated Adverse Device Effect (UAE) report was written and submitted to the Agency and both reviewing IRBs. A detailed root cause analysis and statistical analyses were performed and submitted to the Agency. Ultimately, epithelial remodeling (versus stromal remodeling or laser inaccuracy) was identified as the most likely root cause for the outlier results. To ameliorate the delayed healing, the postoperative medication regimen (Zymar and Pred Mild) and bandage lens (Ciba Night & Day) were standardized between sites for the next cohort of treatments. All eyes were targeted for emmetropia.

An additional 60 subjects ("Group II") were treated (bilateral WFG PRK n=40, bilateral WFG LASIK n=20) using nomogram adjustments established based on 6-month data from the first cohort. The follow-up in both cohorts is now complete and the results analyzed. No retreatments occurred prior to completion of study follow-up.

The objective of the study was to conduct a prospective clinical trial to compare LASIK and PRK for the treatment of naturally occurring myopia with or without astigmatism and wavefront error. Specifically, the aim was to:

1. Determine differences in the safety of WFG LASIK and WFG PRK in terms of maintenance of best spectacle corrected vision and treatment related adverse events.

2. Evaluate differences in the efficacy of WFG LASIK and WFG PRK by assessing improvement of uncorrected visual acuity, achievement of intended refractive correction, and reduction of wavefront aberrations.

3. Evaluate differences in the visual quality after treatment of WFG LASIK and WFG PRK by preoperative to postoperative changes in contrast sensitivity, pre-operative to post-operative changes in detection and identification distances of road signs and hazards during simulated night driving, and subjective appraisal using a psychometric questionnaire.

Although the Sponsor did not enroll the planned primary cohort, the decision to terminate the study has been made. This was a logistic decision based on lack of resources to support this project as originally planned. All subjects enrolled have discontinued or completed the study through 12 months. This report is intended to provide sufficient information to permit

termination of the IDE. Though abbreviated, the intended objectives of this study were met. Abstracts resulting from this protocol are listed below.

(1) **Abstract: VanRoekel RC, Schallhorn SC, Lombardo K, Burka JM, Bower KS, Tanzer D, Stutzman RD, Kuzmowych CP. Alcon LADARVision^{TM} wavefront-guided photorefractive keratectomy and laser in-situ keratomileusis: 6 month results. Association for Research in Vision and Ophthalmology Annual Meeting, Program/Poster #4335/B693, May 2005.**

Purpose: To report the 6-month visual outcomes after wavefront-guided (WFG) photorefractive keratectomy (PRK) and laser in-situ keratomileusis (LASIK) using the Alcon LADARVision excimer laser system. **Methods:** 62 subjects (42 PRK and 20 LASIK) were included in this prospective, multi-center study. All subjects underwent WFG treatment in their dominant eye and conventional treatment in their non-dominant eye. Outcome measures included uncorrected visual acuity (UCVA), best-corrected visual acuity (BCVA), and low contrast acuity (CA) at 6 months postop. High contrast (HC) BCVA, photopic 5% CA (80-140 cd/m^2), and mesopic 25% CA (0.8-1.2 cd/m^2) were performed with best correction and compared to preoperative measurements. Surgically induced changes were compared for the four procedures: WFG PRK, conventional PRK, WFG LASIK, and conventional LASIK. **Results:** There was no difference in UCVA or HC BCVA between treatment groups. The 5% CA improved by a mean of 0.02 logMAR following both WFG PRK and WFG LASIK, compared to a mean decrease of 0.03 logMAR for both conventional procedures. The net difference in postop 5% CA between WFG and conventional procedures was 0.05 logMAR (equivalent to half a line). The 25% CA decreased the most following conventional LASIK (mean 0.04 logMAR) and conventional PRK (mean 0.03 logMAR). 25% CA following WFG LASIK decreased on average by only 0.01 logMAR, and improved by 0.02 logMAR following WFG PRK. **Conclusions:** Although HC visual acuity was equal following all 4 procedures, low contrast acuity was generally better following PRK than LASIK, and better with WFG treated compared to conventional treatments. There was an overall improvement in 5% CA for eyes treated with WFG procedures compared to a slight decrease in performance for those eyes treated with conventional procedures. Of the four procedures, only the WFG PRK improved mesopic 25% CA postoperatively. WFG PRK appears to provide excellent quality vision, particular in low contrast low light environment.

(2) **Abstract: Stutzman RD, Coe CD, Schallhorn SC, Lombardo K, Bower KS, Tanzer D, VanRoekel RC, Burka JM, Sediq DA, Peppers L. A Comparison of Alcon Wavefront Guided PRK and LASIK on US Military Service Members. Association for Research in Vision and Ophthalmology Annual Meeting, Program/Poster #5346/B592, May 2007.**

Purpose: To compare the visual outcomes, optical quality, and efficacy following conventional (STD) or wave-front guided (WFG) photorefractive keratectomy (PRK) and laser in situ keratomileusis (LASIK) for low and moderate myopia. **Methods:** In this prospective 1 year multi-center clinical trial as part of an FDA IDE study conducted at two military institutions, a total of 135 subjects received either STD PRK (50 eyes), STD LASIK (25 eyes), WFG PRK (130 eyes), or WFG-LASIK (65 eyes). 75 patients serving as a nomogram adjustment group had WFG treatment in one eye and STD treatment in the fellow eye (50 PRK and 25 LASIK). The final 60 subjects were treated with bilateral WFG PRK (40 patients) or WFG LASIK (20 patients) using an adjusted nomogram. All procedures were performed using the Alcon LADARVision 4000 excimer laser. Patients were examined at baseline and at 1, 3, 6, and 12 months. Examination included uncorrected visual acuity (UCVA), manifest refraction, best spectacle corrected visual acuity (BSCVA), low contrast acuity (25% contrast) under photopic and mesopic illumination, slit lamp biomicroscopy, wavefront aberrometry, and psychometric questionnaire. **Results:** Results were analyzed separately for the nomogram adjustment group and the adjusted nomogram cohort and are presented in Table 1. **Conclusions:** Visual outcomes and efficacy were similar in the WFG-PRK and WFG-LASIK treatment groups. Both treatments achieved good objective and subjective results after treatment with a second-generation excimer laser. Additional testing is needed to determine if improvements in optical quality and operational performance justify the additional cost of WFG treatments for the large number of US military personnel undergoing refractive surgery.

(3) <u>Abstract:</u> Coe CD, Bower KS, Wang J. Effect Of Centration Technique On The Monochromatic Wavefront Aberration Map. Association for Research in Vision and Ophthalmology Annual Meeting, Program/Poster #1987/B47, May 2007.

<u>Purpose:</u> To determine the effect of centration technique on the monochromatic wavefront aberration map. <u>Methods:</u> Wavefront aberrations up to the 6th order were measured with a clinical aberrometer (Alcon LADARVision 4000) on 82 eyes scheduled to undergo either conventional photorefractive keratectomy (STD PRK) or wavefront guided photorefractive keratectomy (WFG PRK). Two different methods were used to center the wavefront aberration map: (1) the center of a circle formed by the limbus which is approximately equal to the corneal apex (2) the center of the circle formed by the non-dilated pupil margin. For each patient and the two methods of centration, a Zernike polynomial series was calculated using a 6mm pupil. This was done pre-operatively and at either 6 or 12 months post-operatively. To determine if wavefront aberration map is dependent on the method of centration, our analysis consisted of paired samples t-Tests comparing total root mean square (RMS) wavefront error, higher order aberrations (HOA) RMS wavefront error, and individual Zernike modes. Objective optical quality was quantified for each method by the area underneath a 2-D radially averaged modulation transfer function normalized to the diffraction limited case. <u>Results:</u> Across centration methods, the difference between Total RMS wavefront error and HOA RMS were not significantly different from zero. This was true for both the pre-operative and post-operative eyes. In pre-operative eyes, 5 individual Zernike modes were dependent on centration method: regular astigmatism, vertical and horizontal coma, secondary astigmatism, spherical aberration, and 6th order spherical aberration. Optical quality as defined by the area underneath the rMTF was 7% greater (p=4.7e-12) when derived from the wavefront centered in the middle of a non-dilated pupil when compared to the center of the limbal circle. In post-operative eyes receiving STD-PRK, a total of 8 individual Zernike modes were significantly different as a function of centration method. In post-operative eyes receiving WFG-PRK, 4 individual Zernike modes were different as a function of centration method: horizontal coma, 5th order horizontal coma, and 6th order spherical aberration. In post-operative eyes the area of a 2-D MTF did not significantly differ from zero as a function of centration method for either STD-PRK or WFG-PRK. <u>Conclusions:</u> The wavefront can vary as a function of centration method. Therefore, wavefront measurements derived from very large pupils may not accurately reflect the optical quality of the human eye.

K. A prospective comparison of Alcon LADARVision wavefront guided LASIK enhancement vs. conventional LASIK enhancement for the correction of residual refractive errors following LASIK procedures. PI: Stutzman RD. AI: Bower KS, VanRoekel RC, Kuzmowych CP. (WU #04-23011) (CLOSED)

Wavefront-guided LASIK (laser in-situ keratomileusis) is a refractive surgery technique that can correct not only sphere and cylinder (i.e. the prescription for glasses) but also naturally occurring higher order aberrations (HOA), such as coma and spherical aberration. The result of correcting higher order aberrations may be an improvement in visual outcome over conventional LASIK enhancement, which only corrects sphere and cylinder. The FDA has approved wavefront-guided LASIK for the treatment of naturally occurring low to moderate myopia using the LADARVision®4000 Excimer Laser System (PMA# P970043/S010). Preliminary results show the procedure is very effective with an excellent visual outcome. No published study has compared the visual outcome of wavefront-guided (WFG) enhancements and conventional LASIK treatments using the LADARVision®4000 Excimer Laser System. Previous case studies comparing conventional (non-WFG) to wavefront guided LASIK enhancement have shown improvement in reducing HOA with wavefront guided LASIK. This project will be a prospective, randomized 12-month comparison of two surgical techniques, WFG LASIK and conventional LASIK enhancements. Ten patients will first be entered into the study to develop a more precise wavefront-guided nomogram for treatment Forty (40) patients will then be

randomized into two groups (20 WFG-LASIK enhancements right eye and conventional LASIK enhancements left eye; 20 WFG-LASIK enhancements left eye and conventional LASIK enhancements right eye. Forty (40) subjects will be randomized into two treatment groups (20 for wavefront and 20 for conventional LASIK). Outcome measures will be based on the safety (complications), efficacy (acuity and refraction), and visual performance (contrast sensitivity, higher order aberrations, and psychometric evaluation) of the procedure. To date only 2 patients have been enrolled, largely due to the preponderance of surface procedures performed by Army refractive surgeons. The study will be closed.

L. A prospective comparison of photorefractive keratectomy (PRK), PRK with mitomycin-C, and laser subepithelial keratomileusis in the treatment of moderate and high myopia. PI: Bower KS. AI: Stutzman RD, Burka JM, VanRoekel RC. (WU #04-23009) (OPEN)

In May 2000, the Army established the Warfighter Refractive Eye Surgery Program (WRESP) to increase individual and force readiness by providing excimer laser refractive surgery to eligible combat arms soldiers. The excimer laser is approved for the treatment of myopia, hyperopia and astigmatism. There are two basic types of excimer laser treatment, laser-assisted in situ keratomileusis (LASIK) and surface ablations, which include photorefractive keratectomy (PRK) and laser-assisted subepithelial keratectomy (LASEK). Over 16,000 soldiers have been treated to date, two-thirds of which have had PRK. Concerns over post-PRK corneal haze have lead refractive surgeons to seek alternative approaches to reduce the risk of corneal haze after excimer laser keratectomy. Several small case series, clinical trials, and anecdotal experiences suggest that there is a lower incidence of haze associated with mitomycin C PRK (MMC PRK) and LASEK than there is with PRK. The purpose of this protocol is to assess whether there is a significant difference in visual outcomes or corneal haze after surface ablation for moderate and high myopia in active duty service members treated with PRK, MMC PRK and LASEK. This study is a 1-year prospective, multicenter, randomized clinical trial. Patients will be divided into 3 groups based on their refractive error. Within each group they will be randomized to be treated with MMC PRK or LASEK in the treatment eye. All patients will be treated with PRK in the fellow eye for the control group. Outcome measures will be based on the safety (maintenance of best spectacle corrected visual acuity, corneal haze, complications), efficacy (uncorrected visual acuity and refraction), and visual performance (contrast sensitivity, higher order aberrations, and psychometric evaluation) of the procedure. To date we have enrolled and treated 135 subjects. Preliminary analysis of available 6 and 12-month data are reported in the abstract below. . The study is ongoing, and will enroll a total of 480 subjects.

(1) Abstract: Bower KS, C.D. Coe CD, Stutzman RD, VanRoekel RC, Burka JM, Sediq DA, Peppers L. US Army Surface Ablation Study: Prospective Comparison of PRK, MMC-PRK and LASEK in Moderate to High Myopia. Association for Research in Vision and Ophthalmology Annual Meeting, Program/Poster #5325/B571, May 2007.

Purpose: To compare visual outcomes, corneal haze, and complications following photorefractive keratectomy (PRK), PRK with mitomycin-C (MMC-PRK) and laser epithelial keratomileusis (LASEK) for moderate and high myopia. **Methods:** Active Duty Army soldiers, age 21 or over with stable myopia between -4.00D and -10.00D manifest spherical equivalent (MSE) were randomized to treatment of their dominant eye with either MMC-PRK (0.1 mg/ml x 1 minute) or LASEK. The fellow eye received conventional PRK. All procedures were performed using the LADARVision 4000 with Jupiter 2 software version 5.11. Patients were examined at baseline and at 1, 3, 6, and 12 months. Examination included uncorrected visual acuity (UCVA), manifest refraction, best spectacle corrected visual acuity (BSCVA), slit

lamp biomicroscopy, and corneal haze score. **Results:** 56 subjects with at least 6 months follow-up were analyzed for this report: 32 LASEK (age 35.6 +/- 7.9 years) and 24 MMC-PRK (age 34.9 +/- 6.7 years). Pre-op MSE in the LASEK group was -6.08D +/- 1.36D in the LASEK eye (range -4.00 to -9.25D) and -6.19D +/- 1.43D in the PRK eye (-4.00 to -9.38D). In the MMC-PRK group, pre-op MSE was -6.23D +/- 1.41D (-4.00 to -9.38D) in the LASEK eye and -6.27D +/- 1.37D (-4.00 to -9.38D) in the PRK eye. Post-op MSE at the last visit (6 or 12 month) for MMC-PRK eyes was +0.05D (SE 0.16) and the fellow PRK eye was +0.05D (SE 0.12D). For LASEK treated eyes, post-op MSE was +0.06D (SE 0.11D) and -0.01D (SE 0.11D) for the fellow eye. Analysis of variance showed that the effect of treatment on refractive outcome was insignificant, $F(3,108) = .73$, $p = .53$. At 6 months post-op, 83% of MMC-PRK eyes (20/24) and 87.5% (21/24) of the fellow eye achieved an UCVA of 20/20 or better. 84% (27/32) of LASEK eyes and 93% of the fellow PRK eye achieved 20/20 or better. A chi-square test of independence was performed and the relationship between corneal haze and surgical treatment is not significant (X^2 (2, N = 112) = 1.17, p =.558). A Mann-Whitney test, comparing either MMC-PRK or LASEK to fellow eye, showed there was no significant difference in incidence or severity of corneal haze (MMC-PRK v. PRK, n=48, p=.301; LASEK v. PRK, n=64, p=.644). **Conclusions:** Preliminary results demonstrate no significant difference in refractive outcome, incidence of corneal haze, or adverse events across surgical procedures when compared to conventional PRK. Additional recruitment and follow-up are needed to establish procedure preference in terms of long-term safety and efficacy for the treatment of higher degrees of myopia.

M. Evaluation of Epi-lasik in U.S. Army Personnel. PI: Bower KS. AI: Stutzman RD, Coe CD, Sediq DA, Kuzmowych CP, Eaddy J. (WU #06-23020). (OPEN)

To reduce the risk of corneal haze, efforts have been directed towards altering post-operative wound healing in a number of ways. These efforts have included chemical modulation with agents such as topical mitomycin-C and mechanical methods such as laser sub-epithelial keratomileusis (LASEK). In the LASEK procedure, a dilute alcohol solution is used to separate the corneal epithelium in an intact layer or sheet before applying the laser treatment. After the photo-ablation, the epithelial layer is then repositioned on the eye. It is thought that with the presence of the epithelium, the post-operative LASEK eye will suffer less inflammation. Also, because there is no corneal flap, LASEK eyes have the same resistance to trauma as PRK eyes, but a potentially reduced risk for post-operative haze. However, recent studies performed by USAF investigators show no benefit of LASEK over PRK, and to date no large, long-term, prospective study has convincingly demonstrated the superiority of LASEK over PRK in term of either short term healing (pain control, return to visual function) or long term results (vision, complications).

Mechanical separation of the epithelium from the underlying corneal stroma may result in more normal cell morphology and physiology when compared to the chemical separation method of LASEK. Termed Epi-lasik, this procedure involves an automated instrument similar to the LASIK microkeratome adapted with a blunt epithelial separator that removes the epithelium and its basement membrane from the underlying corneal stroma. The excimer laser is applied and the epithelial flap repositioned as in LASEK. All together, the Epi-lasik process only adds approximately 30 seconds to the refractive surgery procedure when compared to the PRK procedure.

Preliminary studies have shown it to be safe and efficient treatment, and Epi-lasik may prove some of the potential benefits sought by proponents of LASEK, namely reduced pain, faster healing, and improved postoperative visual results with less corneal haze. Nevertheless, long term results are so far lacking. The purpose of the present study is to evaluate the safety and

efficacy of Epi-lasik in a young Active Duty population of US Army soldiers with refractive error. Specifically, to:

1. Determine the safety of conventional Epi-lasik in terms of maintenance of best spectacle corrected vision and treatment related adverse events.
2. Evaluate the efficacy of Epi-lasik by assessing improvement of uncorrected visual acuity, achievement of intended refractive correction, and reduction of wavefront aberrations.
3. Evaluate the visual quality after treatment of Epi-lasik by pre-operative to post-operative changes in contrast sensitivity, and subjective appraisal using a psychometric questionnaire.

This study is a prospective non-randomized un-blinded investigation. One hundred fifty (150) subjects will be treated with Epi-lasik. Pre- and post-operative evaluations will include the best spectacle-corrected visual acuity (BSCVA), uncorrected visual acuity (UCVA), psychometric questionnaire, pupil size, biomicroscopic examination, manifest refraction, wavefront measurements, and other tests that are performed on all non-research patients who receive Epi-lasik at Walter Reed's Center for Refractive Surgery. No investigational drugs or devices will be used in this study. To date, 38 subjects have been enrolled and treated, only about two thirds of whom have 1 month follow-up. We will continue enrollment and treatment of the full cohort. A preliminary analysis will be performed when we have 6 month data on half of the planned subjects.

N. Low-contrast visual acuity and small letter contrast sensitivity in adult patients with refractive error: a retrospective review. PI: Bower KS. AI: Burka JM, Betts AM. Collaborating personnel: Rabin JC (USAF School of Aerospace Medicine, Brooks City Base, San Antonio, Texas). (WU# 04-23001EX) (CLOSED)

This project is a retrospective review of pre-operative low contrast visual acuity and small letter contrast sensitivity in patients treated at the WRAMC Center for Refractive Surgery. This study will establish normative values for contrast testing in patients with clinically significant refractive error. Data will be collected from records of patients who have been treated at the WRAMC Center for Refractive Surgery between August 2003 and June 2004. All patients are active duty personnel aged 19-53. Records from refractive surgery patients will be identified and reviewed for pertinent data. All data used in this analysis will come from data that was collected in routine clinical pre-operative evaluation of refractive surgery patients. Records for patients who were treated at the Center for Refractive Surgery between August 2003 and June 2004 will be reviewed for date of treatment, age at time of treatment, low-contrast visual acuity, small letter contrast sensitivity, manifest refraction, cycloplegic refraction, and corneal curvature. Preliminary analysis of contrast sensitivity data were presented in the following abstract:

(1) Abstract: Betts AM, Bower KS, Bigelow DK, Rabin JC, Burka JM, VanRoekel RC. Low-contrast visual acuity and small letter contrast sensitivity in adult patients with refractive error. Association for Research in Vision and Ophthalmology Annual Meeting, Program/Poster #4374/B732, May 2005.

Purpose: To establish normative values for a low-contrast visual acuity (CA) test and a small letter contrast sensitivity test (SLCT) in a sample of patients with refractive error. **Methods:** Pre-op records of 438 patients who underwent refractive surgery at an Army laser center were reviewed. 5% CA, SLCT score, manifest and cycloplegic refraction, and age were recorded from each patient's record. The

distribution of scores for contrast testing was analyzed and examined for correlations with age and refractive error. **Results:** The mean logarithmic 5% CA was 0.34 for both right and left eyes (20/44 Snellen equivalent). The mean logarithmic SLCT score was 0.38 (contrast threshold of 42%) for the right eyes and 0.40 (threshold 40%) for the left eyes. The mean SLCT score was lower than previously reported. Higher levels of myopia were associated with poorer performance on both tests. Neither test showed significant correlation with age in this sample. **Conclusions:** This retrospective review provides normative values for two methods of contrast testing in a military refractive surgery clinic. The inverse correlation between myopic refractive error and performance on contrast testing may be attributed to optical effects of spectacle correction and/or retinal factors in myopic eyes. The reduction in SLCT compared to previously established values is likely attributed to the non-standard luminance conditions under which the SLCT was administered in this clinical setting.

O. Higher order optical aberrations in adult patients with refractive error: a retrospective review. PI: Bower KS. AI: Burka JM, Betts AM, Bigelow DK. Collaborating personnel: Rabin JC (USAF School of Aerospace Medicine, Brooks City Base, San Antonio, Texas). (WU #04-23002EX) (CLOSED)

This project is a retrospective review of pre-operative low contrast visual acuity and small letter contrast sensitivity in patients treated at the WRAMC Center for Refractive Surgery. This study will establish normative values for higher order wavefront aberrations in patients with clinically significant refractive error. Data will be collected from records of patients who have been treated at the WRAMC Center for Refractive Surgery between January 2003 and June 2004. All patients are active duty personnel aged 19-53. Records from refractive surgery patients will be identified and reviewed for pertinent data. Records for patients who were treated at the Center for Refractive Surgery between January 2003 and June 2004 will be reviewed for date of treatment, age at time of treatment, wavefront analysis including lower order aberrations, total higher order aberrations, and specific higher order variables, pupil size, manifest refraction, cycloplegic refraction, and corneal curvature. Preliminary analysis of wavefront data were presented in the following abstract:

(1) Abstract: Bishop R, Bower KS, Rabin JC· Comparison between Induced Higher Order Wavefront Aberrations Following LASIK Surgery and LASIK Enhancement Surgery. Association for Research in Vision and Ophthalmology Annual Meeting, Program/Poster #2610/B449, May 2003.

Introduction: Understanding how optical aberrations vary after LASIK surgery is fundamental to the future development of aberration-free guided ablations. Previous research has shown that LASIK induces higher order optical aberrations in the human eye. Custom ablations, which target higher order aberrations, are now possible. If the amount of generated aberration from LASIK surgery could be shown to decrease with subsequent treatments to the same eye, then the potential might exist to neutralize or at least minimize the induced aberrations by performing enhancement surgery. **Purpose:** To compare the induced total higher order aberrations from primary LASIK surgery with that from LASIK enhancement surgery to the same eye. **Methods:** Wavefront analysis using a Hartmann-Shack aberrometer (Complete Ophthalmic Analysis System, Wavefront Sciences, Albuquerque, NM) was performed on 19 consecutive eyes undergoing LASIK enhancement over a 10 month period for under-treatment of either simple myopia or myopia with astigmatism. The surgical parameters were controlled across treatments. The difference in total higher order wavefront aberration preoperatively and one-month post-operatively was compared between the initial and enhancement procedures, using the paired student t-test. **Results:** Both the initial and enhancement procedures were found to generate increases in the value of total higher order aberrations (RMS (root mean square) pre-LASIK 0.084+/-0.040 to post-LASIK 0.12+/-0.052 [P=0.02]; RMS pre-enhancement 0.12+/-0.038 to post-enhancement 0.16 +/- 0.080 [P=0.06]). The amount of higher order

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aberration generated by LASIK was statistically equal between the initial and enhancement procedures (0.038 +/- 0.046 and 0.039 +/- 0.075 [P=0.04]). **Conclusions:** Our results suggest that subsequent LASIK treatment generates as much higher order optical aberration as initial treatment in a myopic eye. Therefore, the limiting step in achieving aberration-free vision may involve factors beyond the technical limit of identifying and treating higher order aberrations. Such factors could include corneal healing and varying corneal surface characteristics over time, for example.

P. Goblet cell response and dry eye symptoms after LASIK and PRK. (WU #06-23014). PI: Bower KS. AI: Stutzman RD, Coe CD, Sediq DA, Kuzmowych CP, Eaddy J. Collaborating personnel: Dartt DA (Schepens Eye Research Institute, Harvard Medical School Boston, Massachusetts). (OPEN)

Military operations often take place in geographic and environmental extremes of cold or heat, altitude, dust/sand, and high UV exposure. It is well known that refractive surgery can lead to increased dry eye symptoms. In an extreme environment these symptoms may be aggravated. The environmental conditions that face the modern soldier must be considered when selecting the most appropriate surgery in the military setting.

It is well known that both LASIK and PRK damage the corneal sensory nerves that drive tear secretion and result in dry eye. In one study, the incidence of dry eye symptomatic subjects post-LASIK was 95% after the first day, 85% after 1 week, and 60% after 1 month. No comparable study was performed for PRK. In PRK dilute alcohol is used to remove the corneal epithelium from the anterior stroma. The corneal epithelium is removed at the level of the basement membrane. In PRK, the neural damage occurs at the nerve endings that terminate in the anterior stroma and epithelium. In LASIK, however, there is deeper damage to the nerves. In creating the corneal flap, the nerves are cut at their trunks as they enter the eye in the peripheral cornea at the level of the mid-stroma. Additional damage occurs during the photo-ablative phase of the LASIK procedure. It has been reliably shown that the greater the myopic correction, the incidence and severity of dry eye symptoms increase as well. Studies have demonstrated that these severed nerves grow back slowly over many months and may take up to even a year to approach preoperative levels. Studies suggest that a population of these nerves never returns to the original state. Therefore, it should not be surprising that immediately for the first two weeks after LASIK, it has been documented that corneal sensation is depressed to its lowest values. In conjunction with the depressed corneal sensitivity, the signs and symptoms of dry eye are most severe immediately after surgery and slowly improve with time over a 3-6 month period. A consequence of long term ocular surface desiccation is the development of corneal haze, a potentially debilitating complication, as well as the potential for significant degradation in quality of vision.

This study is a twelve-month prospective non-randomized investigation. In conjunction with psychometric questionnaires and various measures of tear film quality (e.g. Schirmer's test, tear break up time, etc), impression cytology will be used to assess the intracellular signaling pathways of conjunctival goblet cells and to determine if alterations in this pathway exist. Alterations in this pathway would result in a reduced response by the mucin secreting conjunctival goblet cells thereby promoting the development of dry eye after refractive surgery.

The purpose of this study is to determine if there is reduced mucin secretion by conjunctival goblet cells in post-refractive surgery patients and whether this change in mucin secretion is associated with an altered intracellular signaling pathway thereby promoting the development of dry eye after refractive surgery. We hypothesize that by identifying these alterations in the intracellular signaling pathways of the conjunctival goblet cells preoperatively, patients that are predisposed to developing dry eye postoperatively can be identified and counseled. To this end, we will:

1. Compare incidence, duration and severity of dry eye between the LASIK and PRK treatment groups.

2. Determine if patients with no subjective complaints of dry eye pre-operatively exhibit altered intracellular signaling pathway within conjunctival goblet cells and subsequently suffer from dry eye post-operatively.

3. To develop a screening metric by examining both the characteristics of the preoperative tear film and the intracellular signaling pathways of conjunctival goblet cells in order to determine if there are certain characteristics which might predict those patients who will experience serious dry eye symptoms and complications after refractive surgery.

4. Evaluate the efficacy of the Tomey TMS4 tomographer for predicting dry eye. The Tomey TMS4 has proprietary software that evaluates the regularity of the ocular surface, the surface regularity index (SRI), surface asymmetry index (SAI), irregular astigmatism index (IAI), and the visual acuity index (PVA). In the past, these surface indices have proven to be well correlated with the subjective symptoms of dry eye. Because of their sensitivity and specificity, these regularity indices have the potential to be used as objective diagnostic indices for dry eye, as well as a means to evaluate the severity of the disease. Validation, however, is needed for the post–refractive surgery patient.

5. Using multivariate statistical analysis and principle component analysis we hope to determine which tear film characteristics are most important in predicting which incidence of dry eye. By incorporating factor analysis, we also hope to construct new variables, which might improve our metric's predictive ability.

The study is approved for 73 PRK and 73 LASIK subjects. All equipment and supplies have been ordered and final preparations for enrollment are underway. We expect to start enrollment by June 2007.

Q. Miscellaneous reports:

A number of presentations, abstracts, and papers have been published by staff of the WRAMC Center for Refractive Surgery since its opening in 2001. Some of the pertinent ones are listed below:

(1) **Abstract: Cute D, Subramanian P, Warren BB, Fannin L, Rabin JC, Bower KS. An evaluation of two different methods of marking the horizontal axis during excimer Laser keratorefractive surgery for myopic astigmatism. Association for Research in Vision and Ophthalmology Annual Meeting, Program/Poster #2655/B494, May 2003.**

Purpose: In treating astigmatism it is important to properly align the cylinder axis. A treatment off the desired axis by even a small degree may reduce the treatment efficacy. One excimer laser system allows the surgeon to

align the ablation pattern to correct for eye torsion in the supine position. We evaluate the efficacy of two different methods of marking the horizontal axis on the outcomes of excimer laser keratorefractive surgery for myopic astigmatism. **Methods:** A retrospective chart review was conducted on 65 eyes of 39 patients who underwent laser refractive surgery for myopic astigmatism. Patients with manifest astigmatism of 0.75D and greater were marked with a surgical marking pen at the 3:00 and 9:00 limbus to identify the horizontal axis. In one group (38 eyes), marks were placed with the patient seated on the edge of the bed immediately before positioning under the laser ("laser room group", mean preop astigmatism 1.78D $\pm$ 0.83D). In the other group, marks were placed at the slit lamp with the slit beam set at 180 degrees as a reference ("slit lamp group", mean preop astigmatism 1.75 D $\pm$ 1.08 D). All treatments were performed with the ALCON LADARVision excimer laser system. Postop mean manifest cylinder, reduction in cylinder, uncorrected visual acuity (UCVA) and best-corrected visual acuity (BCVA) were evaluated for both groups. **Results:** Mean postop astigmatism was 0.47D $\pm$ 0.37D in the laser room group and 0.54D $\pm$ 0.36D in the slit lamp group (p=0.494, NS). Mean reduction in astigmatism was 1.31D $\pm$ 0.71D in the laser room group and 1.21D $\pm$ 1.03D in the slit lamp group (p=0.657, NS). Cylinder was reduced by 71.9 $\pm$ 19.3% from preop in the laser room group compared to 62.1 $\pm$ 28.6% in the slit lamp group (p=0.104). There was no significant difference in the UCVA or BCVA between the two groups. In subset analysis, patients with a mean preop astigmatism of less than 2.00D had a mean reduction in astigmatism of 0.95D $\pm$ 0.45D in the laser room group vs 0.60D $\pm$ 0.40D in the slitlamp group (p=0.019). **Conclusions:** Overall, there was no significant difference between postop mean cylinder, reduction in cylinder, UCVA or BCVA between the laser room and the slit lamp groups. However, in patients with a mean preop astigmatism under 2.00D, the laser room group experienced a significantly greater mean reduction in astigmatism compared with the slit lamp group. Surgeon handedness or other factors may play a role. Larger numbers and longer followup will determine whether this difference is of clinical significance.

(2) **Paper: Madigan WP, Bower KS. Refractive surgery and protective eyewear in the military. Ophthalmology 2004 May;111(5):855-6. Editorial. No abstract available.**

(3) **Presentation: Hammond MD, Bower KS, Madigan WP. Refractive surgery in the US Army 2000 - 2003: clinical outcomes and impact on operational readiness. Association for Research in Vision and Ophthalmology Annual Meeting, Program/Paper # 1104, April 2004.**

Introduction: The Army Warfighter Refractive Eye Surgery Program (WRESP) was established to improve individual and force readiness, with the goal of reducing the limitations posed by corrective eyewear requirements of combat arms soldiers. **Purpose:** The objective of this study is to evaluate the Army WRESP program in terms of individual outcomes as well as impact on military readiness. **Methods:** Results were collected from monthly reports from the 7 WRESP laser centers to the Office of the Surgeon General from May 2000 through October 2003. Reports included the number and types of procedures, uncorrected visual acuity (UCVA), best spectacle-corrected visual acuity (BSCVA), and significant intraoperative or postoperative complications. In addition, questionnaires were administered to refractive surgery patients returning from deployments to southwest Asia in the global war on terrorism. Soldiers rated the impact of refractive surgery on their ability to perform select operational tasks, including night operations, weapons sighting, operations in extreme environmental conditions, and ability to use personal protective equipment. Soldiers also rated their contribution to unit mission as well overall individual readiness. Items were scored on a scale of 1 (much worse) to 5 (much better). **Results:** Between May 2000 and October 2003, 25,642 eyes of 16,091 service men and women were treated. PRK was performed in 59.6%, LASIK in 32.1%, and LASEK in 8.3%. Post-op UCVA was 20/20 in 85.6%, 20/25 in 91.8%, and 20/40 in 98.1% of eyes with at least 3 months follow-up. No eye lost greater than 1 line of BSCVA at 3 months or longer post-op. 90.2% of surveyed patients rated their overall individual readiness better or much better after surgery when compared to before surgery. Mean survey scores were: Overall readiness 4.69, Unit mission 4.69, Night operations 4.41, Weapons sighting 4.65, NBC equipment (gasmask) 4.61, Environmental conditions 4.10. Two individuals (3.9%) reported night operations worse or much worse after surgery, and 2 reported difficulty with harsh environmental conditions (heat, dust, sand, dry). No patient reported worse overall individual readiness after surgery. **Conclusions:** Soldiers treated under the Army WRESP program achieved excellent clinical outcomes in keeping with previously published standards. Surveys demonstrated a significant advantage to overall soldier readiness. Reports of night

vision difficulties and dry eye are infrequent but merit further investigation to determine the impact on military operations.

(4) Paper: Hammond MD, Madigan WP, Bower KS. Refractive Surgery in the US Army: 2000 – 2003. Ophthalmology 2005 Feb;112:184-190.

Purpose: To examine the history, current status, outcomes, and future direction of the Army Warfighter Refractive Eye Surgery Program (WRESP), which was established to reduce the limitations posed by corrective eyewear in combat arms soldiers. **Design:** Retrospective study. **Participants**: Sixteen thousand one hundred eleven Army service members who underwent refractive surgery between May 2000 and September 2003. **Methods:** Results were collected from monthly WRESP reports and from questionnaires administered to refractive surgery patients returning from deployments to southwest Asia. Soldiers rated the impact of refractive surgery on their ability to perform select operational tasks as well as their overall readiness. **Main outcome measures:** Visual acuity (VA) and patient satisfaction. **Results:** Between May 2000 and September 30, 2003, 32 068 eyes of 16 111 soldiers were treated. Postoperative uncorrected VA was better than or equal to 20/20 in 85.6%, 20/25 in 92.4%, and 20/40 in 98.2% of eyes with at least 3 months' follow-up, and 93.7% of 175 surveyed patients rated their overall readiness better or much better after surgery. **Conclusions:** This program has provided excellent outcomes and enhanced the overall readiness of over 16 000 Army service members. Reports of night vision difficulties, LASIK flap dislocation, and dry eye are infrequent, and do not seem to have a significant negative impact on military operations or individual readiness.

(5) Paper: Burka JM, Bower KS, Cute DL, Stutzman RD, Subramanian PS, Rabin JC. Comparison of two techniques of marking the horizontal axis during excimer laser keratorefractive surgery for myopic astigmatism. Am J Ophthalmol. 2005 Apr;139(4):735-7.

Purpose: To compare two methods of limbal marking used during laser refractive surgery for myopic astigmatism. **Design:** Retrospective chart review. **Methods:** Forty-two eyes of 42 patients who underwent photorefractive keratectomy (PRK) or laser-assisted in-situ keratomileusis (LASIK) for myopic astigmatism were marked preoperatively to identify the horizontal axis. In 18 eyes, marks were placed at the slit lamp (SL) with the slit beam set at 180 degrees as a reference. In 24 eyes, marks were placed in the laser room (LR) immediately before reclining under the laser. All treatments were performed with the Alcon LADARVision excimer laser system. Vector analysis of postoperative cylinder and reduction in cylinder and uncorrected and best-corrected visual acuity were evaluated for both groups. **Results:** The mean postoperative magnitude of error was -0.19 +/- 0.44 diopters for the LR group and -0.09 +/- 0.42 diopters for the SL group (P = .439, NS). Both groups had a mean angle of error indicating an overall counterclockwise rotation of axis with an angle of error of 6.3 +/- 8.7 degrees for the LR group and 8.0 +/- 10.2 degrees for the SL group (P = .562, NS). **Conclusions:** We found no significant difference in outcomes with an overall trend toward undercorrection of cylinder in both groups, leaving room for improvement after refractive surgery for myopic astigmatism.

(6) Abstract: Bower KS, Hope RJ, Burka JM, Franks JK, Lyon TL, Nelson B, Sliney DH. Scattered laser radiation and broadband actinic ultraviolet plasma emissions during Alcon LADARVision™ excimer refractive surgery. Association for Research in Vision and Ophthalmology Annual Meeting, Program/Poster #4358/B716, May 2005.

Purpose: To evaluate the potential occupational health hazards associated with scattered actinic ultraviolet laser radiation and broadband actinic ultraviolet plasma emissions during refractive surgery. **Methods:** A prospective experimental study. Intraoperative radiometric measurements were made with the Ophir Power/Energy Meter (LaserStar Model with silicon detector, Model PD-10) and the International Light Radiometer/Photometer (Model IL 1400 with actinic ultraviolet detector, Model SEL240) with and without ultraviolet blocking filters (BLK 270 and Schott types WG-280 and WG-230). Measurements made during

laser calibration as well as LASIK and PRK procedures were evaluated using a worst-case scenario and then compared to the ACGIH TLVs to perform a risk/hazard analysis. **Results:** Most optical emissions were between 193nm and 280nm and approximately 25% of the measurement result was due to broadband emissions greater than 270 nm for calibration targets. About 25% of optical emissions during LASIK were beyond 230 nm. No emissions beyond 230 nm were observed during PRK. Ultraviolet scattered radiation level was similar between PRK and LASIK. Maximum measured values of 80 nJ/pulse at 14 cm for PRK and 45 nJ/pulse at 38 cm for LASIK were used as the absolute worst-case analysis for exposure. Assuming the worst-case exposure conditions equal to the maximum measured value during these studies at a patient workload of 20 patients per day, the cumulative occupational exposure at close range of actinic ultraviolet radiation did not exceed the 8-hour occupational exposure limit of 3 mJ/cm2 for any 24-hour period. **Conclusions:** Scattered ultraviolet laser radiation did not exceed occupational exposure limits at distances greater than 30cm from either laser calibration targets or patient treatments over a workday. Laser eye protection is not necessary to protect operating room personnel since exposure levels are very low even under a worst-case scenario.

(7) **Paper: Bower KS, Burka JM, Hope RJ, Franks JK, Lyon TL, Nelson BA, Sliney DH. Scattered laser radiation and broadband actinic ultraviolet plasma emissions during LADARVision excimer refractive surgery. J Cataract Refract Surg. 2005 Aug;31(8):1506-11.**

Purpose: To evaluate the potential occupational health hazards associated with scattered actinic ultraviolet (UV) laser radiation and broadband actinic UV plasma emissions during refractive surgery. **Setting:** Center for Refractive Surgery, Walter Reed Army Medical Center, Washington, D.C., USA. **Methods:** Intraoperative radiometric measurements were made with the Ophir Power/Energy Meter (LaserStar Model with silicon detector, Model PD-10) and the International Light Radiometer/Photometer (Model IL 1400 with actinic ultraviolet detector, Model SEL240) with and without UV blocking filters (BLK 270 and Schott types WG-280 and WG-230). Measurements made during laser calibration as well as laser in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK) procedures were evaluated using a worst-case scenario and then compared with the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Value Limits (TLV) to perform a risk/hazard analysis. **Results:** Most optical emissions were between 193 nm and 280 nm, and approximately 25% of the measurement result was due to broadband emissions greater than 270 nm for calibration targets. About 25% of optical emissions during LASIK were beyond 230 nm. No emissions beyond 230 nm were observed during PRK. Ultraviolet scattered radiation level was similar between PRK and LASIK. Maximum measured values of 80 nJ/pulse at 14 cm for PRK and 45 nJ/pulse at 38 cm for LASIK were used as the absolute worst-case analysis for exposure. Assuming the worst-case exposure conditions are equal to the maximum measured value during these studies at a workload of 20 patients per day, the cumulative occupational exposure at close range of actinic UV radiation did not exceed the 8-hour occupational exposure limit of 3 mJ/cm(2) for any 24-hour period. **Conclusions:** Scattered UV laser radiation did not exceed occupational exposure limits at distances greater than 30 cm from either laser calibration targets or patient treatments over a workday. Laser eye protection is not necessary to protect operating room personnel since exposure levels are very low even under a worst-case scenario.

(8) **Presentation: Bower KS. Army refractive surgery in times of war. Strategies and Solutions: The Changing Landscape of Military Ophthalmology. Schepens Eye Research Institute, Harvard Medical School, Boston, September 2005. No abstract available.**

(9) **Paper: Donnelly SJ, Bower KS, Stutzman RD, Burka JM. Corneal iron line following LASIK with epithelial ingrowth. Cornea. 2005 Oct;24(7):870-3.**

Purpose: To report a new corneal iron line following keratorefractive surgery. **Methods:** Case report and review of the literature. A 51-year-old man developed epithelial ingrowth after otherwise uneventful LASIK surgery. The patient, satisfied with an uncorrected visual acuity of 20/25 and otherwise asymptomatic, declined to have his flap relifted to treat the ingrowth. **Results:** Six months postoperatively a corneal iron line was noted at the leading edge of the epithelial ingrowth. Vision remained stable.

Conclusions: Epithelial iron lines have been reported with a number of conditions, including post-refractive procedures. This is the first report of an iron line associated with epithelial ingrowth following LASIK.

(10) <u>Presentation:</u> Madigan WP, Bower KS. History of refractive surgery in the military. American Academy of Ophthalmology Annual Meeting, Chicago, October 2005. No abstract available.

(11) <u>Presentation:</u> Bower KS. US Army Warfighter Refractive Eye Surgery Program: Update 2006. US Navy Refractive Surgery Symposium, San Diego, California, January 2006. No abstract available.

(12) <u>Presentation:</u> Bower KS. Army Refractive Surgery Information System (RSIS). US Navy Refractive Surgery Symposium, January 2006, San Diego, California, January 2006. No abstract available.

(13) <u>Abstract:</u> Hope RJ, Pasternak JP, Bower KS, Sliney DH, Weber ED. Scattered UV irradiation during VISX excimer laser keratorefractive surgery. Association for Research in Vision and Ophthalmology Annual Meeting, Program/Poster #553/B321, April-May 2006.

Purpose: To evaluate the potential occupational health hazards associated with scattered ultraviolet laser radiation during keratorefractive surgery with the VISX excimer laser system. **Methods:** Intraoperative radiometric measurements were made with the Ophir Optronics Ltd. Power / Energy Monitor (LaserStar with silicon photodiode detector PD-10). The average energy per pulse was measured using the LaserStar in data log mode. The ambient light level was measured in background mode and subtracted from the collected data. Measurements made during laser calibration and PRK procedures were evaluated using a worst-case scenario and then compared to the American Conference of Government Industrial Hygienists (ACGIH) Threshold Value Limits (TLV) to perform a risk/hazard analysis. **Results:** The maximum average UV scattered radiation level for PRK measured at 20.3 cm was 248.3 nJ per pulse. During the study the maximum ablation time was 52 seconds with a pulse frequency of 8 Hz. Therefore at the detector the maximum exposure would be (ablation time x pulse frequency x energy per pulse) / detector area $(0.7854 \text{ cm}^2) = (52 \times 8 \times 248.3) / 0.7854 = 0.132 \text{ mJ} / \text{cm}^2$. Assuming a 20 patient / day work load (40 eyes) the worst case exposure for an operating room technician situated 80 cm from the patient would be, assuming the inverse square law, equal to (40 x energy at the measurement distance) / $(R/r)^2$) where R is the distance of the operator and r is the distance of the measurement = $(40 \times 0.132) / (80/20.3)^2 \text{ mJ} / \text{cm}^2 = 0.34$ mJ / cm^2. Under these worst-case conditions the cumulative occupational exposure for an operating room technician 80 cm from the patient would be $0.34 \text{ mJ} / \text{cm}^2$ for an 8-hour operating day. This is well below the existing TLV of $3\text{mJ} / \text{cm}^2$ for an 8-hour exposure in a 24-hour period. **Conclusions:** Scattered UV radiation from the VISX Excimer Laser does not pose an occupational health risk for operating room personnel during PRK refractive surgery.

(14) <u>Presentation:</u> Bower KS. The state of refractive Surgery in the US Army 2007. First Annual International Military Refractive Surgery Symposium. San Antonio, Texas, February 2007. No abstract available.

(15) <u>Presentation:</u> Bower KS. LASIK flap dislocations in US Military personnel. First Annual International Military Refractive Surgery Symposium. San Antonio, Texas, February 2007. No abstract available.

KEY RESEARCH ACCOMPLISHMENTS

o   16 active or completed clinical protocols to evaluate refractive surgery in the military setting

o   Over 500 AD soldiers treated in one of these clinical trials.

o   Collaboration with Night Vision Laboratory to evaluate night vision goggle and night firing range performance following refractive surgery

o   Collaboration with US Army Aviation Research Laboratory to evaluate safety and efficacy of refractive surgery in rated aviators

o   Collaboration with Center for Health Promotion and Preventative Medicine to evaluate safety of operating personnel from stray laser light

o   Collaboration with Schepens Eye Research Institute to evaluate dry eye following PRK and LASIK

REPORTABLE OUTCOMES

<u>Papers</u>:

1) Subramanian PS, O'Kane B, Stefanik R, Stevens J, Rabin J, Bauer RM, and Bower KS. Visual acuity and night vision performance after photorefractive keratectomy for myopia. Ophthalmology 2003 Mar;110(3);525-30.

2) Madigan WP, Bower KS. Editorial-Refractive surgery and protective eyewear in the military. Ophthalmology 2004 May;111(5):855-6.

3) Thordsen JE, Bower KS, Warren BB, Stutzman RD. Miotic effect of brimonidine tartrate ophthalmic solution 0.15% in normal eyes. J Cataract Refract Surg 2004 Aug;30(8):1702-6.

4) Hammond MD, Madigan WP, Bower KS. Refractive Surgery in the US Army: 2000 – 2003. Ophthalmology 2005 Feb;112:184-190.

5) Burka JM, Bower KS, Cute DL, Stutzman RD, Subramanian PS, Rabin JC. Comparison of two techniques of marking the horizontal axis during excimer laser keratorefractive surgery for myopic astigmatism. Am J Ophthalmol. 2005 Apr;139(4):735-7.

6) Burka JM, Bower KS, VanRoekel RC, Stutzman RD, Kuzmowych CP, Howard RH. The effect of 4th generation fluoroquinolones gatifloxacin and moxifloxacin on epithelial healing following photorefractive keratectomy. Am J Ophthalmol 2005 July;140(1):84-7.

7) Bower KS, Burka JM, Hope RJ, Franks JK, Lyon TL, Nelson BA, Sliney DH. Scattered laser radiation and broadband actinic ultraviolet plasma emissions during LADARVision excimer refractive surgery. J Cataract Refract Surg. 2005 Aug;31(8):1506-11.

8) Donnelly SJ, Bower KS, Stutzman RD, Burka JM. Corneal iron line following LASIK with epithelial ingrowth. Cornea. 2005 Oct;24(7):870-3.

9) Wroblewski KJ, Pasternak J, Bower KS, MD Schallhorn SC, Hubickey WJ, Harrison CE, MD Torres MF, Barnes SD. Infectious keratitis following PRK in the United States Army and Navy. Ophthalmology 2006 Apr;113(4):520-5.

10) Bower KS, Burka JM, Subramanian PS, Stutzman RD, Mines MJ, Rabin JC. Night firing range performance following photorefractive keratectomy and laser in situ keratomileusis. Military Medicine 2006 Jun;171(6):468-71.

11) VanRoekel RC, Bower KS, Burka JM, Howard RS. Anterior segment measurements using digital photography: A simple technique. Optom Vis Sci. 2006 Jun;83(6):391-5.

12) Burka JM, Bower KS, VanRoekel RC, Stutzman RD, Kuzmowych CP. The effect of moxifloxacin and gatifloxacin on long term visual outcomes following PRK. J Refract Surg. In press.

13) VandePol C, Greig JL, Estrada A, Bissette GM, Bower KS. Visual and flight performance recovery after PRK and LASIK in helicopter pilots. Aviation, Space, and Environmental Medicine. In press.

Presentations:

1) Subramanian PS, O'Kane B, Stefanik R, Stevens J, Rabin J, Bauer RM, and Bower KS. Visual acuity and night vision performance after photorefractive keratectomy for myopia. American Society for Cataract and Refractive Surgery Annual Meeting, San Diego, California, May 2001.

2) Hammond MD, Bower KS, Madigan WP. Refractive surgery in the US Army 2000 - 2003: clinical outcomes and impact on operational readiness. Association for Research in Vision and Ophthalmology Annual Meeting, Program/Paper # 1104, April 2004.

3) Bower KS. Army refractive surgery in times of war. Strategies and Solutions: The Changing Landscape of Military Ophthalmology. Schepens Eye Research Institute, Harvard Medical School, Boston, September 2005.

4) Madigan WP, Bower KS. History of refractive surgery in the military. American Academy of Ophthalmology Annual Meeting, Chicago, October 2005.

5) Bower KS. US Army Warfighter Refractive Eye Surgery Program: Update 2006. US Navy Refractive Surgery Symposium, San Diego, California, January 2006.

6) Bower KS. Army Refractive Surgery Information System (RSIS). US Navy Refractive Surgery Symposium, January 2006, San Diego, California, January 2006.

7) Bower KS. The state of refractive Surgery in the US Army 2007. First Annual International Military Refractive Surgery Symposium. San Antonio, Texas, February 2007.

8) Bower KS. LASIK flap dislocations in US Military personnel. First Annual International Military Refractive Surgery Symposium. San Antonio, Texas, February 2007.

Abstracts/Posters:

1) O'Kane B, Stefanik R, Stevens R, Subramanian P, Rabin J, Bower KS. Night vision performance and contrast sensitivity after photorefractive keratectomy. Vision Science and Its Applications 2001 Topical Meeting /2nd International Congress of Wavefront Sensing and Aberration-Free Refractive Correction, Monterrey, California, February 2001.

2) Bauer R, Bower KS, O'Kane B, Stefanik R, Stevens R, Subramanian P, Rabin J. Physical limits on visual resolution through image intensifiers before and after PRK. Association for Research in Vision and Ophthalmology Annual Meeting, Ft. Lauderdale, Florida, May 2001

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CONCLUSION

Laser refractive surgery has proven immensely popular and effective in the military setting. Results of investigations to date have supported its continued use and broader application, and have begun to address some of the initial concerns such as night vision, night vision goggles, and flight performance. There are still many areas where procedures can be improved to provide better quality of vision, faster wound healing, and less risk of complications. Current and future studies should continue to address wavefront-guided surgery, quality of vision metrics, dry eye, epithelial and stromal wound healing, PRK haze, flap stability, as well as the potential role of the femtosecond laser, implantable contact lenses, and other new and emerging technologies in the military refractive surgery arena. Many of these areas are of limited interest to non-military refractive surgeons but critical to military ophthalmologists; therefore, continued research should be encouraged, strongly supported, and also financed. Only through leading edge research can military refractive surgeons be sure to provide the highest quality, safest procedures to the soldiers in their care.

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SUPPORTING DATA

None

APPENDICES

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Visual Performance with Night Vision Goggles after Photorefractive Keratectomy for Myopia

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Jeff Rabin, OD, PhD,[3] Robert M. Bauer, MD, PhD,[1] Kraig S. Bower, MD[1,3]

Objective: To evaluate visual performance and resolution through night vision goggles (NVG) before and after photorefractive keratectomy (PRK).

Design: Nonrandomized, comparative (self-controlled) trial.

Participants: Nineteen patients (38 eyes) of active-duty US Army Special Forces soldiers.

Intervention: PRK for myopia and astigmatism.

Main Outcome Measures: Visual acuity with best optical correction was measured preoperatively and postoperatively (3 months) using acuity charts of various contrast (100%, 10%, 2.5%, 1.25%). Preoperative and postoperative (3 month) uncorrected and best-corrected visual resolutions through NVGs were assessed using a high contrast tribar chart presented at four light levels (3.44×10^{-3}, 1.08×10^{-3}, 1.04×10^{-4}, 1.09×10^{-5} foot Lamberts) simulating a range of night sky conditions. Subjects were trained before testing.

Results: Uncorrected visual acuity at the 3-month postoperative assessment was greater than or equal to 20/20 in 33 of 38 (86.8%) eyes. No eyes lost 2 or more lines of best spectacle-corrected visual acuity. Preoperative and 3-month postoperative best-corrected low-contrast acuity measurements showed no significant differences at all levels of resolution. Preoperative visual resolution through NVGs decreased systematically with decreasing night sky condition. Visual acuities before PRK were reduced without optical correction. Postoperative visual performance with NVGs (without optical correction) equaled or exceeded performance preoperatively with best correction.

Conclusions: This prospective case series provides data on the safety and efficacy of PRK with respect to visual performance under night sky conditions using NVGs. There was no significant loss of visual acuity across a range of contrast levels 3 months postoperatively. There was no change in best-corrected NVG visual resolution postoperatively, whereas uncorrected visual resolution was significantly enhanced compared with preoperative levels. This improvement may translate into better function for soldiers who are unable to or choose not to use optical correction in operational environments. *Ophthalmology 2003;110:525–530 © 2003 by the American Academy of Ophthalmology.*

Photorefractive keratectomy (PRK) has been demonstrated to provide safe and effective correction of low to moderate myopia with or without astigmatism. However, several

studies have shown unwanted optical side effects after PRK.[1-6] These phenomena tend to be most noticeable under night viewing conditions. Glare, halo, and starburst effects all have been reported, with most of these occurring in the early postoperative period and diminishing by 6 to 12 months after surgery.[4,7] A reduction in contrast sensitivity also has been reported after PRK and laser in situ keratomileusis (LASIK).[8,9]

The Armed Forces have a particular interest in the reduction of soldiers' dependence on optical correction (spectacles, contact lenses), because maintenance of these devices in a field environment can be difficult. In addition, wearing spectacles or contact lenses can limit or even preclude use of night vision devices and chemical protective masks.[10] Designing optical systems to accommodate a variety of refractive errors adds complexity and expense to the system. Operations in a military environment often occur under adverse lighting conditions such as night, rain, smoke, or fog. Loss of visual performance under these conditions after refractive surgery would be of concern. The
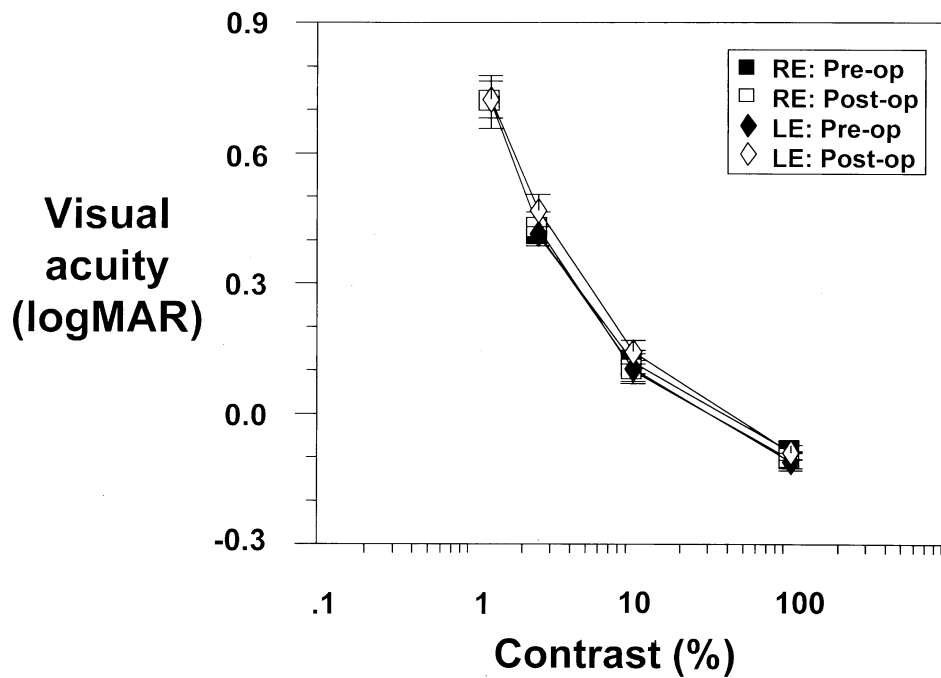
Figure 1. Mean contrast acuity (Pre-op) (±1 spherical equivalent (Post-op)) before and after photorefractive keratectomy. Each eye was tested separately with best spectacle correction used both preoperatively and postoperatively. Preoperative acuity at 1.25% contrast was not assessed. LE = left eye; logMAR = logarithm of the minimum angle of resolution; RE = right eye.

modern soldier also is called on to use devices designed to enhance vision under night sky conditions. Results from a military population treated with PRK showed in the early postoperative period a reduction in contrast sensitivity, which resolved after 3 months,[11] as well as a transient reduction in performance with night vision goggles (Kaupp SR, Schallhorn SC, Baldwin JR, et al. Invest Ophthalmol Vis Sci 1999;40[Suppl]:S532). In this study, we tested 19 patients (38 eyes) both preoperatively and 3 months postoperatively to determine their visual resolution with night vision goggles (NVGs) and to evaluate visual acuity across a range of contrasts under photopic conditions. We report our results that contrast visual acuity was not significantly affected by PRK under best spectacle-corrected testing. Furthermore, uncorrected visual resolution using NVGs enhanced significantly when tested 3 months after PRK.

Patients and Methods

Healthy volunteers were recruited from the Special Operations Group at Fort Belvoir, Virginia. All participants were at least 21 years of age with myopia less than −6 diopters (D) and astigmatism of no more than 4 D (mean spherical equivalent, −2.35 D; range, −0.75 to −5.50 D). All subjects had best spectacle-corrected visual acuity of 20/20 or better with refractive stability (no more than 0.5 D change) for at least 12 months and were able to comply with the examination schedule. Pregnancy, flight status, and prior or current eye disease and/or surgery were reasons for exclusion. Informed consent was obtained from all subjects, and the study protocol was approved by the IRB/Human Use Committee, Department of Clinical Investigation, Walter Reed Army Medical Center.

Nineteen patients (38 eyes; 2 females) were enrolled consecutively in the study. The mean age was 33.9 years (range, 23–45 years). Participants underwent a preoperative evaluation at the Walter Reed Army Medical Center to include medical and ocular history, contact lens history, measurement of pupil size in normal and subdued lighting conditions, slit-lamp examination with grading of corneal clarity, intraocular pressure measurement by applanation tonometry, corneal topography, and fundus examination. Pupil size was measured under photopic and mesopic conditions by estimating pupil size against a standard pupil diameter gauge. Uncorrected visual acuities were recorded at distance and near; after manifest refraction, best spectacle-corrected visual acuity was recorded at distance and near. Cycloplegic refraction was performed in all patients to confirm the manifest refraction results. Best-corrected photopic visual acuity was assessed as a function of letter contrast (100%, 10%, 2.5%, and 1.25%), using retroilluminated low-contrast visual acuity charts (Precision Vision, Inc., La Salle, IL). Acuity was defined as the lowest line at which at least three of five optotypes were identified correctly.

All patients underwent PRK in a sequential manner, with the second eye treated 1 week after the first (unless epithelial coverage was not adequate in the first eye). The treatment goal was emmetropia in all cases; both myopia and astigmatism were treated when present. PRK was performed with a VISX Star2 excimer laser using version 3.1 software. A 6.0-mm optical zone was used with no blend zone. The epithelium was removed by laser scrape with an ablation depth of 45 μm. Postoperatively, patients were examined on day 1, day 3 or 4, and at 1 week, 1 month, and 3 months. More frequent examinations were performed as needed. Manifest refraction was done at the 1-week, 1-month, and 3-month visits with cycloplegic refraction as needed. Final postoperative refractive error was determined at 3 months postoperatively and expressed as the spherical equivalent. All data were recorded on standardized forms. Visual acuity data were converted to their
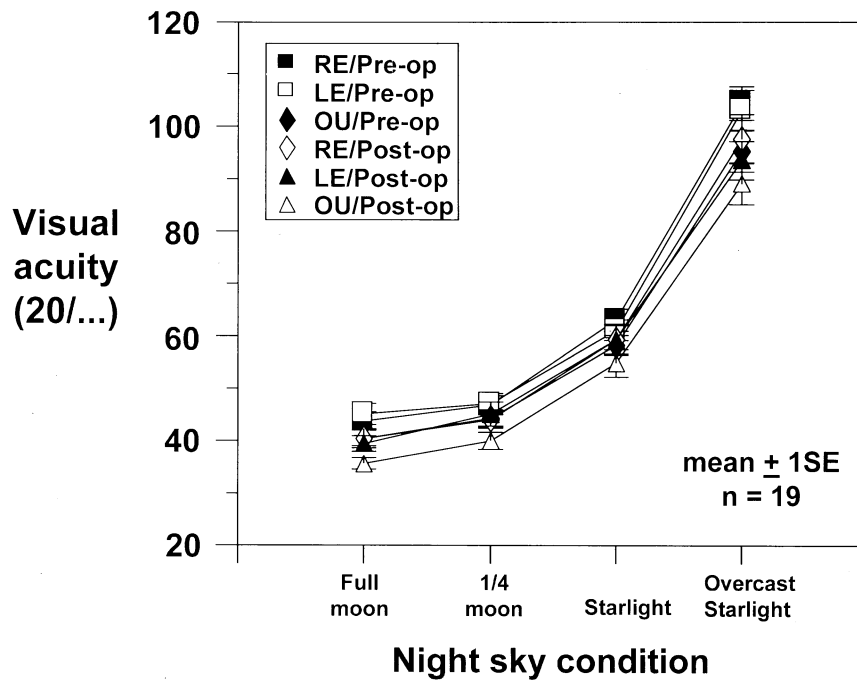
Figure 2. Mean binocular night vision goggle performance (±1 spherical equivalent) is plotted against under night sky illumination. Ability to detect a high-contrast target under the specified lighting level is shown. Tribar chart results are converted to the Snellen equivalent. LE = left eye; RE = right eye; OU = both eyes.

logarithm of the minimum angle of resolution (los MAR) equivalents for statistical analysis.

NVG testing was performed in the Image Intensification Laboratory at the US Army Night Vision & Electronic Sensors Directorate, (Ft. Belvoir, Virginia). Subjects were tested for their ability to read a high-contrast, Air Force three-bar resolution chart while wearing the latest generation biocular NVGs (AN/PVS-7D; single ITT Industries model FL-F4949G tube with dual oculars) under full moon through starlight conditions. In a darkened room, the bar patterns were rear-illuminated at the following light levels: 3.44×10^{-3}, 1.08×10^{-3}, 1.04×10^{-4}, and 1.09×10^{-5} foot Lamberts. These light levels correspond approximately to full moon, 1/2 moon, 1/4 moon, and starlight, respectively. All subjects responded with their highest level of resolution for each of the four lighting conditions monocularly (left and right eye separately) and with both eyes. Monocular and binocular responses were obtained both corrected and uncorrected for each lighting condition, yielding six × four (24) responses for each subject preoperatively. Subjects were tested again 3 months after surgery. Postoperatively, subjects were fitted with trial frame lenses to achieve best-corrected visual acuity and were tested again both corrected and uncorrected with monocular and binocular viewing to provide 24 analogous responses for comparison. Repeated measures of analysis of variance (ANOVA) were used to compare visual acuity across operative condition (preoperative vs. postoperative), contrast, and night sky level.

Results

Refractive Outcomes

The targeted refraction was emmetropia in all patients. Uncorrected visual acuity ranged from 20/30 to 20/400 preoperatively;

postoperative uncorrected visual acuity ranged from 20/12 to 20/40. Thirty-six of 38 eyes achieved uncorrected visual acuity of 20/20 or better. No eye lost 2 or more lines of best spectacle-corrected visual acuity, and all eyes were correctable to 20/20 or better with glasses. Spherical equivalent was within ± 0.5 D of the desired correction in 35 (92.1%) of 38 eyes and ± 1 D in all eyes at the 3-month postoperative examination. One eye was overcorrected to +1.0 D and had an uncorrected visual acuity of 20/30. Another eye developed an anterior stromal scar that reduced best spectacle-corrected vision from 20/15 to 20/20.

Visual Acuity and Contrast

Figure 1 shows mean (±1 spherical equivalent) preoperative and postoperative visual acuity plotted against letter contrast for right and left eyes of 19 subjects. Both preoperative and 3-month postoperative acuities were measured with best spectacle correction. As shown in Figure 1, visual acuity declined systematically with decreasing letter contrast, and this relation was significant ($F = 206$, $P < 0.0001$). However, there was no significant difference between preoperative and postoperative visual acuity at any contrast level ($F = 0.22$; $P > 0.6$) or any difference between right and left eyes ($F = 0.12$; $P > 0.7$). As shown, the preoperative and postoperative functions essentially overlap, indicating no decrement in visual resolution across a range of contrast stimuli. Under mesopic conditions, an inverse relationship was observed between contrast sensitivity and pupil diameter. Pupil diameter averaged 3.5 mm under bright conditions (range, 2–5.5 mm) and 5.7 mm under dim illumination (range, 4–7 mm).

NVG Performance

Resolution values were converted to Snellen equivalents, and the means were plotted against night sky condition (Fig 2). As in
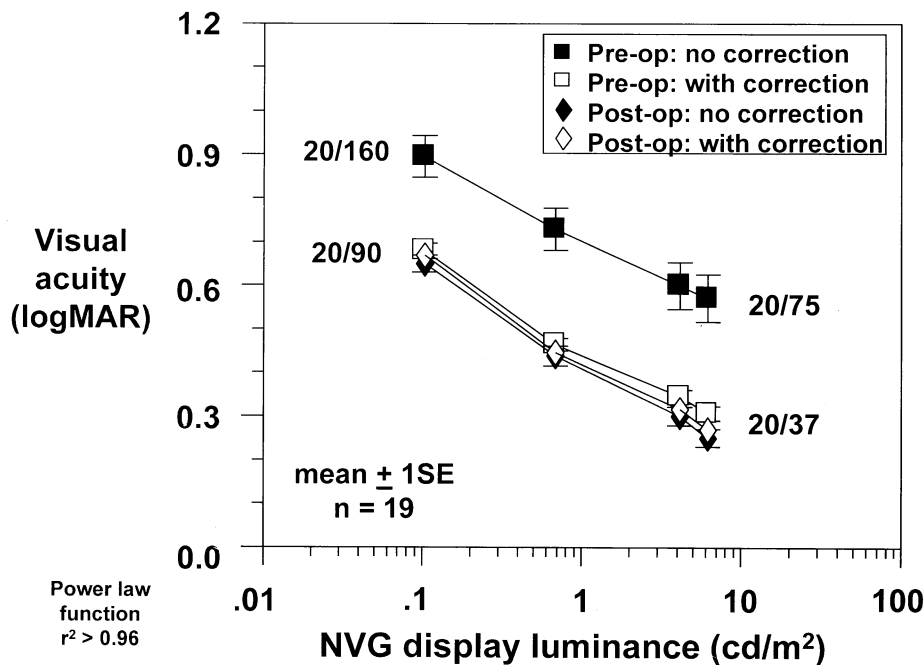
Figure 3. Night vision goggles display luminance and visual acuity. Display luminance at each level of night sky illumination was measured, and the mean visual acuities (logarithm of the minimum angle of resolution equivalents) at each level of background illumination (as shown in Fig 2) were plotted against these values.

previous studies, NVG visual acuity decreased systematically with decreasing night sky condition, and this effect was highly significant ($F = 124.4$, $P < 0.0001$; data were converted to logarithmic values for statistical analyses). Under all night sky conditions, NVG acuity was decreased before PRK without use of optical correction ($F = 81.8$; $P < 0.0001$). After PRK treatment, NVG acuity was assessed at 3 months postoperatively under the same range of night sky conditions. As illustrated in Figure 2, NVG acuity without optical correction under all viewing conditions was as good or better than acuity measured with best correction before PRK ($F = 4.12$, $P = 0.044$), even with correction for postoperative magnification effects on visual acuity.[12]

The NVG acuity data were converted to logarithm of the minimum angle of resolution values and plotted against the luminance of the NVG display (Fig 3). Comparison across the different testing conditions (preoperatively and postoperatively, with or without optical correction) demonstrates that the slope of the relation between acuity and luminance remains constant (power law function; $r^2 = 0.96$). The postoperative NVG acuity function without correction conforms to the same slope as the preoperative data without correction, but with a significant increase in acuity under all tested conditions.

Discussion

Excimer laser refractive surgery, both PRK and LASIK, provides a safe and effective method of correcting refractive errors with or without astigmatism. However, in several studies the most significant and most common short-term and long-term subject complaint is difficulty with night vision.[1,4,6,8,12,13] In particular, a substantial proportion of subjects report a decreased ability to drive comfortably at night. These complaints are generally subjective and diffi-

cult to quantify; furthermore, it is problematic to correlate them with symptoms experienced preoperatively from spectacle or contact lens correction. Insofar as military operations take place at night or under similarly adverse visual conditions (fog, rain), any degradation of vision under these conditions after refractive surgery could compromise operational performance and safety.

Image intensification devices (e.g., NVGs) could conceivably pose a challenge for individuals who have had refractive surgery. NVGs amplify available light reflected by the target from the night sky and surroundings (Fig 4). Long wavelength visible and near infrared light (600–900 nm) from a dimly lit image is brought into focus through the objective lens to strike an infrared-sensitive photocathode, which releases electrons that are multiplied within the microchannel plate. Electrons from the microchannel plate strike the phosphor screen, producing green visible light that is viewed through the eyepiece. The low-light level results in a low signal-to-noise ratio, and an already noisy signal is further amplified by the NVG. Moreover, the luminance of most NVG displays varies directly with ambient light level, decreasing by nearly two log units (100×) from full moon to overcast starlight conditions. The combination of low-contrast, low-luminance, and isochromatic viewing conditions poses substantive challenges for object detection, discrimination, and recognition. Although PRK may allow for detection of high-contrast targets under daylight conditions, less is known about target detection under degraded visual conditions associated with NVGs. The results presented here explored this issue across a range of simulated night sky conditions, as well as low-contrast detection under photopic viewing.
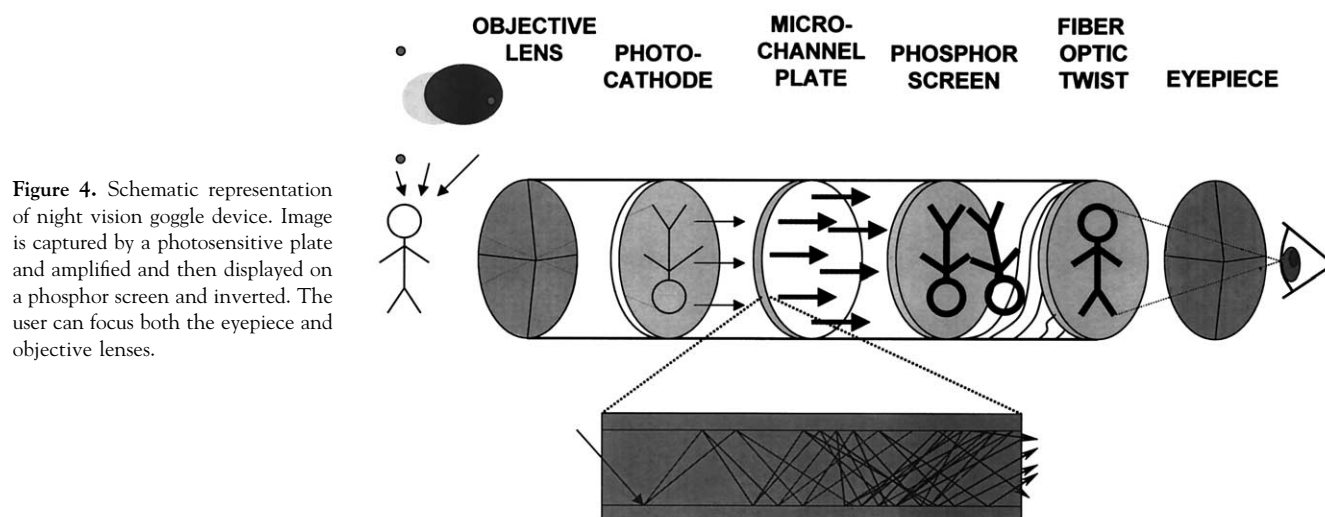
Figure 4. Schematic representation of night vision goggle device. Image is captured by a photosensitive plate and amplified and then displayed on a phosphor screen and inverted. The user can focus both the eyepiece and objective lenses.

This study was designed to evaluate the effect of PRK on night vision performance and resolution with the use of NVGs. Subjects were tested preoperatively and postoperatively to determine their best visual acuities while using NVGs under a range of night sky conditions. Postoperative testing was conducted 3 months after surgery both with and without optical correction. Our data suggest that there was no loss of visual resolution as a result of PRK. In addition, an improvement in unaided visual resolution was achieved at all levels of night sky illumination, and this level of performance was slightly enhanced compared with preoperative best-corrected vision under the same testing conditions.

Further analysis of NVG acuity as a function of display luminance revealed a power law relation between resolution and luminance. Although this decline in NVG acuity with luminance could reflect optical factors (e.g., accommodation, pupil size, and/or higher order aberrations), maintenance of NVG performance at or beyond preoperative levels suggested no increase in adverse optical effects after PRK. Rather, the power-law relation between acuity and luminance may be attributed to quantal fluctuations in light intensity, which imposes limits on performance at low-light levels.[14,15]

Improvement in visual acuity was observed despite quantitative correction of magnification effects on postoperative acuity derived from correction of myopia at the corneal plane.[6] Subtraction of this postoperative magnification effect, which varied from 0.009 to 0.033 log MAR (<2 letters), had minimal impact on the results, which still showed a slight enhancement in unaided NVG acuity compared with preoperative best-corrected values. The slightly lower preoperative acuities may have been due to reflections from multiple surfaces, consequent to wearing spectacles with NVGs.

Reduction in contrast sensitivity and/or low-contrast acuity after PRK or LASIK has been reported previously, and this reduction has been postulated to explain some of the decrement in night vision function.[8,11] We measured photopic contrast acuity in our patients both before and 3

months after PRK, using best spectacle correction. No significant difference in acuity was observed at all levels of contrast tested. Although this finding differs from previous studies showing early decrements in low-contrast target recognition, the data reported herein were obtained 3 months after surgery, when refractive stability typically is achieved and transient postoperative haze resolved. Insofar as our data were collected with best optical correction, it is conceivable that some decrements may have been observed for comparisons between uncorrected postoperative performance and best-corrected preoperative values.

The NVG findings presented represent results under binocular viewing conditions, which are most indicative of expected performance in an actual field environment. Analysis of data from right and left eyes alone revealed identical effects (enhanced postoperative unaided NVG acuity), with no difference between eyes, albeit slightly lower acuity was observed monocularly. Reporting NVG data for binocular viewing, the most operationally relevant posture, did not influence the statistical significance of our findings.

Limitations on visibility, inherent in night vision devices, has been well documented in the literature.[16,17] Performance can improve with experience, emphasizing the role of learning and training in the effective use of these devices. All our subjects were experienced in the use of NVGs through years of training and operational use. Nevertheless, in an attempt to minimize learning effects with regard to the testing protocol used in this study, all subjects were given standardized instruction and training in the use of NVGs and in the reporting of target detection before preoperative testing. No further instruction or NVG training was allowed before the 3-month postoperative assessment. Still, the influence of experience with the testing protocol cannot be excluded from our results. Serial testing of control subjects on night vision performance tasks is planned in future studies.

In summary, this study was intended to determine the effect of PRK on the potential ability of soldiers to function under adverse visual conditions. We measured preoperative and postoperative NVG performance and contrast acuity

under a variety of lighting and contrast conditions. We found no loss of best spectacle-corrected contrast acuity as measured under photopic conditions. In addition, we measured a significant improvement in unaided (no optical correction) NVG resolution after PRK, and this level of unaided resolution was slightly better than preoperative levels using optical correction. Our results are somewhat limited by the relatively short follow-up; however, several studies have demonstrated refractive stability with resolution of any transient corneal changes at the postoperative time chosen (3 months). Longer term follow-up of this study population would be useful in determining stability of the refractive and functional changes reported here and is ongoing. Although laboratory testing of visual function using standardized charts and illumination conditions provides for data that can be analyzed using statistical methods, this testing may not be most representative of function in a battlefield environment. Testing of subjects after refractive surgery under simulated operational conditions (using training simulators) or with more challenging tasks such as firing at a rifle range under night conditions would provide an additional means of assessing the effects of refractive surgery on the ability of soldiers to carry out their military missions.

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Editorial

Refractive Surgery and Protective Eyewear in the Military

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We have seen extensive media coverage of the remarkable young men and women who go in harm's way in service to our country. It is estimated that up to one third of the 1 million active duty Army, Navy, and Air Force service members require corrective lenses. Operational demands in the military present distinct disadvantages to the soldier, sailor, or airman wearing corrective lenses. Glasses can get broken, lost, and clouded by sand, dust, rain, or mist, and are often incompatible with sophisticated helmet-mounted targeting devices, night vision goggles (NVGs), and other combat gear. Although contact lenses offer a potential advantage over glasses, they have problems of their own, particularly the inability to maintain proper lens hygiene. Despite a Department of Defense policy prohibiting contact lenses in combat and field environments such as Kuwait and Iraq, soldiers, marines and airmen continue to wear them in the field. As a result, more than 60 service members developed contact lens–related corneal ulcers/infiltrates in Iraq between April and September 2003 (Madigan, unpublished data).

The applicant pool for military aviation programs has decreased to dangerous levels in recent years. Refractive error is the most common disqualifier for potential applicants who fail to meet flight medical standards. Because of a mean myopic shift of approximately 1 diopter (D) from freshman to senior year, documented in the mid-1980s at the Air Force Academy[1] and at West Point,[2] a young man or woman may enroll at one of the military academies or the Reserve Officer Training Corps hoping for a career in aviation, only to fall outside the proscribed refractive range by graduation. A safe and effective refractive procedure would clearly present a valuable option.

Before refractive surgery was accepted as an organizational policy in the Armed Forces, it had to demonstrate appropriate levels of efficacy, predictability, and safety. Radial keratotomy was never an approved alternative to corrective lenses in the Armed Forces due to concerns over structural integrity and fluctuating vision at altitude.[3,4] No branch of service, with rare exception, accepts applicants who have had radial keratotomy.

The excimer laser offered much greater promise, and in 1993 preliminary investigations demonstrated the safety and efficacy of photorefractive keratectomy (PRK) in the Navy's elite special operations branch, known commonly as SEALS.[5] Work since then has offered additional insight into the role of refractive surgery in the military operational environment.[6,7] Although refractive surgery may allow high-contrast target discrimination in daylight conditions, loss of contrast sensitivity resulting from the procedure may make targets difficult to see through NVGs. Evaluating patients 3 months after PRK under a full range of night-sky conditions using NVGs, Subramanian et al demonstrated that postoperative visual performance without correction equaled or exceeded preoperative spectacle-corrected abilities.[7] In a study now under way, this visual improvement seems to translate to enhanced performance on the night firing range with standard metal sights at simulated dusk and through NVGs at starlight (Bower, unpublished data). In 2000, the Army began observational studies of soldiers enrolled in Ranger and Airborne (Parachute) School after LASIK. Benefits anecdotally reported in professional athletes, firemen, and policemen seemed to hold true when studied in our unique population. Soldiers continued to perform safely, and well, without complications after refractive surgery and, importantly, without the need for corrective lenses (Madigan, unpublished data).

In late 2000, recognizing the tremendous potential for refractive surgery to enhance military readiness, a new policy was adopted allowing enlistment after laser refractive surgery, and the Warfighter Refractive Eye Surgery Program was launched. This is an ambitious program with the objective of enhancing battlefield effectiveness and increasing individual safety and survivability in our front-line combat soldiers through refractive surgery. To date, the military has established 19 Warfighter Refractive Eye Surgery Program centers worldwide and treated approximately 35 000 service members. Because regulations prohibit enlistment of

myopes over −8.00 D, the majority of treatments are for low and moderate myopia. To date, about two thirds have been surface ablations (primarily PRK) and one third LASIK. In fiscal year 2003, the Army treated 15 401 eyes of 8449 soldiers. Uncorrected visual acuity (VA) is 20/40 or better in 98.1%, 20/25 or better in 91.8%, and 20/20 or better in 85.6%. Less than 10 lost more than one line of best spectacle-corrected VA (BSCVA), and no soldier has required medical separation due to loss of BSCVA.

Although emphasis is placed on the benefits of reducing the need for corrective lenses, this is not to say that the military aims to eliminate eyewear altogether. Casualties in modern warfare frequently have serious globe injuries, usually caused by small fragmentation projectiles.[8,9] Although the eyes represent only 2% of the body surface area, 16% of military injuries involve the eye or ocular adnexa. Several factors are responsible for the disproportionate number of ocular injuries in the combat setting. Visual target-seeking behavior directs our eyes toward the source of danger. Terrorists make use of this when they precede the large blast with a small noise to attract the victim towards the awaiting bomb, thereby inflicting greater damage. More importantly, as body armor (flak jacket and helmet) has become standard issue, explosions that would have resulted in fatal chest or abdominal wounds in the past are now survived. However, these new survivors have more injuries to the relatively unprotected extremities, face, neck, and eyes. Between April and September 2003, the 286th Eye Surgical Team in Iraq treated 97 serious ocular and adnexal injuries, including over 40 ruptured globes.[10] Most of these injuries would have been prevented by the appropriate use of protective eyewear.

Wraparound polycarbonate lenses designed to block the force of a 22-caliber bullet from 20 feet have been developed by and for the Armed Forces. This eye armor is now a standard supply item thanks to the pioneering vision and hard work of Col Francis LaPiana, MD, FACS (Ret), and others.[11,12] We recommend that all combat soldiers wear eye armor along with their body armor, and every soldier is issued a pair when they leave a Warfighter Refractive Eye Surgery Program center after refractive surgery.

Exciting research continues to define the contribution of refractive surgery to our individual and force readiness. The ability of wavefront-guided ablations to reduce postoperative higher order aberrations has opened up a whole new field for investigation. The potential to achieve better than 20/20 vision while simultaneously improving night vision in warfighters is an exciting possibility. We look forward to working with our colleagues to advance our knowledge in this field and apply it not only to civilians but also to the men and women of the Armed Forces as they serve in defense of our nation.

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Miotic effect of brimonidine tartrate 0.15% ophthalmic solution in normal eyes

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Purpose: To evaluate the effect of brimonidine tartrate 0.15% ophthalmic solution (Alphagan® P) on pupil diameter in eyes of healthy adults under different luminance conditions.

Setting: Center for Refractive Surgery, Ophthalmology Service, Department of Surgery, Walter Reed Army Medical Center, Washington, DC, USA.

Methods: Using a Colvard pupillometer, the pupil diameter was measured in 15 eyes of 15 healthy adults under 3 luminance conditions (scotopic, mesopic, photopic). The luminance of the room was measured using the Minolta LS-110 Luminance Meter. Pupil diameter was remeasured using the same technique 30 minutes, 4 hours, and 6 hours after administration of 1 drop of brimonidine tartrate 0.15% ophthalmic solution.

Results: Under scotopic conditions (luminance 0.0 candelas [cd]/m^2), the pupil diameter decreased by 1.0 mm or more in 100%, 87%, and 60% of eyes at 30 minutes, 4 hours, and 6 hours, respectively ($P<.005$); under mesopic conditions (luminance 0.2 cd/m^2), in 93%, 73%, and 40% of eyes, respectively ($P<.005$); and under photopic conditions (luminance 150.2 cd/m^2), in 73%, 87%, and 67% of eyes, respectively ($P<.005$).

Conclusions: Brimonidine tartrate 0.15% ophthalmic solution produced a significant miotic effect under all 3 luminance conditions. The reproducible miotic effect under scotopic and mesopic conditions may help postoperative refractive patients who report night-vision difficulties related to a large pupil.

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Since the advent of the excimer laser, keratorefractive surgery has become an effective and increasingly popular option to treat naturally occurring myopia, hyperopia, and astigmatism. Despite the ability to reduce refractive errors and improve uncorrected visual acuity, questions regarding the "quality of vision" after laser refractive surgery remain. After photorefractive keratectomy (PRK) and laser in situ keratomileusis (LASIK), some patients, even those with excellent vision during the day,[1–3] report night-vision difficulties including reduced contrast sensitivity, glare disability, and visual aberrations such as starburst and halos. These undesired effects are more pronounced when the mesopic or scotopic pupil is larger than the optical zone diameter, exposing the transition zone at the junction of the ablated and unablated cornea in low-light settings.[2,4–7]

Brimonidine tartrate 0.2% ophthalmic solution (Alphagan®) is an α-2 adrenergic agonist agent that the U.S. Food and Drug Administration has approved for lowering intraocular pressure (IOP) in patients with open-angle glaucoma and ocular hypertension.[8,9] It is well documented that the 0.2% solution selectively inhibits nighttime pupil mydriasis.[10] Because of this effect, it has been advocated as an off-label treatment to decrease postoperative glare, starbursts, and halos in patients with significant night-vision problems after LASIK and PRK. Recently, a 0.15% concentration of

Table 1. Inclusion and exclusion criteria.

Inclusion Criteria	Exclusion Criteria
Adult men or women 18 years and older	Younger than 18 years
Best corrected visual acuity of 20/20 or better	Pregnant/lactating patients or women not on birth control pills
Nornal pupil size, shape, and reactivity	History of serious ocular, neurological, or cardiovascular disease
Absence of significant medical condition	History of severe systemic disease
No previous ocular intraocular surgery	History of arrhythmia or high blood pressure
	Patients currently taking any ocular medication
	Patients on any type of systemic medication except birth control pills or multivitamins
	Patients with abnormal pupil shape, Adie's pupil, anisocoria, or abnormal pupil defect

brimonidine tartrate (Alphagan® P) became commercially available. Alphagan P has an IOP-lowering ability similar to that of the 0.2% solution.[11,12]

Our study evaluated the effect of brimonidine tartrate 0.15% solution on the pupil diameter of healthy adults to see whether it has miotic effects similar to those of the 0.2% solution.

Subjects and Methods

This prospective observational trial evaluated the miotic effects of brimonidine tartrate 0.15% under different lighting conditions. Before the study, the research protocol was drafted and reviewed by the Department of Clinical Investigations and Human Use Committee at Walter Reed Army Medical Center. All study participants provided informed consent. Table 1 shows the inclusion and exclusion criteria.

Each potential study candidate had a medical screening before enrolling in the study. The entrance examination included a review of medical history, a heart rate and blood pressure check, and a baseline undilated ocular examination including Snellen visual acuity, IOP by Goldmann applanation tonometry, pupil size and reactivity, slitlamp biomicroscopy, and optic disc evaluation by direct ophthalmoscopy.

Pupil Measurement

The study was conducted in a standard 20-foot eye examination lane. The luminance of the room under the 3 lighting conditions (photopic, mesopic, and scotopic) was measured with a Minolta LS 110 Luminance Meter and expressed as candelas per meter squared (cd/m²). The photopic environment was created by turning on the overhead fluorescent room lights (mean luminance 150.2 cd/m²). The mesopic environment was created by turning off the overhead room lights and turning on the light source built into the visual acuity chart projector (Reichert Selectra POC, Leica, Inc.), giving a mean luminance of 0.2 cd/m². The scotopic environment was created by turning off all light sources in the room (mean luminance 0.0 cd/m²).

All patients were brought into the same examination lane and seated in the examination chair. Thirty seconds of dark adaptation was allowed before all measurements under mesopic or scotopic conditions. With an infrared Colvard pupillometer,[13] the pupil diameter in the right eye of each patient was measured under the 3 lighting conditions while the patient was instructed to fixate on a distant target 20 feet away. Then, 1 drop of brimonidine tartrate 0.15% ophthalmic solution was administered in the right eye. The pupil diameter was measured under the 3 lighting conditions using the technique described above 30 minutes, 4 hours, and 6 hours after administration of the brimonidine tartrate drop. The pupil size was measured to the nearest 0.5 mm under the 3 lighting conditions and recorded in an Excel spreadsheet. For analysis, a change in pupil size of 1.0 mm or more from baseline was defined as clinically significant.

Statistical Analysis

The pupil-constricting effects of the brimonidine tartrate 0.15% ophthalmic solution (before and after administration) were evaluated using the 2-tailed Student paired t test. A P value less than 0.05 was considered statistically significant.

Results

After the screening process, 15 healthy adults with no underlying ocular disease participated in the study. The mean age of the 12 men and 3 women was 29 years (range 21 to 44 years).

Pupil Size

Table 2 shows the effect of brimonidine tartrate 0.15% on pupil size under different luminance conditions. Before the instillation of brimonidine, the mean pupil diameter under scotopic conditions was 7.0 mm ± 0.2 (SD). The pupil diameter decreased by 1.0 mm or more in all eyes 30 minutes after drop administration

Table 2. Pupil size after the administration of brimonidine tartrate 0.15% ophthalmic solution (N = 15).

Measurement Time	Mean Pupil Size (mm) ± SD		
	Scotopic (150.2 cd/m^2)	Mesopic (0.2 cd/m^2)	Photopic (0.0 cd/m^2)
Before drop administration	7.0 ± 0.2	6.1 ± 0.2	4.5 ± 0.2
After drop administration			
30 min	5.4 ± 0.2	4.8 ± 0.2	3.6 ± 0.1
4 h	5.5 ± 0.2	4.7 ± 0.2	3.4 ± 0.1
6 h	6.2 ± 0.2	5.3 ± 0.2	3.5 ± 0.1
Change in pupil size			
30 min	1.6 ± 0.1	1.1 ± 0.1	0.9 ± 0.1
4 h	1.5 ± 0.2	1.4 ± 0.2	1.1 ± 0.1
6 h	0.8 ± 0.2	0.9 ± 0.2	1.0 ± 0.2

($P<.0005$), in 13 eyes (86%) at 4 hours ($P<.0005$), and in 9 eyes (60%) at 6 hours ($P<.005$).

Before brimonidine tartrate instillation, the mean pupil diameter under mesopic luminance was 6.1 ± 0.2 mm. The pupil diameter decreased by 1.0 mm or more in 14 eyes (93%) 30 minutes after drop administration ($P<.0005$), in 11 eyes (73%) at 4 hours ($P<.0005$), and in 6 eyes (40%) at 6 hours ($P<.007$).

Before brimonidine tartrate instillation, the mean pupil diameter under photopic conditions was 4.5 ± 0.2 mm. The pupil diameter decreased by 1.0 mm or more in 11 eyes (73%) 30 minutes after drop administration, in 13 eyes (86%) at 4 hours ($P<.0005$), and in 10 eyes (67%) at 6 hours ($P<.0005$).

Adverse Effects

There were no cases of conjunctival injection or other adverse effects with the 1-time use of brimonidine tartrate 0.15% ophthalmic solution.

Discussion

The incidence of night-vision disturbances immediately after PRK and LASIK is high. The problems gradually improve so that by 6 months to 1 year postoperatively, most parameters have returned to preoperative baseline values.[2] In some patients, however, night-vision difficulties are significantly bothersome and permanent.[1–3]

The cause of night-vision disturbances can be multifactorial. Many complaints result from residual refractive errors and improve significantly with optical correction for certain circumstances such as night driv-

ing. Dry-eye syndrome, which is commonly reported after PRK and LASIK, can cause night-vision difficulties and significantly reduce contrast sensitivity.[14–16] Other causes of night-vision difficulties include ocular surface abnormalities, flap irregularities, interface opacities, and postoperative haze. Even patients who have none of these findings can have significant night-vision disturbances.

These undesired effects are more pronounced with higher degrees of refractive error and when the transition zone at the junction of the ablated and unablated cornea lies within the pupil diameter. The small optical zone ablations (4.0 mm) created in procedures performed in the early years led to a higher incidence of such symptoms. Decentered ablations and large pupils under mesopic and scotopic illumination may exacerbate the problem. Advanced eye-tracking systems seem to have reduced the incidence of decentration of the laser treatment.[17–19] Larger ablation zones allow treatments that are larger than the dark-adapted pupil.[4–7]

Higher-order aberrations, especially spherical aberration, trefoil, and coma, are induced after PRK and LASIK and are more significant when measured over a larger pupil. These aberrations may in part account for the reduced contrast sensitivity and subjective reports of night-vision difficulty.[4] Making the entrance pupil smaller reduces some higher-order aberrations and may improve visual performance in low-light settings.[4]

The decrease in low-contrast visual acuity associated with refractive surgery is further increased with a dilated pupil, as would be expected to occur under scotopic and mesopic conditions. Unfortunately, to date no good

standard treatment is in place to help patients who are symptomatic from night-vision aberrations. Some refractive surgeons currently use topical selective α-2 receptor agonists for treatment.

Most studies that have documented change (or no change) in pupil diameter associated with the use of α-2 receptor agonists primarily concentrated on the IOP-lowering ability of these drugs and their side-effect profiles. This could account for the conflicting results between studies.[8,9,20–22] A study of the effect of brimonidine 0.2% on the pupil in normal eyes by McDonald and coauthors[10] was one of the first published whose primary focus was the miotic effects of this selective α-2 agonist.

The primary purpose of our study was to evaluate how brimonidine tartrate 0.15% ophthalmic solution affects the pupil in normal eyes and to see whether this lower concentration had miotic effects similar to those of the 0.2% solution. Thus, we tried to structure our study to be similar to that of McDonald and coauthors.[10] The times at which we measured pupil diameter after administration of the brimonidine tartrate drops were the same as in McDonald and coauthors' study; however, the luminance levels concentrated more on low-light conditions.

McDonald and coauthors placed 1 drop of brimonidine tartrate 0.2% ophthalmic solution in 1 eye of 16 patients and measured pupil diameter 30 minutes, 4 hours, and 6 hours after drug administration under 3 luminance conditions (outside light, 200 cd/m^2; normal room light, 5 cd/m^2; and scotopic conditions, 1 cd/m^2). They found that brimonidine tartrate 0.2% effectively decreased scotopic pupil diameter but did not significantly change photopic pupil size.

In our study, a 0.15% concentration of brimonidine tartrate effectively decreased pupil diameter in scotopic (luminance 0.0 cd/m^2) and mesopic (luminance 0.2 cd/m^2) conditions but also produced miotic effects under photopic conditions (luminance 150.2 cd/m^2). We believe the main reason for this discrepancy is the difference in the mean pupil diameter under photopic conditions before drug administration between our study and that of McDonald and coauthors (4.5 mm and 2.9 mm, respectively).

A closer look at the effects of brimonidine tartrate in relation to mean pupil diameter shows that our results do not contradict those of McDonald and coauthors.

They found a statistically significant decrease in pupil diameter when the mean diameter was 4.1 mm or smaller. In our study, there was a statistically significant decrease in pupil size when the mean pupil diameter was 4.5 mm or larger, despite significant differences in the measured luminance between the studies. Just as important, our study population had no subjective complaints or adverse events with the 1-time use of brimonidine tartrate 0.15%.

In conclusion, our study shows that brimonidine tartrate 0.15% ophthalmic solution has a significant ability to decrease pupil diameter under both scotopic and low-light (mesopic) conditions, which may benefit postoperative refractive patients who report night-vision difficulties related to a large pupil. In fact, brimonidine tartrate could be incorporated into the preoperative evaluation of patients with large pupils to assess before surgery how the pupil will react to the medication. The use of brimonidine for preoperative assessment could serve an important role in the informed consent process for refractive surgery as it documents that patients were told about the possibility of night-vision problems related to their large pupil and that they may require drops postoperatively to help minimize symptoms.

The ability of the 0.15% concentration of brimonidine tartrate to constrict the pupil appears to be equivalent to that reported for the 0.2% solution. Also, brimonidine tartrate 0.15% ophthalmic solution significantly decreased pupil diameter under photopic conditions, a finding not observed in a previous study of brimonidine tartrate 0.2% ophthalmic solution.

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Refractive Surgery in the United States Army, 2000–2003

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Purpose: To examine the history, current status, outcomes, and future direction of the Army Warfighter Refractive Eye Surgery Program (WRESP), which was established to reduce the limitations posed by corrective eyewear in combat arms soldiers.

Design: Retrospective study.

Participants: Sixteen thousand one hundred eleven Army service members who underwent refractive surgery between May 2000 and September 2003.

Methods: Results were collected from monthly WRESP reports and from questionnaires administered to refractive surgery patients returning from deployments to southwest Asia. Soldiers rated the impact of refractive surgery on their ability to perform select operational tasks as well as their overall readiness.

Main Outcome Measures: Visual acuity (VA) and patient satisfaction.

Results: Between May 2000 and September 30, 2003, 32 068 eyes of 16 111 soldiers were treated. Postoperative uncorrected VA was better than or equal to 20/20 in 85.6%, 20/25 in 92.4%, and 20/40 in 98.2% of eyes with at least 3 months' follow-up, and 93.7% of 175 surveyed patients rated their overall readiness better or much better after surgery.

Conclusions: This program has provided excellent outcomes and enhanced the overall readiness of over 16 000 Army service members. Reports of night vision difficulties, LASIK flap dislocation, and dry eye are infrequent, and do not seem to have a significant negative impact on military operations or individual readiness. *Ophthalmology 2005;112:184–190 © 2005 by the American Academy of Ophthalmology.*

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Approximately a third of the 1 million active duty United States Army service men and women, reservists, and national guardsmen require corrective lenses. Because of the unique operational demands placed on military service members, there are distinct disadvantages to the soldier wearing corrective lenses.

One of the most important advances in the treatment of refractive errors is the use of a laser to change the shape of the cornea. Since the Food and Drug Administration approved the first excimer laser for the treatment of low to moderate myopia in 1995, laser eye surgery has been performed on more than 6 million people worldwide. Almost 2 million more Americans are expected to undergo laser eye surgery in the coming year. Recognizing the tremendous potential for refractive surgery to enhance military readiness, the Army now supports the surgery under the Warfighter Refractive Eye Surgery Program (WRESP). The purpose of this article is to review the history and development of the Army WRESP, examine the results to date, and discuss the current status and potential future developments in the program.

Materials and Methods

Eligibility Criteria

The Chief of Staff of the Army has established guidelines prioritizing soldiers according to defined operational readiness criteria. Eligibility criteria for the WRESP are summarized in Table 1. In addition to meeting military eligibility criteria, each soldier is carefully evaluated on an individual basis to ensure that he or she is a suitable surgical candidate. All surgery is elective, and the decision to undergo surgery as well as the decision as to the type of surgery are made by the patient and surgeon after discussing alternatives, risks, and benefits. Special operations soldiers and active Army pilots are not allowed to have LASIK, unless enrolled in an investigational protocol.

WRESP Reporting System

Each WRESP center director reports on a monthly basis to the Ophthalmology Consultant to the Surgeon General, who prepares

Table 1. Army WRESP (Warfighter Eye Refractive Surgery Program) Eligibility Criteria*

- At least 18 months on active duty at the time of surgery, or in conjunction with a reenlistment action that is executed
- Assigned to a unit whose mission involves operations at the line of battle or behind hostile lines
- Special operations and combat arms units such as infantry, field artillery, and armor battalions should be given first priority
- Combat Service Support unit personnel in present assignments in a division or separate brigade should be the second priority
- Other active duty service members as space is available
- Nonactive duty personnel are not authorized treatment under this program
- Personnel selected should have at least 12 months remaining in the same or similar unit and should have no adverse personnel actions pending

Memorandum, United States Army Chief of Staff, 2001.
*Shinseki EK. Warfighter Refractive Eye Surgery Program (WRESP) guidance.

an annual report to the Surgeon General providing the basis for future policy and funding decisions. In this article, we review the reports from the 7 WRESP centers from the inception of the program in May 2000 through September 30, 2003. Reports include the number and types of procedures, uncorrected visual acuity (UCVA), best spectacle-corrected visual acuity (BSCVA), and significant intraoperative or postoperative complications.

Adverse Event Reporting

Significant adverse events related to refractive surgery in active duty Army personnel are reported from Army medical treatment facilities throughout the world. Any undesired significant event, either clinical or operational, related to an operative eye is recorded on an Adverse Event Report Form. All reports include a brief description of the event's severity, frequency, required treatment, and outcome. The original report is entered into the patient's medical record, and a copy is forwarded to the Ophthalmology Consultant to the Office of the Surgeon General. If the patient is enrolled in a clinical trial, the reported event is forwarded to the appropriate institutional review board by the principal investigator. Adverse events include, but are not limited to, the conditions listed in Table 2.

Deployment Questionnaire

To assess the impact of refractive surgery on military readiness in the operational environment, questionnaires were administered to refractive surgery patients returning from deployments to southwest Asia in the global war on terrorism (additional online-only Fig 1, available at http://www.ophsource.com/periodicals/ophtha). Soldiers rated the impact of refractive surgery on their ability to perform select operational tasks, including night operations, weapons sighting, and operations in extreme environmental conditions, and to use personal protective equipment. Soldiers also rated their contribution to the unit's mission as well as overall individual readiness and, when possible, compared their most recent deployment to previous deployments before refractive surgery. Items were scored on a scale of 1 (much worse) to 5 (much better). All questionnaires were confidential. Results were collected and analyzed.

Results

The total number of patient treated by fiscal year since inception of the WRESP is summarized in Table 3 (available at http://www.ophsource.com/periodicals/ophtha). Between May 2000 and September 30, 2003, 32 068 eyes of 16 111 service men and women were treated. Postoperative UCVA was 20/20 or better in 85.6%, 20/25 or better in 92.4%, and 20/40 or better in 98.2% of all eyes with at least 3 months' follow-up. There was no significant difference in postoperative outcomes between the 3 treatment groups (Table 4). Overall, 20 eyes (0.06%) had a loss of BSCVA of >1 line at 3 months or longer after the operation. No final BSCVA was worse than 20/40, no soldier failed to meet Army retention standards, and all treated soldiers were fit to return to duty.

Complications reported in the monthly WRESP reports are summarized in Table 5 (available at http://www.ophsource.com/periodicals/ophtha). No intraoperative photorefractive keratectomy (PRK) complications were reported in the monthly WRESP reports. Postoperatively, no complication was reported at an incidence of >1%. The most common postoperative complications after PRK were steroid-induced glaucoma in 93 eyes (0.45%) and persistent epithelial defects in 52 eyes (0.25%). A corneal haze grade 2 or greater was seen in 30 eyes (0.14%). There were 3 cases of infectious keratitis. Corneal infiltrates that were either culture negative or felt clinically to be noninfectious were reported in 15 eyes (0.07%). Dry eye requiring punctal plugs was reported in only 8 eyes (0.04%). The only intraoperative laser epithelial keratomileusis (LASEK) complication was inability to create the epithelial flap in 2 eyes (0.07%), resulting in conversion to PRK. No postoperative complication occurred at a frequency of >1%.

The most common intraoperative LASIK complication was epithelial defect, in 83 eyes (0.97%). Reports did not distinguish between small peripheral epithelial defects and larger central abrasions. There were 16 (0.19%) intraoperative flap complications, all involving suction loss. No postoperative complication was seen at an incidence of >1%. The most common postoperative complication was diffuse lamellar keratitis in 68 eyes (0.77%); however, of these, only 2 had stage 3, and none progressed to stage 4. Dry eye requiring punctal plugs was seen in 21 eyes (0.25%).

Through December 2003, a total of 20 adverse events were reported, 7 involving PRK and 13 involving LASIK. Photorefractive keratectomy adverse events included a total corneal epithelial

Table 2. Reportable Adverse Events

- Limited duty or a physical evaluation board examination as a direct or indirect result of the refractive surgery (include a copy of the board's findings in the report)
- Persistent epithelial defect or corneal erosion
- Diplopia (ghost images) at 3 mos or more after the operation that does not resolve with spectacle correction
- Corneal infiltrate or ulcer
- Corneal edema at 1 month or more after the operation
- Intraocular pressure increase of >15 mmHg above baseline, or any reading above 30 mmHg
- BSCVA loss of ≥2 lines at 6 mos or more after the operation
- Corneal haze or scarring rated moderate or severe (PRK) that causes a loss of BSCVA
- Slipped, wrinkled, or lost flap (LASIK)
- Epithelial ingrowth into the flap interface (LASIK)
- Retinal detachment or retinal vascular accidents
- Endophthalmitis
- Penetrating eye trauma

BSCVA = best spectacle-corrected visual acuity; PRK = photorefractive keratectomy.

Table 4. Army Warfighter Eye Refractive Surgery Program. Cumulative Results*—May 2000 to October 2003

Postoperative Result	PRK (n = 20 745)	LASIK (n = 8528)	LASEK (n = 2795)	Total (n = 32 068)
UCVA 20/40 or better	97.8%	98.6%	98.0%	98.2%
UCVA 20/25 or better	91.4%	93.6%	92.4%	92.4%
UCVA 20/20 or better	83.9%	88.8%	79.8%	85.6%
Loss of BSCVA of >1 line	0.07%	0.06%	0.23%	0.08%

BSCVA = best spectacle-corrected visual acuity; LASEK = laser epithelial keratomileusis; PRK = photorefractive keratectomy; UCVA = uncorrected visual acuity.
*Follow-up at least 3 mos postoperatively.

defect after trauma (1 patient), infectious keratitis (2 patients), and grade 3 or higher PRK haze (4 patients). There were no adverse events reported for LASEK patients. LASIK adverse events included 2 intraoperative free caps due to suction loss. Both cases had treatment aborted, and both eyes healed without loss of BSCVA. One patient was subsequently treated with uncomplicated LASIK, with good results. The other ultimately elected against surgery. An additional 14 intraoperative flap complications were reported on the monthly WRESP report but not followed up with a separate adverse event report. Postoperative LASIK adverse events included traumatic flap dislocation in 8 patients (10 eyes). All occurred from 3 to 18 months postoperatively (mean, 7.1 months).

To date, 175 soldiers returning from overseas deployment to Afghanistan, Kuwait, or Iraq have completed postdeployment questionnaires. One hundred sixty-three respondents (93.1%) felt that their ability to contribute to their unit's mission was enhanced by the surgery, and 93.7% of surveyed patients rated their overall individual readiness better or much better after surgery when compared with before surgery. The large majority reported improvements in 3 specific tasks of military importance: weapons-sighting ability (86.2%), ability to employ personal nuclear–biological–chemical equipment (91.4%), and ability to utilize night vision goggles (NVG) and perform night operations (85.7%) (Table 6).

Discussion

Approximately a third of the 1 million active duty Army service men and women require corrective lenses. A study conducted by McAlister and Wingert found that, of 3247 recruits, only 2117 passed the vision screening with no correction.[1] This means that 34% of the candidates during the study period required spectacle correction. A similar study by Lattimore and Schrimsher found that the prevalence of spectacle wear among Army aviators was as high as 22%.[2]

Approximately 300 000 soldiers require new spectacle prescriptions each year. Each soldier requires 2 pairs of spectacles and mask inserts, which are replaced on average every 3 years. In 2001, nearly 1 000 000 glasses or inserts were provided to the active duty regular Army, at a cost of $23 million (Madigan, unpublished data). Although glasses are a good solution in the garrison environment, there are numerous disadvantages in military operations and field exercises, where glasses can get scratched; broken; lost; or clouded by sand, dust, rain, fogging, or mist. Spectacles can also cause unwanted glare, discomfort, and a reduced visual field, and are often incompatible with sophisticated helmet-mounted targeting devices, NVG, and other combat gear. The impact of spectacle requirements on force readiness was demonstrated in Operation Desert Shield/Desert Storm, where 44% of deploying personnel did not have the required optical devices, necessitating the fabrication of over 1 000 000 pairs of optical devices to prepare soldiers for the war.[3]

Contact lenses, though eliminating many of the problems with spectacle correction, have numerous problems of their own, especially the inability to maintain proper lens hygiene

Table 6. Deployment Questionnaire Results

Readiness Questionnaire Item	Mean Score* (n = 175)	Better or Much Better		No Change		Worse or Much Worse	
		n	%	n	%	n	%
Overall individual readiness	4.66	164	93.7	10	5.7	1	0.5
Ability to contribute to my unit's mission	4.60	163	93.1	11	6.2	0	0.0
Ability to employ NBC equipment and personal mask	4.70	160	91.4	14	8	1	0.5
Weapons-sighting ability	4.50	151	86.2	19	10.8	5	2.8
Ability to utilize night vision goggles/night operations	4.44	150	85.7	17	9.7	7	4.0
Personal hygiene	4.26	133	76	42	24	0	0.0
Requirements for optical support (replacement/repair of glasses, mask inserts)	4.48	149	85.1	26	14.8	0	0.0
Ability to weather extreme environmental conditions (dust storms, high heat, cold, etc.)	4.14	125	71.4	34	19.4	8	4.5
Frequency of sick call visits for eye complaints	4.03	105	60	49	28	9	5.1

NBC = nuclear–biological–chemical.
*5 = much better; 4 = better; 3 = neutral; 2 = worse; 1 = much worse.

in a combat or field environment. Since Operation Iraqi Freedom began, over 200 contact lens–related corneal ulcers have been treated, despite policy forbidding their use (Madigan, unpublished data). The potential logistical, economic, and readiness benefits of refractive surgery to the Army are considerable. In May 2000, the U.S. Army Medical Command established the WRESP and opened the first Army laser center at Fort Bragg, North Carolina. The WRESP offers soldiers access to corrective laser eye surgery and provides commanders with an important medical resource to support combat arms soldiers. The objective is to enhance battlefield effectiveness while providing increased safety and survivability. Additional Army centers have since opened at Fort Campbell, Kentucky; Fort Hood, Texas; Landstuhl Regional Medical Center, Germany; Madigan Army Medical Center, Fort Lewis, Washington; Tripler Army Medical Center, Hawaii; and Walter Reed Army Medical Center, Washington, DC.

Between May 2000 and September 2003, surface ablations were performed in nearly three quarters of cases: PRK was performed in 20 745 eyes (64.7%) and LASEK in 2795 (8.7%). LASIK was performed in 8528 eyes (26.6%) and accounted for the other one quarter (Table 4). In our series, patients treated with PRK, LASIK, and LASEK achieved comparable postoperative outcomes that match or exceed what has been previously reported in the literature. Intraoperative and postoperative complications associated with PRK are infrequent, but of significance is the fact that PRK is associated with an increased incidence of corneal haze and regression, especially for higher degrees of myopia (greater than −6.00 diopters [D]).[4] In our series, corneal haze of grade 2 or greater was reported in 30 eyes on the monthly WRESP reports. Adverse event reports were filed on an additional 4 patients with grade 3 or greater haze. Two of the latter patients were noncompliant and lost to follow-up after their early postoperative period. The other 2 were deployed to locations with high ultraviolet exposure within the first 3 months after their surgeries: 1 to Afghanistan and 1 to multiple locales, including Egypt, Jordan, Qatar, and Botswana. To date, 1 has responded to treatment with topical steroids and has a recovered UCVA of 20/15; 2 have stable vision in spectacles and are pending follow-up and treatment after returning from their present overseas assignments; the status of the fourth patient is not known. Because of the large number of surface ablations for a wide range of refractive errors, including moderate and high myopia, treatment alternatives such as LASEK and the prophylactic use of mitomycin C require further study to determine their proper role in military refractive surgery.

Although LASIK results are comparable to PRK results, advantages include quicker postoperative visual recovery, with less discomfort, and less risk of corneal haze than PRK, especially in higher myopes.[4] Flap-related complications, including late traumatic flap dislocation,[5,6,7] are potentially a significant problem for an active population, such as those in the military, who may be subject to trauma. In our series, we report 10 eyes of 8 patients with late traumatic flap dislocations. One patient had bilateral flap dislocation due to a severe motor vehicle accident that resulted in multisystem trauma. The other case of bilateral flap dislo-

cation occurred during 2 separate physical altercations, at 3.5 and 5 months postoperatively in the same patient. Additional causes included a dog's paw, playing basketball, playing flag football, a tree branch, a rifle sight, and eye rubbing. The latter 3 incidents occurred on duty while performing military-related tasks. The remaining incidents occurred in off-duty nonmilitary activities. Five of the 8 patients were seen on the same day of their injury, often within a few hours. This included 1 soldier in Kuwait who was seen and treated by an Army ophthalmologist within 2 hours of his injury. One patient evacuated from Iraq was treated 4 days after the injury, and 1 patient evacuated from Korea was treated 13 days after injury. One soldier in Italy waited 3.5 weeks to be seen, even though care was immediately available to him at his post. He was evacuated and treated within 4 days after the injury was diagnosed. All 10 eyes reported here all had a final BSCVA of 20/30 or better.

The 4-year Army experience of traumatic LASIK flap dislocation in 10 eyes of 8 patients is reported here. Even if we consider only the 7 eyes treated at Army WRESP centers, the incidence remains 0.085% (1/1174 eyes). It is important to point out that the Army adverse event reporting system requires reporting of *all* significant adverse events in military personnel, regardless of the site (civilian or military) of their treatments. Three of the 10 eyes included in our study were treated outside the WRESP, and there are undoubtedly many more soldiers in the Army today who have had LASIK. Because the demand currently exceeds the treatment capacity of the program, only 5% to 10% of potentially eligible soldiers are treated each year at WRESP centers. It is estimated that, for every soldier treated under the WRESP, another 2 to 3 soldiers are treated on their own expense outside of the program (Madigan, unpublished data). The true incidence of late traumatic flap dislocation is therefore probably 2- to 3-fold smaller than suggested by the above estimate. No traumatic flap dislocation has been reported as a direct result of combat actions in operations Enduring Freedom or Iraqi Freedom. Nevertheless, the role of LASIK in light of the risk for traumatic flap dislocation requires continued surveillance.

LASEK may address some of the shortcomings of LASIK and PRK. Discomfort and visual recovery are similar to PRK in the early postoperative healing period, but LASEK may provide improved long-term results with less corneal haze than PRK in patients with high myopia who are unable or unwilling to undergo LASIK. Preliminary results, however, suggest no real advantage to LASEK compared with PRK or LASIK.

Clinically successful outcomes, defined as improvement of UCVA to 20/40 or better without loss of BSCVA, seem to translate into improved job performance, as reported on the postdeployment surveys, where the large majority of surveyed patients (93.7%) rated their overall individual readiness better or much better after surgery relative to before surgery. This is also consistent with anecdotal reports from patients and unit commanders praising the program and its benefits. Nevertheless, several concerns are of particular importance to the military—notably, night vision, harsh environmental conditions, aviation, and special operations. These are discussed in more detail below.

Night Operations and Night Vision Goggles

A relatively common and sometimes significant patient complaint after refractive surgery is difficulty with night vision. Such difficulties include reduced contrast sensitivity, glare disability, and visual aberrations such as starbursts and halos.[8–11] The incidence of night vision disturbances is highest immediately after both PRK and LASIK, and gradually improves such that by 3 months postoperatively most night vision complaints have returned to preoperative baselines.[8] In some patients, however, night vision difficulties can be significantly bothersome and permanent.

Military operations often take place at night or under conditions with reduced contrast; therefore, any further degradation of vision under these conditions after refractive surgery could compromise operational performance and safety. In addition, limitations inherent in night vision devices have been well documented in the literature. The combination of low contrast, low luminance, and isochromatic viewing conditions pose significant challenges for object detection, discrimination, and recognition.[12,13] Glasses interpose an additional optical interface and prevent a good fit with NVG. Moreover, unwanted reflections from glasses may lead to unwanted detection during covert operations. Obviously, the ability to perform night operations without corrective lenses is a critical military consideration. Although most respondents in this study reported night operations the same (9.7%) or improved (85.7%) after their surgery, 7 individuals (4.0%) reported night operations worse or much worse after surgery. The cause of the night vision complaints in these individuals is not known, but many such complaints are due to residual refractive error and improve with additional refractive correction. Although much work has been done regarding the quality of vision after laser refractive surgery, the true incidence, cause, nature, and optimal treatment of night vision difficulties, as well as the effect on NVG performance, remain areas of concern to the military.

Extreme Environmental Conditions

Military operations often take place in geographic and environmental extremes of temperature, altitude, dust/sand, and ultraviolet radiation exposure. It is well known that refractive surgery can lead to increased dry eye symptoms.[8,14–16] In an extreme environment, these symptoms may be aggravated. Although the incidence of postoperative dry eyes requiring plugs was low in this report, it was greater after LASIK relative to surface ablations (0.25% vs. 0.04%). These data were largely compiled from soldiers in garrison, and the effect of the severely harsh desert conditions in Iraq and Afghanistan has not yet been fully established. Deployment questionnaire results suggest that these conditions are difficult for some refractive surgery patients. Eight of 175 surveyed individuals (4.5%) reported difficulty with harsh environmental conditions (heat, dust, sand, dryness); 3 reported their tolerance of extreme conditions as "much worse" (Table 6). In analysis of the adverse event reports, we found that eye rubbing led to one LASIK flap dislocation. The environmental conditions that face the modern soldier must be considered when selecting the most appropriate surgery in the military setting.

Army Aviation

LASIK and PRK have the benefit of increasing the applicant pool of aviation trainees, which has decreased from a traditional ratio of 3:1 to a current low level of 1.3 applicants per position. Inability to meet vision standards is the primary cause for flight applicant medical disqualification. Applicants with myopia beyond −0.75 D, hyperopia beyond +3.00 D, or astigmatism of >0.75 D are ineligible in accordance with paragraph 4-12b, AR 40-501 (class 1A flight physical standards). Because over 25% of the population have refractive errors that exceed these standards,[17] this imposes significant limitations on the applicant pool and excludes individuals who may otherwise be exceptional candidates.

Moreover, these procedures have the potential to improve flight performance in the active aviator population by improving uncorrected vision and reducing interface problems. Despite the use of advanced instrumentation, sensors, warning devices, and automation systems, high velocity/low altitude flight is guided primarily by direct visual input, frequently requiring accurate, time-limited visual discriminations under degraded conditions.[18] Although corrective lenses provide clear vision, displacement or loss of optical correction during flight can lead to loss of aircraft control. Moreover, spectacle incompatibility has been a major problem with NVG and helmet-mounted displays, such as the Integrated Helmet and Display Sighting System used on the AH-64 Apache attack helicopter, because the proximity of the optical system of helmet-mounted displays and the eye does not allow for spectacle wear.[19] Although contact lenses lessen compatibility problems, the successful use of contacts in operational flight environments is limited, and considerable tactical support is required.[17,20] Army aviation combat doctrine often requires night flight operations, frequently using NVG, and the same concerns over night vision discussed above apply to the aviator.

Special Operations

In 1993, preliminary investigations by Schallhorn et al demonstrated the safety and efficacy of PRK in the Navy's elite special operations branch, known commonly as SEAL (Sea Air and Land).[9] Based on early successes of the program, the Special Operations Command has been an important beneficiary of refractive surgery. In 2000, the Army began longitudinal observational studies of soldiers enrolled in Ranger and Airborne (parachute) schools after LASIK. To date, no adverse events have been reported from that group of soldiers. LASIK is approved for students enrolling in the Special Forces qualification course if they agree to enter an ongoing observation study. At this time, only PRK and LASEK are offered to HALO (high altitude, low opening)– or diving-qualified soldiers.

Ballistic Eye Armor

Historically, up to 16% of injuries in modern warfare and terrorist attacks have been to the eye or ocular adnexa, usually caused by small fragmentation projectiles.[21,22] Through December 2003, Army ophthalmologists have treated numerous serious ocular and adnexal injuries from recent military operations in Afghanistan and Iraq, including over 100 perforated globes and 40 enucleations (Madigan, unpublished data). Ballistic eye armor, capable of blocking the force of a 22-caliber bullet from 20 feet, has been developed by the Army.[23] Typical refractive spectacles do not meet the required protection standards of the specially developed polycarbonate eye armor. Unfortunately, many of the soldiers with serious eye trauma were not wearing this eye armor, which may have prevented serious injury.

The Army fields 2 types of ballistic eyewear: SPECS (special purpose eyewear cylindrical system) and BLPS (ballistic laser protective spectacles). The SPECS is intended for soldiers who do not require prescription lenses. These wraparound lenses have ultraviolet and ballistic protection and include gray and clear interchangeable lenses for day and night operations. BLPS are fielded for soldiers requiring corrective lenses. The frame is designed to accommodate a specially manufactured prescription lens, which fits behind the protective lenses on the back of the BLPS frame. The logistical advantage of supplying the generic item to a prescription-free force is obvious: the emmetropic soldier who loses his or her gear would be able to easily replace the nonprescription SPECS with another pair without the requirement of personalized prescription lenses or lens inserts. An emmetropic soldier who can wear any targeting device when necessary and can wear an interchangeable SPECS is the soldier best prepared to operate on the modern battlefield.

Conclusions

The WRESP has provided excellent outcomes and enhanced the overall readiness of over 16 000 servicemen and servicewomen. The program has been enthusiastically received by soldiers who have had the procedures, as well as by unit commanders who recognize the positive impact on soldier readiness and morale. This is reflected in the positive responses on the postdeployment questionnaires in this report, and by anecdotal reports and word of mouth from soldiers who have been treated under the WRESP. Reports of LASIK flap dislocation, night vision difficulties, and dry eye are infrequent but merit further investigation to determine the impact on military operations.

A significant drawback to this retrospective review is the potential to try to extrapolate the results to the nonmilitary population. The fact that our soldiers are often younger, with lower refractive errors (soldiers are prevented from enlisting if they have myopia over −8.0 D), may affect clinical outcomes. In addition, the complications reported in the monthly WRESP summaries and adverse event reports may not be a true reflection of our complication rate. We have a rapidly mobile geographically diverse population who are at risk of becoming lost to follow-up, despite our best efforts. This is especially true in the current era of conflict. Even if seen by eye care providers after deployment, those results are not always reported back to the treating laser center. Furthermore, because Army policy was changed to allow enlistment after laser refractive surgery and to allow service members to obtain such surgery at their own expense at civilian centers, it is estimated that the number of service members who have undergone refractive eye surgery exceeds 50 000. It is obvious that neither the numerator nor the denominator is clearly established. Therefore, our findings may not generalize to the civilian practice setting. Nevertheless, because most patients do not deploy for the first 3 months postoperatively, the 3-month results should be reasonably accurate in describing outcomes and identifying early postoperative complications that occur during this period.

It is imperative that the WRESP be able to accurately track patients to analyze outcomes, complications, and adverse events. The Army has developed a database system for the WRESP over the past 2 years and has recently completed beta testing of a web-based version. This Refractive Surgery Information System will provide a complete database for all WRESP patients as well as an electronic record that will follow them throughout the Army. Only in this way can efficacy and safety be maximized so that Army ophthalmology can continue to provide the highest quality of care to the young men and women who give so much in the service of their country.

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US Army Refractive Surgery Questionnaire
for Soldiers Returned from Overseas Deployment

Thank you for your service to our country. You are one of a select few who have served under combat conditions in a harsh environment after refractive surgery. In an effort to understand issues surrounding use of this new technology to support our Army's individual and unit readiness we would appreciate your insights in the below questionnaire. Thank you for your assistance.

Initials_____ Rank:_____ MOS_____ Area Assigned (e.g. Iraq)_____

Unit Assigned to:_____Dates of Deployment(e.g. 3/03-9/03)_____

As a result of my refractive surgery I felt that my capabilities in the following areas were:
(please circle the appropriate
response to the right):

	Much worse		Neutral		Much Better
Over all individual readiness	1	2	3	4	5
Ability to contribute to my unit's mission	1	2	3	4	5
Ability to utilize night vision goggles/night operations	1	2	3	4	5
Weapons sighting ability	1	2	3	4	5
Ability to employ NBC equip & personal mask	1	2	3	4	5
Personal Hygiene	1	2	3	4	5
Ability to weather extreme environmental conditions (dust storms, high heat, cold, etc)	1	2	3	4	5
Frequency of sick call visits for eye complaints	1	2	3	4	5
Requirements for optical support in theater (replacement/repair of glasses, mask inserts)	1	2	3	4	5

If I had it to do over I would have the surgery?   YES   NO

If you participated in other deployments prior to this one (e.g. Desert Storm) BEFORE you underwent refractive surgery please complete the below:

Prior Deployment_____

As regards my visual capabilities and readiness:
This deployment, after refractive surgery,

compared to my prior deployment before	Much worse		Neutral		Much Better
surgery, was:	1	2	3	4	5

Comments:_____

Figure 1. United States Army refractive surgery questionnaire. MOS = military occupational skill; NBC = nuclear–biological–chemical.

Table 3. Army Warfighter Eye Refractive Surgery Program: Total Patients—May 2000 to October 2003

Service	FY 2000	FY 2001	FY 2002	FY 2003	Total
Army	600	2067	4720	7620	15 007
USAF	0	0	96	452	548
Navy	0	0	157	393	550
USMC	0	0	2	4	6
Total	600	2067	4975	8469	16 111

FY = fiscal year (October 1–September 30); USAF = United States Air Force; USMC = United States Marine Corps.

Table 5. Army Warfighter Eye Refractive Surgery Program Complications (Cumulative through September 30, 2003)

	Complication	n	%
PRK (n = 20 745)			
Intraoperative	None	5	0.02
Early postoperative	Sterile infiltrate (includes 1 ring infiltrate)	15	0.07
	Persistent epithelial defect (>1 wk)	52	0.25
	Recurrent corneal erosion	4	0.02
	Infectious keratitis	3	0.01
Late postoperative	Corneal haze (grade 2 or greater)	30	0.14
	Steroid responder	93	0.45
	Dry eye (requiring punctal plugs)	8	0.04
	Induced cylinder	6	0.03
	Corneal scar	2	0.01
	Loss of BSCVA of >1 line (from any cause)	9	0.04
LASEK (n = 2795)			
Intraoperative	Unable to complete flap—converted to PRK	2	0.07
Early postoperative	Delayed epithelial healing (>1 wk)	3	0.11
	Loss of flap	1	0.04
Late postoperative	Corneal haze (grade 2 or greater)	2	0.07
	Steroid responder	2	0.07
	Loss of BSCVA of >1 line (from any cause)	5	0.18
LASIK (n = 8528)			
Intraoperative	Refloat (slipped flap, macrostriae, significant debris)	12	0.14
	Epithelial defect	83	0.97
	Suction loss—free cap	3	0.04
	Suction loss—incomplete resection	13	0.15
Early postoperative	DLK (stages 1–2)	66	0.77
	DLK (stages 3–4)	2	0.02
	Dry eye (requiring punctal plugs)	21	0.25
	Epithelial defect/recurrent erosion	7	0.08
	Flap striae (loss of BSCVA or requiring refloat)	10	0.12
	Interface debris (loss of BSCVA or requiring refloat)	4	0.05
	Corneal infiltrate	3	0.04
	Flap dislocation (all postoperative day 1)	2	0.02
Late postoperative	Corneal haze	2	0.02
	Induced astigmatism	4	0.05
	Glare/night vision difficulty	2	0.02
	Epithelial ingrowth (loss of BSCVA or requiring refloat)	21	0.25
	Iritis	1	0.01
	Traumatic flap dislocations (after first 24 hrs postoperatively)	10	0.12
	Loss of BSCVA of >1 line (from any cause)	6	0.07

BSCVA = best spectacle-corrected visual acuity; DLK = diffuse lamellar keratitis; LASEK = laser epithelial keratomileusis; PRK = photorefractive keratectomy.

malities were found. Her fundus appearance and renal abnormality led us to examine her parents. Both had normal fundus and no renal abnormalities.

After obtaining informed consent, molecular genetic analysis of the PAX2 gene by direct sequencing of all coding regions revealed a heterozygous insertion of a G at position 619 (Figure 2). This substitution was not detected in the parents or 42 healthy volunteers, suggesting that this was a de novo mutation.

The atypical coloboma in our patient is apparently different from a typical optic nerve head "coloboma" that results from defective closure of the embryonic fissure in the inferior part of the optic disk. This is consistent with a recent report that PAX2 is expressed in all cells of the optic stalk of developing mice.[2] We thus hypothesize that an abnormal development of the optic stalk led to the abnormal optic nerve head seen in congenital optic nerve anomalies caused by mutations in PAX2. Therefore, this is a dysplastic rather than a typical colobomatous disk, and "papillorenal syndrome" may be a more appropriate designation for the PAX2-associated optic disk anomaly.[3,4] Our findings suggest that we should consider renal abnormalities whenever an atypical round coloboma is observed, even if the patient has normal blood chemistry and urinalysis.

Our study combined with other studies confirmed that exon 2 of PAX2, especially a sequence of seven Gs in the exon, may be particularly prone to mutations.[5] This would suggest that a common mutational mechanism may be involved, such as slippage during DNA replication, irrespective of the race. The presence of a mutational hot spot would also suggest the diagnostic value of PAX2 gene. Molecular analysis of PAX2, especially exon 2 in combination with renal ultrasonography, may help in an earlier diagnosis at an early stage of the disease.

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Comparison of Two Techniques of Marking the Horizontal Axis During Excimer Laser Keratorefractive Surgery for Myopic Astigmatism

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PURPOSE: To compare two methods of limbal marking used during laser refractive surgery for myopic astigmatism.
DESIGN: Retrospective chart review.
METHODS: Forty-two eyes of 42 patients who underwent photorefractive keratectomy (PRK) or laser-assisted in-situ keratomileusis (LASIK) for myopic astigmatism were marked preoperatively to identify the horizontal axis. In 18 eyes, marks were placed at the slit lamp (SL) with the slit beam set at 180 degrees as a reference. In 24 eyes, marks were placed in the laser room (LR) immediately before reclining under the laser. All treatments were performed with the Alcon LADARVision excimer laser system. Vector analysis of postoperative cylinder and reduction in cylinder and uncorrected and best-corrected visual acuity were evaluated for both groups.
RESULTS: The mean postoperative magnitude of error was −0.19 ± 0.44 diopters for the LR group and −0.09 ± 0.42 diopters for the SL group (P = .439, NS). Both groups had a mean angle of error indicating an overall counterclockwise rotation of axis with an angle of error of 6.3 ± 8.7 degrees for the LR group and 8.0 ± 10.2 degrees for the SL group (P = .562, NS).
CONCLUSIONS: We found no significant difference in outcomes with an overall trend toward undercorrection of cylinder in both groups, leaving room for improvement after refractive surgery for myopic astigmatism (Am J Ophthalmol 2005;139:735–737. © 2005 by Elsevier Inc. All rights reserved.)

AXIAL MISALIGNMENT MAY RESULT IN RESIDUAL ASTIGmatism after excimer laser keratorefractive surgery.[1–3] Misalignment by 15 degrees reduces efficacy, as measured by the flattening index, by 14%. A 50% reduction occurs with a misalignment of 30 degrees. The magnitude of postoperative astigmatism, however, is increased by 14% with an angle of error of only 4 degrees and by 50% with a 15-degree angle of error.[4] Limbal marking has been shown to improve surgical outcomes for 1.25 diopters of

	Refractive Data*			Corneal Data*		
	Laser Room n = 24	Slit Lamp n = 18	P value†	Laser Room n = 20	Slit Lamp n = 11	P value†
Magnitude of error (D)	−0.19 ± 0.44	−0.09 ± 0.42	.439	−0.42 ± 0.64	−0.66 ± 0.45	.235
Range	−1.22 to 0.61	−1.00 to 0.70		−1.66 to 0.97	−1.20 to 0.09	
Angle of error, arithmetic (degrees)	−0.36 ± 10.8	3.2 ± 12.7	.346	3.4 ± 25.6	9.6 ± 17.8	.433
Range	−28 to 33	−10 to 35		−15 to 88	0 to 56	
Angle of error, absolute (degrees)	6.3 ± 8.7	8 ± 10.2	.562	15.5 ± 20.4	12.5 ± 15.7	.652
Range	0 to 33	0 to 36		0 to 88	0 to 56	
Correction index (geometric)	1.20 ± 0.81	1.22 ± 1.0	.659	1.13 ± 1.65	0.57 ± 1.60	.316
Range	0.65 to 4.00	0.47 to 3.9		0.31 to 6.38	0.16 to 6.15	
Astigmatism corrected (%)	120 ± 81	122 ± 95		113 ± 165	57 ± 160	
Index of success (geometric)	0.07 ± 0.68	0.14 ± 0.91	.487	0.26 ± 1.37	1.27 ± 1.96	.898
Range	0 to 2.64	0 to 3.05		0.26 to 5.28	0.29 to 7.15	
Success of surgery (%)	93 ± 68	86 ± 91		74 ± 137	27 ± 196	
Flattening effect (D)	1.23 ± 1.02	1.02 ± 0.95	.488	0.75 ± 0.66	0.93 ± 0.79	.546
Flattening index	0.73 ± 0.56	0.76 ± 0.61	.863	0.53 ± 0.82	0.46 ± 0.37	.743

*Reported as means ± SD.
†Two-tailed t test.

astigmatism or greater.[2] We evaluated whether marking at the slit lamp (SL) or at the laser room (LR) bedside resulted in better outcomes in terms of postoperative astigmatism.

A retrospective chart review was conducted on patients who underwent laser-assisted in-situ keratomileusis (LASIK) or photorefractive keratectomy (PRK) at Walter Reed Army Medical Center between May and November 2002. Patients were included who had preoperative astigmatism ≥0.75 diopters, whose marking method was known, and who had at least 3 months follow-up. All treatments were performed with the LADARVision excimer laser system (Alcon Surgical, Fort Worth, Texas, USA). Nasal-hinged LASIK flaps were created using the Amadeus microkeratome (AMO Surgical, Irvine, California). Pre- and postoperative uncorrected and best-corrected visual acuity, manifest refraction, and keratometry were recorded for right eyes only, except for three patients who underwent treatment on the left eye only. Forty-two eyes (39 right, 3 left) were included in the final analysis. The SL group consisted of 18 eyes (15 LASIK, 3 PRK), and the LR group consisted of 24 eyes (21 LASIK, 3 PRK).

Vector analysis of refractive (corneal plane) and topographical astigmatism was conducted using the Alpins method.[5] Magnitude of error, angle of error, correction index, and index of success were calculated using the surgically induced astigmatism and targeted induced astigmatism. Aggregate data analysis was done using the means of the Cartesian coordinates, which were then converted back to the polar coordinates. Within-subject and between-group differences were assessed using the unpaired t test, and a P value <.05 was considered statistically significant. Results are summarized in Tables 1 and 2.

TABLE 2. Visual Acuity and Preoperative and Residual Refractive Cylinder After Myopic Excimer Laser Keratorefractive Surgery (All Eyes)

	Laser Room Group n = 24	Slit-lamp Group n = 18
Preoperative cylinder, n (%)		
0.50–1.00 D	9 (38)	8 (44)
1.25–2.00 D	9 (38)	7 (39)
≥ 2.25 D	6 (25)	3 (17)
Residual cylinder, n (%)		
0 to 0.25 D	7 (29)	8 (44)
0.50 D	13 (54)	4 (22)
0.75 D	2 (8)	4 (22)
≥ 1.00 D	2 (8)	2 (11)
Uncorrected visual acuity, n (%)		
≥ 20/40	22 (92)	16 (89)
≥ 20/25	17 (71)	16 (89)
≥ 20/20	15 (63)	14 (78)
Best-corrected visual acuity, n (%)		
Loss of ≥ 2 lines	0 (0)	0 (0)
Loss of 1 line	6 (25)	1 (6)
No change in lines	16 (67)	15 (83)
Gain of 1 line	2 (8)	2 (11)

D = diopter.

We found no significant difference between the SL and LR groups. Refractive analysis of both yielded a correction index indicating a slight overcorrection of astigmatism and an index of success demonstrating close to 100% success. The mean magnitude of error of both groups was small,

indicating that the majority of the error in treating the astigmatism was due to axis error. There was no significant difference in the degree of axis error between the two groups.

Our data suggest that marking the horizontal axis with or without the slit lamp leads to comparable results. The study was a retrospective, noncontrolled study with data for a limited number of eyes; a larger study population may have uncovered a significant difference between the two groups. In the future, limbal marking may be unnecessary, as image recognition technology is used to align treatments. This is increasingly important with wavefront-guided treatments that aim to correct higher-order aberrations that are axis dependent, such as coma and trefoil.

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Induction of Apoptosis in Rat Retinal Cell Cultures by Partially Fluorinated Alkanes

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PURPOSE: To test whether the partially fluorinated alkanes (PFAs) perfluorobutylbutane (O_{44}), perfluorohexylethan (O_{62}), and the oligomer OL_{62HV}, recently proposed as artificial vitreous replacements (AVRs), have pro-apoptotic effect in rat retinal cultures.
DESIGN: Laboratory investigation.

METHODS: Rat retinal cell cultures were seeded onto microporous inserts to study AVR-cell interaction without impairing cell survival. Cells were treated for 24 hours with O_{62}, O_{44}, and OL_{62HV}. Apoptosis was analyzed by transferase-mediated dUTP-biotin nick end-labeling assay and Hoechst stain.
RESULTS: O_{44} and O_{62} did not affect structural organization and cell survival in retinal cell cultures; however, OL_{62HV} induced increased apoptosis compared with control cultures.
CONCLUSIONS: OL_{62HV}, a high-viscosity PFA, induces severe retinal damage in human eyes, although it successfully passed animal experimentation. Our in vitro study showed a remarkable pro-apoptotic effect of OL_{62HV} and suggests that in vitro tests can contribute to AVR biocompatibility assessment. (Am J Ophthalmol 2005;139:737-739. © 2005 by Elsevier Inc. All rights reserved.)

ARTIFICIAL VITREOUS REPLACEMENTS (AVRS) ARE USED during vitreoretinal surgery as a mechanical tamponade to improve retinal reattachment. A new generation of compounds, partially fluorinated alkanes (PFAs), such as perfluorohexyloctane (F_6H_8), perfluorobutylbutane (O_{44}), and perfluorohexylethan (O_{62}), have recently been introduced with the aim of improving long-term intraocular compatibility because of their lower specific gravity.[1,2] To decrease emulsification of PFA monomers, an event that may severely impair visual acuity in long-term replacement, a fluorocarbon oligomer with increased viscosity, OL_{62HV}, has been developed.[2] Although it was well tolerated in rabbit eyes,[2] its clinical application led to inflammatory reactions and retinal damage.[3]

In this study, we have analyzed the effects of OL_{62HV} in rat primary retinal cell cultures to ascertain whether in vitro testing may reveal adverse cellular reactions to the material.

Retinal cell cultures were obtained from rat embryos, as already described.[4,5] Animal handling was performed at the Istituto Superiore di Sanità, Rome, Italy, in accordance with the European Community Council Directive (86/609/EEC). Briefly, after dissociation, cells were suspended in Minimum Essential Medium (MEM, Invitrogen, Milan, Italy) with 10% fetal calf serum and seeded onto poly-L-lysine-coated Falcon cell culture inserts, with microporous cyclopore bottom (Becton-Dickinson, Franklin Lakes, New Jersey). The inserts were then transferred to standard 25-mm wells containing the same medium. The microporous substrate allowed the cell layer to be in contact with the material to be tested at the apical side and with the medium, at the basal side. At 9-day in vitro, the medium on top of the cells was replaced by O_{44}, O_{62}, OL_{62HV} or fresh medium. After 24 hours, apoptotic nuclei were identified by the terminal transferase-mediated dUTP-biotin nick end-labeling (TUNEL) assay (DeadEnd kit, Promega, Madison, Wisconsin, USA), with hematox-

The Effect of Fourth-Generation Fluoroquinolones Gatifloxacin and Moxifloxacin on Epithelial Healing Following Photorefractive Keratectomy

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• PURPOSE: To compare the rate of epithelial healing following photorefractive keratectomy (PRK) with two commercially available fourth-generation fluoroquinolones, gatifloxacin (Zymar, Allergan, Irvine, California) and moxifloxacin (Vigamox, Alcon Laboratories, Fort Worth, Texas).

• DESIGN: Double-masked, randomized, prospective trial.

• METHODS: Thirty-five subjects received gatifloxacin in one eye and moxifloxacin in the fellow eye following PRK with a 9.0-mm epithelial defect. Patients were examined daily after surgery until the epithelium had healed completely in both eyes. Beginning on postoperative day 3, photos were taken and used to confirm epithelial healing or measure the area of residual epithelial defects. Healing times and defect sizes were compared using the Wilcoxon signed-ranks test.

• RESULTS: Both eyes healed on the same day in 18 of the 35 subjects (51.4%). In 13 of 35 (37.1%) subjects, the moxifloxacin-treated eye healed first, compared with only four of 35 (11.4%) subjects whose gatifloxacin-treated eye healed first. All six of the eyes that took 2 days longer than their fellow eye to heal were gatifloxacin-treated. Median healing time for both groups was 4 days (moxifloxacin range: 3 to 7 days; gatifloxacin range: 3 to 9 days; $P = .01$), but only 69% of gatifloxacin-treated eyes had healed by day 4 compared with 80% of the moxifloxacin-treated eyes. Overall, on each postoperative day, defect sizes were greater for the gatifloxa-cin-treated eyes. This difference was statistically significant on day 4 ($P = .027$).

• CONCLUSIONS: Eyes treated with moxifloxacin healed faster and had smaller defects compared with those treated with gatifloxacin. This provides another factor to consider in selecting antibiotic prophylaxis for corneal refractive surgery. (Am J Ophthalmol 2005;140: 83–87. © 2005 by Elsevier Inc. All rights reserved.)

P ROPHYLACTIC ANTIBIOTIC DROPS ARE ROUTINELY used after ocular surgery to prevent post-operative infections. Fluoroquinolones in particular have been useful in covering many of the bacterial pathogens that are responsible for infections after intraocular procedures such as cataract, glaucoma, and corneal surgery.

Two fourth-generation fluoroquinolones approved for ophthalmic use in the United States, gatifloxacin 0.3% ophthalmic solution (Zymar, Allergan, Irvine, California) and moxifloxacin 0.5% topical ophthalmic solution (Vigamox, Alcon Laboratories, Fort Worth, Texas), are frequently used for prophylaxis following laser keratorefractive surgery. Selection of the most appropriate antibiotic is often based on considerations such as spectrum of microbial coverage, bioavailability, ocular tolerance, and cost. When there is no clear evidence to support the superiority of one drug over another in these respects, additional factors may be considered. In the case of the fourth-generation fluoroquinolones, subtle differences in the mechanism of action, concentration, vehicle, pH, solubility, and preservative of each compound may lead to a potential difference in their effect on epithelial healing. Such a difference would have important implications on the selection of antibiotic prophylaxis for photorefractive keratectomy (PRK). Faster epithelial healing speeds visual recovery, allows patients to return to work and other daily activities sooner, and decreases the risk of adverse events.

In this study, we performed a prospective within-subject comparison of the rate of epithelial healing between gatifloxacin and moxifloxacin following PRK.

SUBJECTS AND METHODS

THIS PROSPECTIVE, RANDOMIZED, DOUBLE-MASKED STUDY was conducted at the Center for Refractive Surgery, Walter Reed Army Medical Center, Washington, DC, between June and September 2004. All subjects were aged 21 years or older with a manifest spherical equivalent (MSE) of less than −6.00 diopters and astigmatism of less than 3 diopters. All participants demonstrated refractive stability over at least 12 months (no more than 0.5 diopters change in either spherical or cylindrical portion of the manifest refraction) and had a best spectacle-corrected visual acuity of 20/20 or better. Subjects were excluded for current or prior eye disease or eye surgery, pregnancy, flight status, or any medical problems precluding refractive surgery. Subjects were specifically excluded who had dry eyes, ocular surface disease, epithelial basement membrane dystrophy, or a history of recurrent corneal erosions. The study protocol was approved by the Internal Review Board/Human Use Committee, Department of Clinical Investigation, Walter Reed Army Medical Center. All subjects enrolled into the study voluntarily agreed to participate and gave written informed consent.

Subjects were randomized into one of two groups. After surgery, group A used moxifloxacin in the right eye and gatifloxacin in the left. Group B used gatifloxacin in the right eye and moxifloxacin in the left. The bottles were masked and marked only as "right eye" and "left eye." This allowed an analysis of both intersubject and intrasubject differences.

All subjects had PRK performed bilaterally on the same day using the LADARVision excimer laser system (Alcon Surgical, Fort Worth, Texas) with Jupiter 2 5.11 software. A 9.0-mm LASEK trephine was used to mark the cornea and incise the epithelium. Chemical cleavage of the epithelium was performed using an alcohol 20% solution for 25 seconds in a 9.5-mm well. The alcohol was irrigated from the surface of the cornea, and the epithelium was removed using a micro-hoe or Merocel sponge. The dimensions of the defect were measured digitally on the LADARVision treatment screen and recorded in the brief operative note. Immediately after laser ablation was completed, topical antibiotic drops were given and a therapeutic bandage contact lens (Proclear compatibles, Cooper Vision, Norfolk, Virginia; BC 8.6, DIA 14.2, PWR +0.50) was applied to the ablated surface for all patients. Patients used the topical antibiotic four times daily for 1 week or until the epithelial defect had healed. In addition, all patients were instructed to use fluorometholone 0.1% ophthalmic suspension (FML, Allergan) four times daily; non-preserved carboxymethylcellulose sodium 0.5% (Re-
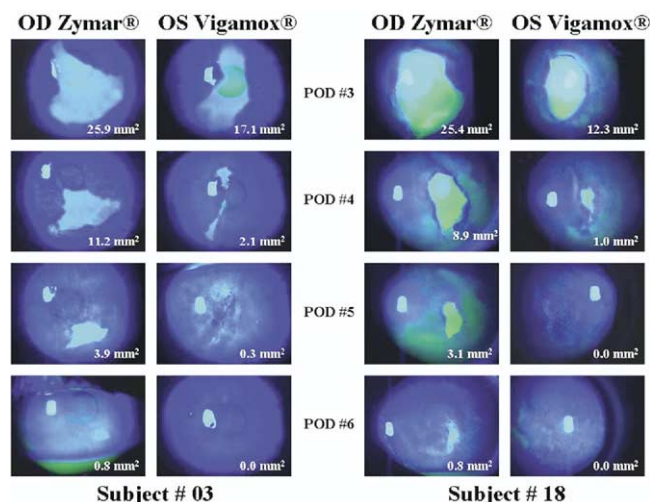

FIGURE 1. Epithelial defect size on post-operative days 3 to 6 in two study participants. Slit-lamp photographs were taken with Cobalt blue filter after instillation of topical fluorescein drops (original magnification ×16). The photographs on the left represent a patient whose moxifloxacin-treated eye healed on day 6 and whose gatifloxacin-treated eye healed on day 7. This subject also had a peripheral corneal infiltrate on post-operative day 4. The photographs on the right represent a patient whose moxifloxacin-treated eye healed on post-operative day 5 and whose gatifloxacin-treated eye healed on day 7. Calculated surface area of epithelial defects is shown at bottom right of each photograph.

fresh Plus, Allergan) every 2 hours while awake for the first 72 hours, then four times daily until complete epithelialization, then four times daily as needed; and diclofenac 0.1% ophthalmic solution (Voltaren, Novartis Ophthalmics, Duluth, Georgia) up to four times daily as needed for pain for the first 48 hours post-operatively.

Post-operatively, patients were examined daily until the epithelium was healed completely in both eyes. The primary outcome measure was epithelial healing time. Specifically, we compared the time in days to complete epithelial healing between the eyes of a same subject. We considered significant a difference of 1 day or more between eyes. Secondary outcome measures included size of defects, subjective complaints, adverse events, and visual outcomes. The size of the defect was measured through the contact lens at the slit lamp on post-operative days 1 and 2. On post-operative day 3, the bandage contact lens was removed and the epithelial defect measured at the slit lamp. Topical fluorescein sodium 2.5% was instilled and the eye examined; photographs were taken and used to document the area of any remaining defects. Images were viewed in Adobe Photoshop 7.0 and the surface area of the remaining defect calculated (Figure 1). If a significant epithelial defect was present, a new bandage contact lens was placed. Subjective complaints of pain, foreign body sensation, photophobia, tearing, stinging with the antibiotics, and quality of vision were assessed using a 10-point
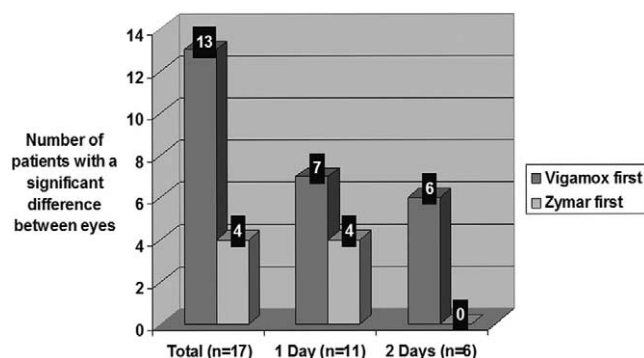
FIGURE 2. Within-subject difference in epithelial healing following photorefractive keratectomy. Graph illustrates which eye healed first in those subjects whose eyes did not heal on the same day. This graph shows the total number of subjects with a difference in healing time and breaks those results down into those with 1- and 2-day differences.

scale and were recorded. Neither the patients nor the examiners were aware of which antibiotics the patients received in which eye.

Results were recorded in an Excel spreadsheet for analysis. Data were analyzed using the Wilcoxon signed-rank test. A *P* value of less than .05 was considered statistically significant.

RESULTS

FORTY SUBJECTS WERE ENROLLED IN THE STUDY. FIVE SUB-jects withdrew from the study: three subjects were excluded before treatment because of abnormal pre-operative corneal topography, one subject withdrew before treatment when it was determined he would be unable to participate in the follow-up schedule, and one subject underwent treatment but withdrew from the study after having general anesthesia for unrelated surgery several days after her PRK. Data from the 35 remaining subjects were analyzed. Twenty-two men and 18 women, aged 21 to 47 years, completed the study. Pre-operative refractive error ranged from −1.00 to −5.75 diopters. The mean MSE was −2.82 ± 1.24 for moxifloxacin eyes and −2.76 ± 1.35 for gatifloxacin eyes (*P* = .551, ns).

Both eyes healed on the same day in 18 of the 35 subjects (51.4%). In the majority of the remaining 17 subjects, however, the moxifloxacin-treated eye healed first. Moreover, all six of the eyes that took 2 days longer than their fellow eye to heal were gatifloxacin-treated (Figure 2). Although median healing time for both groups was 4 days (moxifloxacin range: 3 to 7 days, gatifloxacin range: 3 to 9 days, *P* = .01; Table 1), only 69% of gatifloxacin-treated eyes had healed by day 4 compared with 80% of the moxifloxacin-treated eyes (Table 2). Successful removal of the bandage contact lens was accomplished earlier (*P* = .042) in the moxifloxacin group

(median: 3, range: 3 to 7) than the gatifloxacin group (median: 4, range 3 to 9).

Overall, on each post-operative day, defect sizes were greater for the gatifloxacin-treated eyes. This difference was statistically significant on day 4 (*P* = .027), and a similar trend was seen on day 5 (*P* = .055). Figure 1 shows photographs taken of two subjects that illustrate the difference in defect sizes.

There was no significant difference in subjective symptoms between the moxifloxacin- and gatifloxacin-treated eyes. One gatifloxacin-treated eye developed peripheral corneal infiltrates on post-operative day 4 that resolved after removal of the bandage contact lens (Figure 3). There were no significant adverse effects reported in the moxifloxacin-treated eyes. All subjects were seen for 1-month follow-up at which time no eye had lost more than 1 line of best-corrected visual acuity. Best-corrected visual acuity was comparable for both the moxifloxacin and gatifloxacin-treated eyes, −0.06 and −0.07 logarithm of the minimum angle of resolution (logMAR), respectively (*P* = .695, ns).

DISCUSSION

CORNEAL REFRACTIVE SURGERY HAS BECOME ONE OF THE most frequently performed ophthalmic procedures. Although laser-assisted in-situ keratomileusis is by far the most common procedure, surface ablations are indicated in patients with thin corneas, epithelial basement membrane dystrophy, or recreational or occupational activities that significantly increase the risk of trauma. In the U.S. Army refractive surgery program, PRK constitutes more than 70% of laser refractive procedures.[1] Bacterial keratitis is the most serious and potentially devastating complication of PRK,[2,3] and prophylactic antibiotics are initiated immediately following surgery and continued until epithelial healing is complete to reduce the risk. Fluoroquinolones, with excellent broad-spectrum coverage and good ocular tolerance, have been frequently used for this purpose.

Two newer fourth-generation fluoroquinolones, gatifloxacin (Zymar) and moxifloxacin (Vigamox), have distinct advantages over their predecessors.[4–8] The latter have gaps in coverage, particularly against α-hemolytic *Streptococcus* and some *Staphylococcal* species. This is potentially significant, given that gram-positive organisms are the most common cause of bacterial infections following PRK.[2] *Staphylococcus aureus*, *Streptococcus viridans* and *Streptococcus pneumonia* have been shown to be more susceptible to gatifloxacin and moxifloxacin than to ciprofloxacin, levofloxacin, and ofloxacin.[8] Although current literature has documented developing resistance to the ciprofloxacin, levofloxacin, and ofloxacin,[4–6] emerging antibiotic resistance has not yet been a major problem with the fourth-generation fluoroquinolones. Furthermore, these agents are more effective than earlier generations

TABLE 1. Healing Times and Defect Sizes for Vigamox- and Zymar-Treated Eyes

	Mean ± SD Vigamox	Mean ± SD Zymar	Median (range) Vigamox	Median (range) Zymar	Significance P Value*
Healing time (d)	3.9 ± 1.0	4.3 ± 1.5	4 (3–7)	4 (3–9)	.010
Contact lens out (d)	3.8 ± 1.0	4.1 ± 1.4	3 (3–7)	4 (3–9)	.042
Defect size (mm)					
POD 3	5.0 ± 8.9	6.9 ± 9.9	0.6 (0–43.5)	0.6 (0–30.5)	.233
POD 4	1.4 ± 5.1	3.1 ± 6.9	0.0 (0–27.8)	0.0 (0–30.2)	.027
POD 5	0.5 ± 2.4	1.1 ± 3.3	0.0 (0–13.6)	0.0 (0–18.2)	.055
POD 6	0.1 ± 0.6	0.4 ± 1.7	0.0 (0–3.4)	0.0 (0–10.2)	.250

POD = Postoperative day.
*Wilcoxon signed-ranks test.

TABLE 2. Eyes Showing Complete Epithelial Healing on Each Post-operative Day (POD) Following Photorefractive Keratectomy

Healed by POD	Vigamox (n = 35)		Zymar (n = 35)	
	n	%	n	%
3	14	40.0	13	37.1
4	28	80.0	24	68.6
5	32	91.4	26	74.3
6	34	97.1	32	91.4
7	35	100.0	34	97.1
8	35	100.0	34	97.1
9	35	100.0	35	100.0

FIGURE 3. Peripheral corneal infiltrate following photorefractive keratectomy. Slit-lamp biomicroscope photograph (original magnification ×16) of peripheral corneal infiltrate (arrows) seen in a gatifloxacin-treated eye on post-operative day 4. This is the right eye of Subject 3 shown in Figure 1. The infiltrate was asymptomatic, peripheral, under intact epithelium, and was out of the treatment zone. It was felt to be sterile and resolved after removal of the bandage contact lens and increasing the topical corticosteroids.

against atypical mycobacteria, an important pathogen following refractive surgery.

Fluoroquinolones work by inhibiting topoisomerase II (DNA gyrase) and topoisomerase IV, thereby inhibiting the ability of the bacteria to replicate.[9] The mechanism of action that provides the fluoroquinolones their antibacterial efficacy may delay the healing process, increasing the risk of infection and other complications, particularly haze and scarring, that may have a negative effect on visual outcome.[10]

Previous studies evaluated epithelial healing with second- and third-generation fluoroquinolones. Patel and associates[10] compared epithelial healing rates of ciprofloxacin versus ofloxacin and found that eyes treated with ofloxacin healed significantly faster than those treated with ciprofloxacin. Moreira and associates[11] compared the healing of rabbit corneas treated with ciprofloxacin and ofloxacin to a control group who only received artificial tears. They reported a significantly delayed healing time with both fluoroquinolones relative to the control group, but no difference between the two antibiotics.

Laboratory studies on epithelial healing with fourth-generation fluoroquinolones have so far produced mixed results. An in vivo rabbit epithelial cell culture model, (Matsumoto and associates abstract, presented at Ameri-

can College of Toxicology Meeting, October, 2003) demonstrated less inhibition of epithelial cell migration with gatifloxacin than with moxifloxacin. However, the fluoroquinolones used in that study were not the commercially available preparations, but rather 0.2 to 1.0 mmol/l solutions. Another study compared moxifloxacin and gatifloxacin, (J. Gao and associates unpublished data, 2004) and the rate of epithelial healing in rabbit corneas after anterior keratectomy. In that study gatifloxacin did not affect the rate of epithelial healing, whereas moxifloxacin-treated corneas demonstrated a delay in healing as well as decreased collagen IV expression. Conversely, (R.W. Yee and associates "Wound healing and the importance of proper selection of an antibacterial prophylaxis agent," Refractive Eyecare for Ophthalmologists, 2003) another

found that moxifloxacin was less toxic to corneal epithelium than gatifloxacin, levofloxacin, and ofloxacin in vitro using human corneal epithelial cells. The same investigators also studied wound healing following PRK on chicken eyes and found that both gatifloxacin and moxifloxacin demonstrated faster rates of healing than levofloxacin.

In light of the conflicting laboratory evidence, we conducted a prospective randomized clinical trial to evaluate the effect of commercially available fourth-generation fluoroquinolones on epithelial healing after PRK. The results of our study demonstrate faster epithelial healing with moxifloxacin than with gatifloxacin. Overall, moxifloxacin-treated eyes healed first and had smaller defects than gatifloxacin-treated eyes. For those subjects in whom there was a day or more difference in time to complete re-epithelialization, the faster healing eye was three times more likely to be moxifloxacin treated, and all six patients who had a 2-day difference healed faster in the moxifloxacin-treated eye. Moreover, the therapeutic bandage contact lens was removed earlier in the moxifloxacin-treated eyes.

This study was designed to provide a within-subject comparison where the only difference was the antibiotic used perioperatively. Gatifloxacin and moxifloxacin differ in several key points that may contribute to the effect on epithelial healing. Gatifloxacin comes as a 0.3% solution whereas moxifloxacin is formulated as a 0.5% solution. The pH of moxifloxacin is 6.8, whereas gatifloxacin is prepared at a pH of 6.0. Because of this, moxifloxacin is more soluble than gatifloxacin at tear pH, which is normally approximately 7.5 but can increase during an infection as a result of phagocytosis. As the pH rises, the antibiotics become less soluble and can form precipitates on the corneal surface.[12] Previous studies of ciprofloxacin, the least soluble of the commercially available fluoroquinolones, demonstrated that precipitation of the antibiotic in an epithelial defect might delay corneal re-epithelialization by blocking epithelial migration or inhibiting re-generation.[10,12] We did not observe precipitates on the contact lens or cornea of any eye in this study, so this does not explain the difference in epithelial healing.

Another key difference between the two formulations is the use of preservative. Gatifloxacin is preserved with benzalkonium chloride (BAK) 0.005%, whereas moxifloxacin is preservative-free. Preservatives can have an adverse effect on epithelial stability, and several studies report a delay in epithelial healing with drops containing BAK.[13,14] However, Collin and Grabsch[15] found that BAK 0.01% had no effect on the rate of corneal re-epithelialization following keratectomy.

Although it is not clear which of these or other possible factors play the critical role in epithelial healing, our study suggests that moxifloxacin has a more favorable epithelial healing profile in a clinical post-PRK setting. It remains to be determined whether this difference in epithelial healing time is associated with important differences in visual outcomes. In the meantime, this epithelial healing study provides another factor to consider in selecting antibiotic prophylaxis for corneal refractive surgery.

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Scattered laser radiation and broadband actinic ultraviolet plasma emissions during LADARVision excimer refractive surgery

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PURPOSE: To evaluate the potential occupational health hazards associated with scattered actinic ultraviolet (UV) laser radiation and broadband actinic UV plasma emissions during refractive surgery.

SETTING: Center for Refractive Surgery, Walter Reed Army Medical Center, Washington, D.C., USA.

METHODS: Intraoperative radiometric measurements were made with the Ophir Power/Energy Meter (LaserStar Model with silicon detector, Model PD-10) and the International Light Radiometer/Photometer (Model IL 1400 with actinic ultraviolet detector, Model SEL240) with and without UV blocking filters (BLK 270 and Schott types WG-280 and WG-230). Measurements made during laser calibration as well as laser in situ keratomileusis (LASIK) and photorefractive keratectomy (PRK) procedures were evaluated using a worst-case scenario and then compared with the American Conference of Governmental Industrial Hygeinists (ACGIH) Threshold Value Limits (TLV) to perform a risk/hazard analysis.

RESULTS: Most optical emissions were between 193 nm and 280 nm, and approximately 25% of the measurement result was due to broadband emissions greater than 270 nm for calibration targets. About 25% of optical emissions during LASIK were beyond 230 nm. No emissions beyond 230 nm were observed during PRK. Ultraviolet scattered radiation level was similar between PRK and LASIK. Maximum measured values of 80 nJ/pulse at 14 cm for PRK and 45 nJ/pulse at 38 cm for LASIK were used as the absolute worst-case analysis for exposure. Assuming the worst-case exposure conditions are equal to the maximum measured value during these studies at a workload of 20 patients per day, the cumulative occupational exposure at close range of actinic UV radiation did not exceed the 8-hour occupational exposure limit of 3 mJ/cm^2 for any 24-hour period.

CONCLUSIONS: Scattered UV laser radiation did not exceed occupational exposure limits at distances greater than 30 cm from either laser calibration targets or patient treatments over a workday. Laser eye protection is not necessary to protect operating room personnel since exposure levels are very low even under a worst-case scenario.

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Photorefractive keratectomy (PRK) and laser in situ keratomileusis (LASIK) using an excimer laser operating at a wavelength of 193 nm have proven safe and effective surgical alternatives to glasses and contact lenses.[1–3] Since the U.S. Food and Drug Administration (FDA) approved the first excimer laser for refractive surgery in 1995, laser keratorefractive surgery has become 1 of the most commonly performed surgeries in the world. Laser eye surgery has been performed on more than 6 million people worldwide, and almost 1.5 million people in the United States are expected to have laser eye surgery in the coming year (Croes K. "Market Watch Optical Sector Report."

Optistock 2003 <http://www.optistock.com/>). Although operating room personnel may be exposed to scattered ultraviolet (UV) radiation during procedures, the scattered UV levels are assumed to be at a very low level. Limited guidance on laser eye protection for this application is available from the current American National Standards Institute (ANSI) Z136.3 Standard for the Safe Use of Lasers in the Health-Care Environment, which recommends that laser eye protection be worn within the nominal hazard zone (where the applicable maximum permissible exposure [MPE] is exceeded).[4] The purpose of this study was to evaluate the potential occupational health

hazards associated with scattered UV laser radiation and broadband UV plasma emissions during refractive surgery.

MATERIALS AND METHODS

Surgical procedures included both PRK and LASIK. Measurements were made during the calibration steps in preparation for surgery and intraoperatively during both LASIK and PRK procedures.

Three calibration steps were performed using 2 types of target material before each laser refractive surgery. These procedures are referred to as "configure laser," "volume per shot," and "square PTK." The configure laser procedure determines whether the laser energy is within the acceptable range of 2.4 to 3.0 mJ. Volume per shot calibrates the volume of corneal material removed with each shot of the laser. This should be within the range of 400 micro mm^3 to 600 micro mm^3. The square PTK procedure is performed to ensure uniformity in the transmission of the excimer optics. Black test paper is used for a test ablation. Variations in the tone of the ablation (shadows or dark spots) indicated nonuniformity (LADARVision 4000 Surgeon and Operator Training, 7204-0079 Rev. A, Alcon Laboratories).

For the LASIK procedures, UV measurements were taken during ablation after a nasally hinged flap was cut with an Amadeus microkeratome (Allergan Surgical). For the PRK procedures, UV measurements were made during ablation after the epithelium was removed with the Amoils epithelial scrubber (Innovative Excimer Solutions, Inc.). Because there is no laser scrape for epithelial removal on the LADARVision system, no measurements were possible in these modes.

Measurements were made with the following instruments: (1) Ophir Power/Energy Meter, Model LaserStar, Serial Number (SN) 81514, with silicon detector, Model PD-10, SN110053 and SN 130279. The PD-10 detector is spectrally calibrated beyond 200 nm, and a measurement at 193 nm requires multiplication by a correction factor of 1.2. (2) International Light Radiometer/Photometer, Model IL 1400, SN 1466 with actinic UV detector, Model SEL240, SN 3760. Three UV-blocking filters were used, BLK 270 and Schott types WG-280 and WG-230.

Prior to UV measurements were taken, the distance from the laser and the angle from the axis of the laser were measured and recorded. The UV measurements were then taken at that precise location during the photoablation and recorded.

The data were analyzed assuming the worst-case exposure conditions. The highest measured exposure per pulse was used to determine the exposure per pulse at the closest distance the operating room personnel would likely be to the laser. The total daily exposure was calculated using the mean pulses per eye and the number of eyes treated on a busy day.

RESULTS

A table of radiometric abbreviations used in this report is given in Appendix A.

Nineteen calibration procedures, 7 LASIK procedures, and 8 PRK procedures were recorded. On a preliminary measurement session, both radiometers were used and compared. The EG&G Radiometer agreed with the Ophir Radiometer within a reasonable difference; however, the EG&G Radiometer provided a larger degree of measurement uncertainty due to drift. Approximately 25% of the measurement result was due to broadband emissions greater than 270 nm for these calibration target results. Additional measurements were also made to determine the level of potentially interfering emissions from the tracking lasers, background light, and electromagnetic interference (EMI). The tracking lasers and the EMI had no measurable impact on the levels of the emissions of interest. Background light added 1 nJ/pulse. Subsequent measurements were made using only the Ophir Radiometer and are shown in Tables 1 through 3. Results for the calibration procedures are shown in Table 1. Tables 2 and 3 show the results for PRK and LASIK, respectively.

DISCUSSION

The excimer laser uses a combination of argon (Ar) and fluoride (F) gases to create an unstable, high-energy ArF molecule that, when excited, releases UV radiation with a wavelength of 193 nm. The process through which the excimer laser removes tissue is called ablative photodecomposition, or photoablation. The 193 nm excimer laser is very highly absorbed by the surface of the cornea and has very little penetration beneath the surface. The 193 nm photon has sufficient energy to cause the breakdown of molecular bonds within corneal collagen and the release of fragments. It is able to create very precise margins with very little adjacent tissue damage.[3]

The 193 nm wavelength falls in the UV range, which includes radiation with wavelengths between 100 nm and 400 nm. Ultraviolet radiation can be further divided into 3 regions, ultraviolet-A (UV-A) (315 to 400 nm), ultraviolet-B (UV-B) (280 to 315 nm), and ultraviolet-C (UV-C) (<280 nm).[5] The organs primarily affected by UV exposure

Table 1. Calibration results.

Procedure	Laser Parameters	Distance (cm)	Angle* (Degrees)	Filter	Results[†] (nJ/pulse)
Calibration–configure laser	2.7 mJ/pulse at 63 Hz	16	NR	None	18 nJ/pulse
Calibration–configure laser	2.7 mJ/pulse at 63 Hz	16	NR	WG 230	7–8 nJ/pulse
Calibration–configure laser (patient 1)	2.7 mJ/pulse at 63 Hz	16	NR	WG 280	0 nJ/pulse
Calibration–configure laser	2.7 mJ/pulse at 63 Hz	24	NR	None	9–10 nJ/pulse
Calibration–configure laser (patient 5)	2.7 mJ/pulse at 63 Hz	27	40	None	5 nJ/pulse
Calibration–configure laser (patient 6)	2.7 mJ/pulse at 63 Hz	30	30	None	5 nJ/pulse
Calibration–configure laser	2.7 mJ/pulse at 63 Hz	35	NR	None	6 nJ/pulse
Calibration–configure laser (patient 4)	2.7 mJ/pulse at 63 Hz	38	40	None	0 nJ/pulse
Calibration–configure laser (patient 2)	2.89 mJ/pulse at 64 Hz for 14 sec	NR	NR	WG 230	0 nJ/pulse
Calibration–volume/shot	2.7 mJ/pulse at 63 Hz	17	NR	None	12 nJ/pulse
Calibration–volume/shot	2.7 mJ/pulse at 63 Hz	35	NR	None	4 nJ/pulse
Calibration–volume/shot	2.7 mJ/pulse at 63 Hz	35	NR	WG 230	0 nJ/pulse
Calibration–square PTK	2.7 mJ/pulse at 63 Hz	35	NR	None	4 nJ/pulse

NR = not recorded
*Measurement angles are approximate from the axis of the laser or vertical axis.
[†]All measurements made with Ophir with PD-10, SN 130279.

are the eyes and skin. Ultraviolet radiation in the range of 180 to 400 nm can cause photokeratoconjunctivitis, a transient occurrence that typically lasts for 24 to 48 hours after an acute exposure. Cataracts can occur from chronic exposure to UV radiation in the range of 295 to 400 nm. Erythema of the skin occurs after an acute exposure of UV radiation in the range of 200 to 400 nm and is temporary. Ultraviolet-B exposure contributes to most of the health effects of ultraviolet radiation, causing nonmelanoma and melanoma skin cancer, cortical cataracts, photokeratitis, and photoconjunctivitis.[6] Radiant energy around 297 nm is most effective in contributing to cataract formation.[7] Ultraviolet-A radiation also induces cataracts but has less effect on the skin. Ultraviolet-C radiation has few adverse effects. It is well absorbed by the top layers of

dead skin so that very little deeper penetration occurs.[7,8] Ultraviolet radiation of wavelength 193 nm appears to have little if any mutagenic effect on corneal tissue.[9] The reaction of the corneal tissue to UV radiation and the effect of UV radiation on other tissue may still have some potential for mutagenesis.[9–13] Chronic exposure to UV radiation between 315 nm and 400 nm can cause both nonmelanoma and melanoma skin cancers.[14] The risk for mutagenesis from 193 nm radiation is 1000 to 10 000 times less than the risk from 248 nm radiation, because 248 nm energy is absorbed predominantly by nucleic acids.[3,11]

Commercial laser products sold in the United States must comply with the Radiation Safety Performance Standards issued by the FDA.[15] This standard requires laser system manufacturers to include certain safety design

Table 2. Photorefractive keratectomy results.

Procedure/ Patient/Eye	Laser Parameters	Distance (cm)	Angle* (Degrees)	Filter	Results[†] (nJ/pulse)
PRK/1/OD	2.79 mJ/pulse at 64 Hz for 30 sec	14	NR	None	2.5–7.5 nJ/pulse
PRK/1/OS	2.87 mJ/pulse at 63 Hz for 36 sec	14	NR	None	4–12 nJ/pulse
PRK/2/OD	2.89 mJ/pulse at 64 Hz for 14 sec	14	NR	None	6–12 nJ/pulse
PRK/2/OS	2.90 mJ/pulse at 63 Hz for 17 sec	14	NR	None	3–12 nJ/pulse
PRK/3/OD	2.89 mJ/pulse at 63 Hz for 14 sec	14	NR	None	0 nJ/pulse
PRK/3/OS	2.90 mJ/pulse at 63 Hz for 17 sec	18	NR	None	3–12 nJ/pulse with 18 nJ/pulse peaks
PRK/4/OD	2.82 mJ/pulse at 63 Hz for 26 sec	38	50	None	0 nJ/pulse
PRK/4/OS	2.88 mJ/pulse at 63 Hz for 22 sec	40	50	None	20 nJ/pulse

OD = right eye; OS = left eye; NR = not recorded; PRK = photorefractive keratectomy
*Measurement angles are approximate from the axis of the laser or vertical axis.
[†]All measurements made with Ophir with PD-10, SN 130279.

Table 3. Laser in situ keratomileusis results.

Procedure/ Patient/Eye	Laser Parameters	Distance (cm)	Angle* (Degrees)	Filter	Results† (nJ/pulse)
LASIK/5/OD	2.87 mJ/pulse at 63 Hz for 50 sec	38	50	none	45 nJ/pulse
LASIK/5/OS	2.73 mJ/pulse at 63 Hz for 48 sec	38	50	none	38 nJ/pulse
LASIK/6/OD	2.82 mJ/pulse at 63 Hz for 40 sec	40	50	none	NR
LASIK/6/OS	2.70 mJ/pulse at 63 Hz for 47 sec	36	50	none	30 nJ/pulse
LASIK/7/OD	2.91 mJ/pulse at 62 Hz for 18 sec	38	50	none	30 nJ/pulse
LASIK/7/OD	2.91 mJ/pulse at 62 Hz for 18 sec	38	50	WG 230	6 nJ/pulse with WG 230 filter
LASIK/7/OS	2.87 mJ/pulse at 62 Hz for 19 sec	35	50	none	40 nJ/pulse
LASIK/7/OS	2.87 mJ/pulse at 62 Hz for 19 sec	35	50	WG 230	9 nJ/pulse with WG 230 filter

OD = right eye; OS = left eye; LASIK = laser in situ keratomileusis
*Measurement angles are approximate from the axis of the laser or vertical axis.
†All measurements were made with Ophir with PD-10, SN 130279.

features such as warning lights, warning labels, and housing interlocks in lasers sold in the United States. However, the manufacturer, not the FDA, certifies laser product compliance with these regulations. The excimer laser is classified from a hazard standpoint as an ANSI Class 4 laser system. Occupational contact directly with the beam can cause serious skin and corneal burns or irritation. Moreover, excimer laser systems for refractive surgery may use technologies that pose additional theoretical concerns for harmful occupational exposure, such as from alignment and tracking laser beams, high voltages, vaporized tissues, and fluorine gas. Nevertheless, the current ANSI Z136.3-1996 standard for health care laser systems does not provide specific guidance for keratorefractive procedures.[4]

Exposure Limits

The occupational exposure limits for exposure to the direct or scattered emissions from an active UV source between 180 nm and 302 nm is 3 mJ/cm^2 cumulative over an 8-hour workday during a 24-hour period.[14,16] This standard is considered highly conservative at 193 nm since the limit at 193 nm and the limited biological data that exist at 193 nm indicate that the acute injury threshold exceeds 1 J/cm^2 and therefore an occupational exposure limit at this wavelength could be increased. The exposure limit for actinic UV radiation emitted by the plasma source is also 3 mJ/cm^2 as though the entire exposure had occurred at a wavelength of 270 nm and spectrally weighted to greater limits beginning at 180 nm and extending to 400 nm. The international light radiometer contained a spectral weighting filter to yield an effective actinic UV exposure relative to the 270 nm peak for injury.

Worst-Case Analysis

Assuming the worst-case exposure conditions, or the maximum measured value during these studies, and also assuming a very heavy patient workload, the cumulative occupational exposure at close range of actinic UV radiation would not exceed the 8-hour occupational exposure limit of 3 mJ/cm^2 for any 24-hour period. The worst-case assumptions were as follows:

1. The exposure during each pulse at 38 cm was 45 nJ per pulse. The radiant exposure levels did follow the inverse square law so the exposure during each pulse for the scrub nurse located at 80 cm would be approximately 11 nJ per pulse. This value must be multiplied by 1.2 to correct for the lower sensitivity of the detector at 193 nm, which results in a value of 13.2 nJ per pulse. The detector was 10 mm in diameter so that the radiant exposure was 16.8 nJ/cm^2.

2. The total daily exposure was determined as follows: The mean number of pulses delivered per eye was 2000. In a busy laser setting, the number of corneal procedures would approach 20 patients (40 eyes) in a day. This results in a total number of pulses of 8 pulses $\times$ 10^4 pulses. The total exposure would therefore be 8 pulses $\times$ 10^4 pulses $\times$ 16.8 nJ/cm^2 or 1.34 mJ/cm^2. This is approximately one half the limit of 3 mJ/cm^2.

3. If the number of cases doubled, the all-day worst-case exposure would approach the safety limits. Another way of increasing an observer's exposure would be to decrease exposure distance. If the operating room personnel were stationed at half the distance, 40 cm from the field, the calculated worst-case exposure would theoretically exceed the exposure limit by a factor of 2 for an all-day worst-case exposure. These types of exposure, however, would be extremely unlikely.

Neglecting the direct excimer laser beam, the occupational concerns are for scattered excimer laser radiation at

193 nm and broadband actinic UV emissions generated by a high-temperature plasma that appeared as a blue ball above both calibration targets and patient tissues. Measurements suggested that roughly one third of the effective actinic UV radiation resulted from 1 of 3 sources, scattered laser radiation, fluorescence, or the plasma source.

Additional laser system components were tested as well as the treatment beam. The LADARVision 4000 System consists of an excimer laser combined with laser beam positioning and an active laser tracking system. The system uses 2 Class 1 cross-beam continuous-wave diode lasers operating at 633 nm for initial patient alignment. The 633 nm lasers produced less than 15 μw. A Class 1 GaAlAs pulsed diode laser operating at 905 nm is used as an active eye tracker. The 905 nm laser produced less than 16 μw mean power in 4 separate beams, sequentially fired, each with a diameter of 1.5 mm and pulse duration of 50 ns to 70 ns and a pulse rate of about 4 kHz. Neither of these posed a concern for occupational exposure.

In conclusion, scattered actinic UV laser radiation and broadband actinic UV plasma emissions did not exceed occupational exposure limits beyond a very short distance from either laser calibration targets or patient treatments over a workday, even taking into consideration the cumulative effects during a heavy patient load. Surgeons and laser technicians worked at much greater distances where a line-of-sight largely did not exist. Consequently, measurements indicated that laser protective eyewear was not normally required for personnel located within the surgical suite. Standing operating procedure (SOP) for the LADARVision 4000 laser system should warn against direct occupational exposure to the laser beam that could result in serious and painful skin or corneal burns or irritation. The SOP should also indicate that scattered laser and other plasma emissions do not pose any occupational health hazards to alleviate unwarranted concerns. Although not required for normal operation, it is nevertheless prudent that laser eye protectors be available to individuals who wish to wear them and to personnel for special use such as during maintenance or service. Prescription or plano spectacles made with glass, CR-39, or polycarbonate with side shields would likely serve as an adequate filter because these materials absorb nearly all 400 μm wavelength light.

The present study was not intended to evaluate all the occupational safety issues possible during laser refractive surgery. Rather, we attempted to address specific occupational concerns surrounding scattered excimer laser radiation and re-radiation from a (high-temperature) plasma source, along with UV tissue fluorescence.

Appendix A. Useful radiometric units.[*][†]

Term	Symbol	Definition	Unit (Abbreviation)
Radiant energy	Q	Energy emitted, transferred, or received in the form of radiation	Joule (J)
Radiant power	Φ	Radiant energy per unit time	Watt (W) defined as J/s
Radiant exposure (dose in photobiology)	H	Energy per unit area incident upon a given surface	Joules per square centimeter (J/cm^{-2})
Irradiance or radiant flux density (dose rate in photobiology)	E	Power per unit area incident upon a given surface	Watts per square centimeter (W/cm^{-2})
Integrated radiant intensity	I_P	Radiant energy emitted by a source per unit solid angle	Joules per steradian (J/sr^{-1})
Radiant intensity	I	Radiant power emitted by a source per unit solid angle	Watts per steradian (W/sr^{-1})
Integrated radiance	L_P	Radiant energy emitted by a source per unit solid angle per source area	Joules per steradian per square centimeter ($J/sr^{-1}/cm^{-2}$)
Radiance[‡]	L	Radiant power emitted by a source per unit solid angle per source area	Watts per steradian per square centimeter ($W/sr^{-1}/cm^{-2}$)
Laser density	OD	A logarithmic expression for the attenuation produced by a medium $OD = -\log_{10}\left(\frac{\Phi_O}{\Phi_L}\right)$	Unitless Φ_O is the incident power; Φ_L is the transmitted power

[*]The units may be altered to refer to narrow spectral bands in which the term is preceded by the word spectral and the unit is then per wavelength interval and the symbol has a subscript λ. For example, spectral irradiance E_λ has units of $W/m^{-2}/m^{-1}$ or more often, $W/cm^{-2}/nm^{-1}$.

[†]While the meter is the preferred unit of length, the centimeter is still the most commonly used unit of length for many of the terms below and the nm or μm are most commonly used to express wavelength.

[‡]At the source $L = \frac{dI}{dA \bullet \cos\theta}$ and at a receptor $L = \frac{dE}{d\Omega \bullet \cos\theta}$.

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Corneal Iron Line Following LASIK With Epithelial Ingrowth

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Purpose: To report a new corneal iron line following keratorefractive surgery.

Methods: Case report and review of the literature. A 51-year-old man developed epithelial ingrowth after otherwise uneventful LASIK surgery. The patient, satisfied with an uncorrected visual acuity of 20/25 and otherwise asymptomatic, declined to have his flap relifted to treat the ingrowth.

Results: Six months postoperatively a corneal iron line was noted at the leading edge of the epithelial ingrowth. Vision remained stable.

Conclusions: Epithelial iron lines have been reported with a number of conditions, including post-refractive procedures. This is the first report of an iron line associated with epithelial ingrowth following LASIK.

Key Words: corneal iron lines, LASIK, refractive surgery, epithelial ingrowth, complications

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I ron deposition in the corneal epithelium occurs in both normal and pathologic conditions, and its location is commonly associated with large variations in corneal topography. Fleischer first documented this in keratoconus in 1906.[1] Hudson[2] and Stähli,[3] only a few years later, independently reported corneal iron lines in approximately 25% of otherwise normal eyes. Stocker and Ferry have demonstrated similar deposition anterior to the heads of pterygia[4] and filtering blebs,[5] respectively. Iron lines have also been shown to occur in association with corneal scars, Salzmann nodular degeneration,[6] and penetrating keratoplasty, on the donor side of corneal grafts.[7,8]

More recently, epithelial iron lines have been reported after a number of refractive corneal procedures, with both uncomplicated and complicated postoperative courses. These include radial keratotomy,[9] intrastromal corneal ring implantation,[10] photorefractive keratectomy (PRK),[11] and laser in situ keratomileusis (LASIK).[12] In one case reported by Ozdamar et al,[13] an iron line was noted at the base of iatrogenic keratectasia following myopic LASIK, mimicking Fleischer ring. Iron lines have been reported even after nonsurgical corneal manipulation, such as orthokeratology,[14] in which rigid gas-permeable contact lenses are applied over a period of time to temporarily reduce myopic refractive error.

To date, there have been no reports of an iron line found in association with epithelial ingrowth after LASIK. In this paper, such a case is presented, and a discussion of corneal iron lines follows.

CASE REPORT

A 51-year-old white man had LASIK performed to correct myopic astigmatism in both eyes. The patient had no past ocular history and presented with no contraindications to LASIK. Preoperative manifest and cycloplegic refractions were consistent within 0.25 D and were as follows: $-2.25 -0.75 \times 160$ OD and $-2.00 -1.00 \times 15$ OS. Keratometry readings measured 41.0/43.0 D at 75 degrees in the right eye and 41.2/42.7 D at 100 degrees in the left eye. Corneal thickness was 529 and 526 μm in the right and left eyes, respectively. The patient's LASIK procedure was performed under a nasal-hinged flap (Automated Corneal Shaper, Chiron Surgical, Claremont, CA). The surgery and initial postoperative course were uncomplicated.

At the 1-month postoperative visit, an island of epithelial cells measuring 3.1 mm vertically and 1.1 mm horizontally was noted under the inferonasal quadrant of the LASIK flap of the left eye. It remained peripheral to the pupillary axis, and the flap itself was in good position. No surface irregularities were noted to slit lamp biomicroscopy, and there was no evidence of flap melting. Examination of the right eye was unremarkable with a well-positioned, clear flap. Treatment to relift the left corneal flap and remove the epithelial cells was discussed with the patient. The patient declined the procedure, however, because he was happy with his vision and noted only mild halos in the dark (in his left eye only). The epithelial ingrowth remained unchanged at postoperative month 3 with the exception of a demarcation line at its leading edge. Again, no flap melting was evident.

Six months postoperatively, a well-demarcated brown line in the left cornea was noted with slit lamp biomicroscopy (Fig. 1). It was isolated to the surface epithelium by optical section and had a
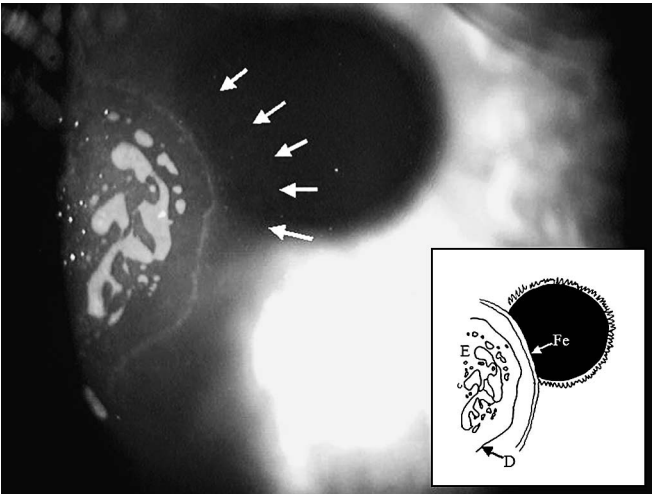
FIGURE 1. Epithelial ingrowth and iron line (arrows). Inset shows location of epithelial ingrowth (E), demarcation line (D), and iron line (Fe).

rust-brown coloration. The line was located along the central, leading edge of the epithelial ingrowth, and it abutted the inferonasal pupillary margin. The location and character of this line remained unchanged at subsequent visits (through the 18-month postoperative examination).

Uncorrected acuity, BSCVA, and manifest refraction were measured at each postoperative visit and remained stable through 18 months following LASIK. Measurements at the 12-month post-operative visit are listed. Uncorrected visual acuity was 20/20 OD and 20/25 OS. BSCVA was 20/15 OD and 20/20 OS, with manifest refraction of −0.25 −0.50 × 147 OD and 0.75 −1.75 × 20 OS, respectively. Keratometry values of 39.7/41.5 D at 96 degrees in the right eye and 36.2/41.7 at 105 degrees in the left eye were obtained with Orbscan. These measurements along with float readings can be found in Figure 2. As shown, a large corneal elevation exists in the inferonasal quadrant of the left cornea (Fig. 3). Along the central half of the base of this elevation is the location of the corneal iron line described.

DISCUSSION

Many reported cases of corneal iron lines lie adjacent to a region of aberrant elevation, as in this case. Historical

FIGURE 2. Orbscan anterior elevation map OS.

FIGURE 3. 3-Dimensional reconstruction of anterior elevation map OS.

examples include Fleischer ring,[1] found at the base of the cone in keratoconus, and Stocker line,[4] first reported in 1939 as a pigmented line located parallel to and near the border of a pterygium head. Ferry line also can be grouped into this category—an iron line immediately anterior to a filtering bleb, reported by Ferry in 27 of 50 eyes after filtration surgery.[5] Recently, corneal iron lines, similar to Fleischer ring, were reported as occurring in patients with secondary keratoconus.[15]

More recent examples come as sequelae of refractive surgery. Koenig et al[16] found that 21 of 55 patients following refractive keratoplasty had corneal iron lines along the margin of the keratectomy scar. They suggested that this might be related to the steepness of the cornea in that region. In 1984, Steinberg reported stellate iron lines in the corneal epithelium after refractive keratotomy.[9] The radial extensions of the lines he described were located in depressions between each elevated radial incision site. Assil and associates in 1993[10] reported crescentic iron lines central to intrastromal corneal ring segments (Intacs®). The lines appeared in 5 of 10 patients 9 months after implantation and ran concentric to the ring implants. Following hyperopic PRK, 15% of patients in another recent study were noted to have ring-shaped corneal iron deposits,[11] where the iron ring was located in the peripheral flat ablation zone adjacent to the steepened central cornea. Similarly, a "pseudo-Fleischer ring" was reported in 1 case following hyperopic LASIK,[17] so named because of its resemblance to the line found in association with keratoconus. Finally, analogous to keratoconus, an acquired—actually iatrogenic—keratectasia with a comparable iron line was reported in a patient after myopic LASIK,[13] occurring after laser ablation left only 300 μm of central corneal thickness. All of the above iron lines are located in regions adjacent to
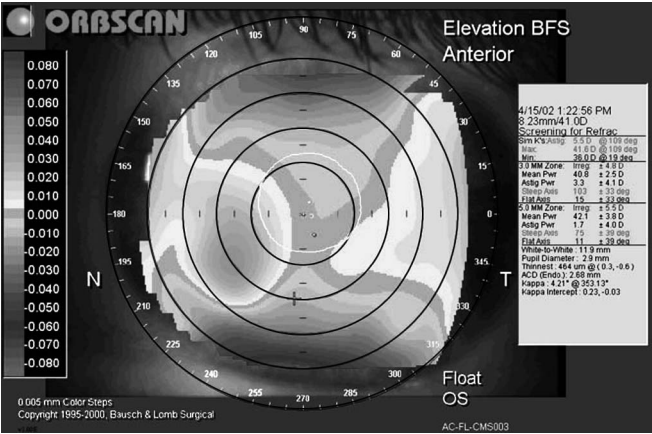
significant corneal elevations, but other iron lines have been reported in situations where this is not the case.

Seiler and Holschbach[18] found central corneal iron spots in 84% of patients 1 year after myopic PRK. They reported an increase in pigmentation with higher refractive changes. Furthermore, they noted thickened epithelium in the central cornea relative to the periphery. Thus, they postulated that thickened epithelium might be a factor in the development of iron deposition. In a more recent study, Krueger et al[19] described findings of corneal iron rings in 2 patients with persistent steep central islands following myopic PRK. Vongthongsri et al[20] reported the occurrence of iron lines in 35 of 83 eyes following myopic LASIK. These lines, configured in rings, partial rings, or patches were located at the margin of the flattened ablation zone and were more likely to occur in patients with higher preoperative myopia (more than −4.5 D) or attempted correction of more than −3.7 D. These findings suggests that iron lines occur in association with any drastic change in corneal topography, not only at the border of significant corneal elevations. This does not explain the occurrence of the most commonly seen iron line—the Hudson-Stähli line.[2,3] This horizontal line found at the junction of the middle and lower thirds of the cornea can be found in approximately one quarter of the normal elderly population and is unassociated with any dramatic change in corneal curvature.

That the iron, predominantly ferritin, is deposited in the basal corneal epithelium has been demonstrated histologically. Barraquer-Somers and associates used Prussian blue stain on recipient penetrating keratoplasty buttons to reveal iron deposition predominantly in the deeper layers of the epithelium.[21] This pattern was most closely linked with scenarios such as the Hudson-Stähli line or Fleischer ring, where the rust-brown pigment was clinically arranged in irregular curvilinear configurations. Less commonly, iron deposits stained diffusely through all layers of the epithelium in a fine stippled pattern. This seemed to occur more often with diffuse corneal scars secondary to keratitis, chemical burns, or mechanical trauma, according to the same study.[21]

The exact pathophysiologic mechanism by which iron is deposited in the corneal epithelium is still unknown and frequently debated. Several theories have been presented, mainly focused on the tear film and the replication/migration of the corneal epithelial cells. The tear pool hypothesis, first proposed by Gass in 1964,[22] proposed localized pooling of tears as the source for iron deposition into the epithelial basal cell layer. This theory has been used to explain the location of the Hudson-Stähli line, occurring just superior to the lower lid margin where gravitationally dependent tears pool between each blink and at rest. In contrast, the tear desiccation hypothesis[10] was proposed by Assil and associates, who found that iron deposition in their patients was located at sites of early tear breakup. They propose that in regions where tears evaporate quickly, the concentration of soluble iron increases, thus creating an increased gradient to facilitate iron uptake in the epithelium. Other theories center on the mitotic activity of the epithelial cell layer. The basal cell migration theory,[23] proposed by Rose and Lavin in 1987, suggests that the abrasive interactions of the eyelids against the corneal surface

dictate the rate of epithelial cell turnover. This, in turn regulates the mitotic activity of the underlying basal cells. Simply put, as the rate of mitosis increases to replace the surface cells, basal cells migrate less and hence become relatively mature, accumulating iron. Conversely, another hypothesis was presented by Assil, termed the senescent basal cell hypothesis.[10] He proposed that in regions adjacent to corneal elevations, less frictional force is applied to the local corneal surface by the sweeping motion of the eyelids, thereby shielding the surface epithelial cells from repeated sloughing. This in turn would decrease the need for rapid mitosis to replenish the epithelial cell surface. Decreased mitotic activity thus allows basal cells to mature and accumulate iron.

In the case reported here, an iron line was found partially surrounding an island of epithelial ingrowth after LASIK. The presence of a demarcation line 3 months postoperatively strongly suggests stability of the ingrowth by that time. The iron line that subsequently developed and was visible by the 6-month postoperative visit was further evidence of lack of progression. As shown by Orbscan, this ingrowth resulted in localized elevation of the cornea (Fig. 3), and the iron accumulated adjacent to this elevation, consistent with numerous reports discussed above. Abnormal tear film likely overlies this region of iron deposition, but whether tear pooling or early evaporation occurred was not investigated. The corneal apposition of the eyelids is also likely altered by the ingrowth-associated elevation, and abrasive forces of the lids are likely decreased, giving support to the senescent basal cell hypothesis, but no data were collected to support this assumption.

It should be noted that the iron line discussed here was not seen until 6 months after LASIK. It is likely that similar cases have not been reported because epithelial ingrowth in the flap interface is commonly treated early on discovery. In this instance, the patient chose close observation. It is imperative, however, that during counseling, all patients with ingrowth be made aware of the possible, albeit rare, complications that can result if treatment is declined. In addition to decreased visual acuity from the partially opacified epithelial ingrowth itself or induced astigmatism, cases of stromal edema, diffuse lamellar keratitis, persistent epithelial defect, infectious keratitis, and stromal melting of the flap edge have all been reported in association with this complication of LASIK.[24,25] Different strategies to manage epithelial ingrowth, including flap lift, scraping of the ingrowth, alcohol application to the stromal bed, adjunctive excimer laser, use of a postoperative bandage contact lens, and flap suturing have all been advocated but are not discussed here.[26–28]

In conclusion, this is the first report of a corneal iron line found in association with epithelial ingrowth after LASIK. We suspect that both tear film alterations and modified epithelial cell replication/migration contributed to the development of this line, but by what process has yet to be determined.

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Infectious Keratitis after Photorefractive Keratectomy in the United States Army and Navy

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Purpose: To review the incidence, culture results, clinical course, management, and visual outcomes of infectious keratitis after photorefractive keratectomy (PRK) at 6 Army and Navy refractive surgery centers.

Design: Retrospective study.

Participants: Twelve thousand six hundred sixty-eight Navy and Army sailors and service members.

Methods: Army and Navy refractive surgery data banks were searched for cases of infectious keratitis. A retrospective chart review and query of the surgeons involved in the care of those patients thus identified provided data regarding preoperative preparation, perioperative medications, treatment, culture results, clinical course, and final visual acuity.

Results: Between January 1995 and May 2004, we performed a total of 25 337 PRK procedures at the 6 institutions. Culture proven or clinically suspected infectious keratitis developed in 5 eyes of 5 patients. All patients received topical antibiotics perioperatively. All cases presented 2 to 7 days postoperatively. Cultures from 4 cases grew *Staphylococcus,* including 2 methicillin-resistant *S. aureus* (MRSA). One case of presumed infectious keratitis was culture negative. There were no reported cases of mycobacterial or fungal keratitis. In addition, we identified 26 eyes with corneal infiltrates in the first postoperative week that were felt to be sterile, and which resolved upon removal of the bandage contact lens and increasing antibiotic coverage.

Conclusions: Infectious keratitis is a rare but potentially vision-threatening complication after PRK. It is often caused by gram-positive organisms, including MRSA. Early diagnosis, appropriate laboratory testing, and aggressive antimicrobial therapy can result in good outcomes. *Ophthalmology 2006;113:520–525 © 2006 by the American Academy of Ophthalmology.*

In the civilian community, LASIK has surpassed photorefractive keratectomy (PRK) as the most common form of refractive surgery. However, in the military PRK remains the most common form of refractive surgery. Infectious keratitis after either LASIK or PRK is rare, but may be recalcitrant to standard topical therapy and vision threatening. In this retrospective study, our purpose was to review the incidence and characteristics of infectious keratitis after PRK at 6 Army and Navy refractive surgery centers. We sought to identify risk factors, culture results, and visual outcomes of patients with infectious keratitis after PRK in our military population.

Materials and Methods

We searched the Army and Navy data banks containing preoperative and postoperative patient information for cases of infectious keratitis, corneal ulcer, or corneal infiltrate. We conducted a retrospective chart review and queried all the surgeons involved in the care of those patients identified. Where possible, we obtained culture results and clinical photographs. We obtained the following information for review and analysis: preoperative preparation (povidone–iodine preparation, lid drapes), perioperative medications (including antibiotics, topical anesthetics, nonsteroidal anti-inflammatory agents), time to presentation, treatment and course, time to clinical resolution, culture results, duration of follow-up, and final uncorrected visual acuity (UCVA) and best spectacle-corrected visual acuity (BSCVA). The Army and Navy have established guidelines or eligibility criteria. A service member should have 18 months on active duty at the time of surgery or in

Table 1. Summary of Cases of Infectious Keratitis after Photorefractive Keratectomy at 6 Army and Navy Refractive Surgery Centers between 1994 and May 2004

Patient	Day of Presentation	Antibiotic	Culture	Follow-up (mos)	Final UCVA	Final BSCVA	Postoperative Anesthetic*	Postoperative NSAIDs
1	6	Ofloxacin	MRSA	5	$20/30^{-1}$	20/30	No	Acular[†]
2	2	Polytrim[‡]	*Staphylococcus aureus*	3	20/25	NA	Tetracaine	Acular[†]
3	3	Levofloxacin	MRSA	7	20/16	20/16	Tetracaine	Acular[†]
4	7	Ofloxacin	Negative	12	20/20	20/15	No	Voltaren[§]
5	3	Ofloxacin	Coagulase (−) *Staphylococcus*	12	20/20	20/20	No	Voltaren[§]

BSCVA = best spectacle-corrected visual acuity; MRSA = methicillin-resistant *Staphylococcus aureus;* NA = not available; NSAID = nonsteroidal antiinflammatory drug; UCVA = uncorrected visual acuity.
*Nonpreserved tetracaine hydrochloride 0.5% (Alcon Laboratories, Ft. Worth, TX).
[†]Ketorolac tromethamine (Allergan, Irvine, CA).
[‡]Trimethoprim sulfate/polymyxin b sulfate combination (Allergan).
[§]Diclofenac sodium 0.1% ophthalmic solution (Novartis Ophthalmics, Duluth, GA).

conjunction with a reenlistment. Also, personnel selected should have at least 12 months remaining in the service and should have no adverse personnel actions pending. Our policies specifically require each patient to remain in town until complete epithelial healing and contact lens removal or up to 7 to 10 days after surgery. All our patients are placed on profile, inhibiting field duty or deployment for a minimum of 30 days after refractive surgery, and the patients are instructed to follow up at 1 month, 3 months, and 1 year and to send the postoperative evaluations to the treating laser center.

Results

From January 1995 until May 2004, the United States Army and Navy completed 25 337 PRK procedures at the 6 different institutions. All patients had a preoperative best-corrected visual acuity (BCVA) of 20/20 bilaterally. All patients were given a therapeutic bandage contact lens (BCL) and prophylactic antibiotics during surgery. All patients were discharged on topical antibiotics 4 times daily. Infectious keratitis developed in 5 eyes of 5 patients. These patients' cases are summarized in Table 1 and discussed in more detail below.

Case 1

The patient underwent uncomplicated PRK for myopic astigmatism and was started on ofloxacin, fluorometholone, and ketorolac. On postoperative day 4, he had small remaining epithelial defects in both eyes, so the BCLs were replaced in both eyes. On postoperative day 6, he presented with pain in the right eye. Examination revealed a partial ring infiltrate in the superior cornea, a 7×4-mm epithelial defect, and a 3+ anterior chamber (AC) reaction with small hypopyon. The BCL was removed, and cultures were done. The ofloxacin drops that had been started 4 times daily postoperatively were stopped, and he was started on fortified vancomycin and gentamicin every hour. Four days later, the cultures grew methicillin-resistant *Staphylococcus aureus* (MRSA). On further query, the patient's wife had lung cancer and was colonized with MRSA. The gentamicin was stopped, and the patient continued on fortified vancomycin hourly. He was treated with mupirocin calcium ointment to the nares and axillae. By the 21st postoperative day, the infiltrate had resolved, and the epithelial defect had healed. Five months after surgery, the patient has a UCVA of $20/30^{-1}$ and a BCVA of 20/30 and mild central haze.

Case 2

The patient had uneventful PRK in both eyes and was given trimethoprim–polymyxin B (Polytrim, Allergan Inc., Irvine, CA) and fluorometholone 4 times daily postoperatively. On postoperative day 1, he had visual acuities (VAs) of 20/32 and 20/32 but presented 1 day later complaining that he may have poked himself in the right eye. Increased redness and pain were noted by the patient. On examination, he had a VA of 20/200 and a central 2×1-mm defect with no infiltrate. On postoperative day 4 (Fig 1), the contact lens was absent, and the epithelial defect had increased to 4×6 mm. He had multifocal stromal infiltrates, linear keratic precipitates, and a small hypopyon. He was started on fortified cefazolin and tobramycin and observed daily. Culture on the seventh postoperative day revealed *S. aureus*. Ciprofloxacin was added, and tobramycin was discontinued. Three months later, the UCVA improved to 20/25, with some central haze.

Case 3

The patient had uncomplicated PRK for myopia and astigmatism and was given levofloxacin and fluorometholone 4 times daily postoperatively. On postoperative day 1, his UCVAs were 20/32 and 20/20. On postoperative day 3, he presented with increased pain, decreased VA, and redness in his right eye. His VA was 20/160, and it was noted that he had a 1-mm central epithelial defect with a 3-mm total diameter infiltrate centrally. The BCL was removed, and cultures were drawn. Fortified cefazolin and gentamicin were started. Culture results revealed MRSA. Fortified vancomycin was instituted, and other antibiotics were stopped. Three months later, UCVA had improved to 20/16, but central haze remained. Seven months postoperatively, before his deployment to Iraq, his UCVA was 20/16, with patchy central haze.

Case 4

The patient underwent PRK for hyperopia requiring a 9.5-mm epithelial defect for a 9-mm hyperopic treatment zone. The patient was started on ofloxacin and fluorometholone 4 times daily postoperatively. On postoperative day 6, he had a residual 1- to 2-mm central epithelial defect in the right eye, and the BCL was replaced. By postoperative day 7, the epithelial defect had healed, but there was a stromal infiltrate centrally underlying the previous day's epithelial defect. The BCL was removed, the ofloxacin was increased to hourly while awake, and fortified cefazolin and erythromycin ophthalmic ointment were added 4 times daily. On post-
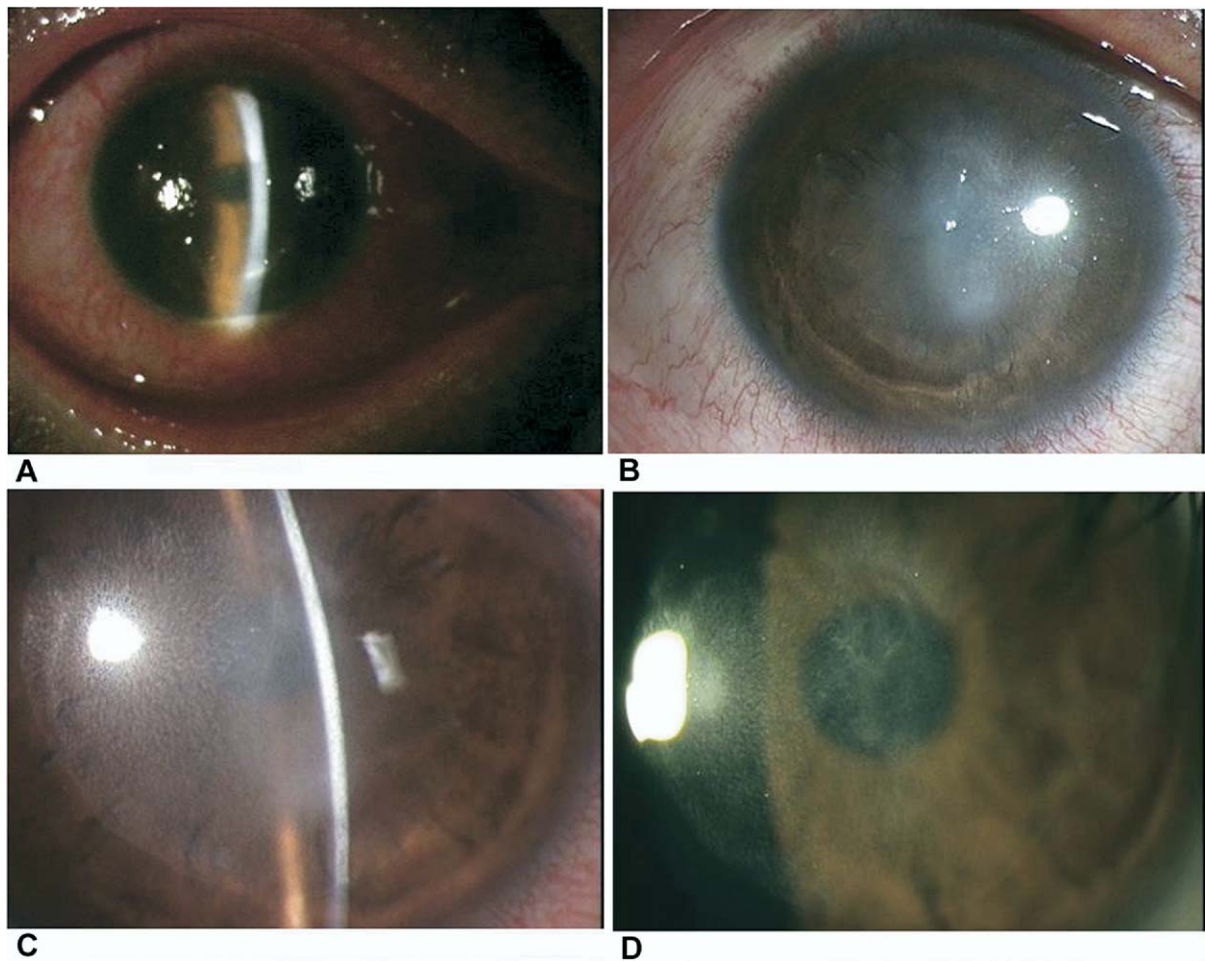
Figure 1. Slit-lamp photographs of the right eye of the patient described in "Case 2." **A,** Clinical presentation of postoperative day 4 with a 6-mm epithelial defect, multifocal stromal infiltrates, and a small hypopyon. Cultures grew *Staphylococcus aureus*. **B, C,** One month after the operation. The epithelium had healed, but there was dense central haze. **D,** By 3 months after the operation, the cornea had healed, with residual central haze and uncorrected visual acuity of 20/25.

operative day 8, the epithelium remained intact, the central infiltrate was resolving, but a new ring infiltrate had formed around the initial central infiltrate (Fig 2). Bacterial, fungal, viral, *Acanthamoeba*, and mycobacterial cultures were negative. The patient responded to topical fortified antibiotics and removal of the BCL. One year postoperatively, he had a UCVA of 20/20 and retained a BSCVA of 20/15 without significant corneal scarring.

Case 5

The patient underwent uncomplicated PRK for myopic astigmatism. The patient was started on ofloxacin and fluorometholone 4 times daily postoperatively. She presented on postoperative day 3 with a central 2- to 3-mm infiltrate with an overlying epithelial defect and 1+ AC reaction (Fig 3). Cultures were positive for coagulase-negative *Staphylococcus*. The BCL was removed, and she was treated by increasing her ofloxacin to hourly and adding fortified cefazolin hourly and erythromycin ointment 4 times daily. On this therapy she improved, with a resulting UCVA of 20/20, but a 1-line loss in BSCVA (20/20, from 20/15) due to a small central scar 1 year postoperatively.

In addition to the 5 cases of culture-proven or suspected infectious keratitis after PRK, we found 26 eyes with corneal infiltrates

in the first postoperative week that were felt to be sterile. Three of these patients were cultured, and the cultures were negative. All of these were peripheral or midperipheral and small (1–3 mm), with no AC reaction. Figure 4 illustrates one such case. Many had intact epithelium or only localized superficial punctate keratopathy overlying the infiltrate, and some infiltrates were outside the area of the surgically induced epithelial defect. All infiltrates were identified on postoperative days 1 to 4. Most of these infiltrates were treated by increasing the frequency of the topical fluoroquinolone, adding gram-positive coverage in the form of either bacitracin or erythromycin ophthalmic ointment, and replacing or removing the bandage soft contact lens. All resolved with good visual results, although 1 patient lost 1 line of BCVA.

Discussion

Our review of 25 337 PRK procedures at 6 institutions is the largest retrospective review of infectious keratitis after PRK. All of our patients except one received topical fluoroquinolones until the corneal epithelium healed. The other patient received trimethoprim–polymyxin B. Our cases pre-
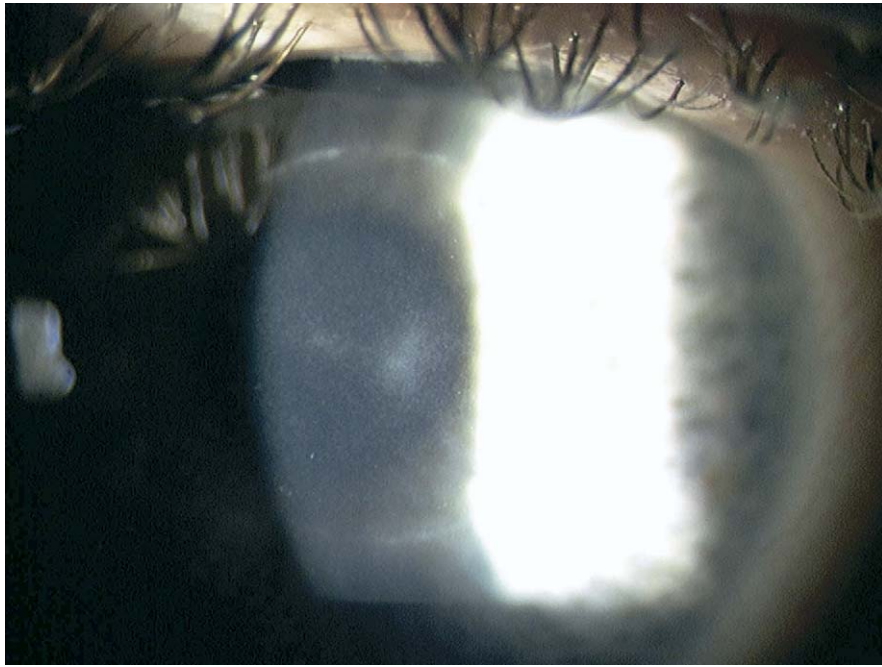
Figure 2. Right eye of patient 4 on postoperative day 8 after hyperopic photorefractive keratectomy. Note the 2-mm central infiltrate with surrounding ring infiltrate. Although cultures were negative, the patient was treated as presumed infectious keratitis, with final uncorrected visual acuity of 20/20.

sented within the first week after surgery, and despite the use of prophylactic fluoroquinolones and trimethoprim–polymyxin B in 1 patient, we had 4 culture-proven cases of gram-positive infectious keratitis. Two MRSA infections are reported in our series, with early diagnosis and good outcome in one but loss of BSCVA to 20/30 in the other. In fact, our culture results are similar to those in the case series of 13 patients reported by Donnenfeld et al.[1] Risk factors of contact lens manipulation and working in a medical environment were identified. Kouyoumdjian et al reported 2 cases involving scopulariopsis and *Mycobacterium chelonae*.[2] Wee et al reported a case of infectious keratitis involving *Pseuomonas aeruginosa*.[3] Sampath et al reported a case involving *Streptococcus pneumoniae* with a poor vi-

Figure 3. Right eye of patient 5 on postoperative day 3 after photorefractive keratectomy. Slit-lamp photograph shows a 3-mm central corneal infiltrate with mild central corneal edema and an overlying epithelial defect (**inset**). Cultures grew coagulase-negative *Staphylococcus*.
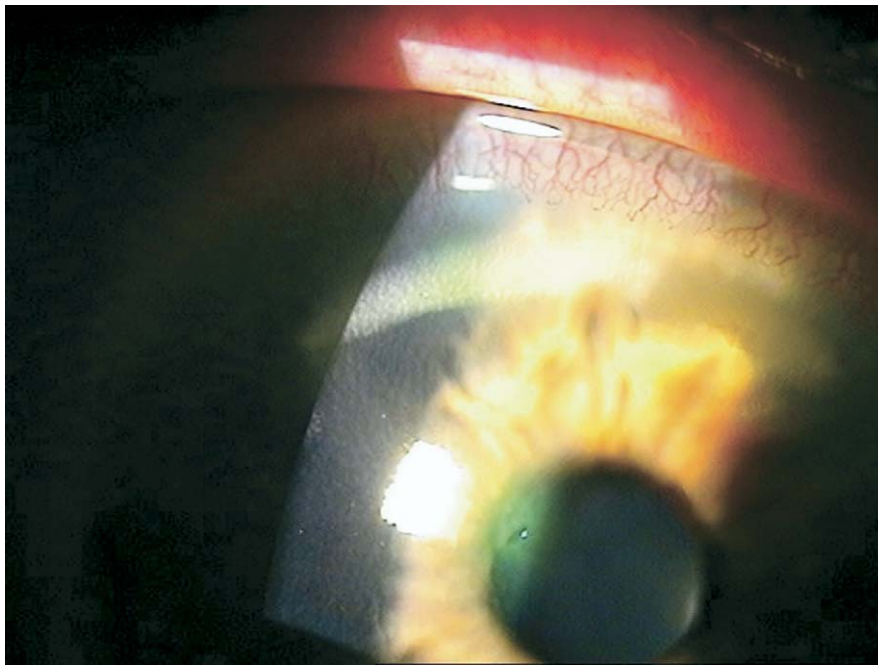
Figure 4. This linear perilimbal superior infiltrate was seen at day 4 after routine photorefractive keratectomy in an asymptomatic patient. There was no epithelial defect, and no anterior chamber reaction. Etiology was considered to be hypoxia induced secondary to wearing an 8.7BC Acuvue II soft contact lens (Johnson & Johnson Vision Care, Inc., Jacksonville, FL). The patient was also receiving standard fluorometholone, ofloxacin, and tetracaine topical therapy. The infiltrate was not treated, other than continuing standard steroid tapering over 1 month, and although residual haze was visible at 1 month, at 3 months all stromal opacification had resolved.

sual outcome.[4] Unlike previous reports, we had no proven cases or culture-positive cases involving mycobacterial or fungal organisms.[5–7] Karp et al showed a high incidence of mycobacterial and fungal infections after LASIK, yet reported excellent outcomes after *S. aureus* infections.[8] Yet, in that series of patients the time of presentation ranged from 2 to 450 days after the procedure.

Machat and Leccisotti et al estimated the incidence of infectious keratitis as 1/1000 and 1/5000, respectively, in their case series.[9,10] Leccisotti et al reported a case of infectious keratitis developing 4 days after surgery, when the patient removed the soft contact lens, squeezed a presumed hordeolum with his hands, and then replaced the same contact lens in the eye.

In our experience, the presentation of corneal infiltrates in the first postoperative week after PRK necessitates aggressive treatment. Although we assumed, like others, that many of these infiltrates were sterile, contact lens related, or associated with topical nonsteroidal antiinflammatory agents, our management included aggressive antibiotics, with the addition of gram-positive coverage and removal of the soft contact lens.[11–16] We did not routinely culture all small corneal infiltrates, because such cultures are technically difficult. However, we recommend that any infiltrate that is central or paracentral, is larger than 2 mm, is associated with significant pain or AC reaction, or fails to respond rapidly to the above therapy should be smeared, cultured, followed closely, and treated aggressively as a sight-threatening condition. We believe that this vigilance has been effective in identifying and treat-

ing postoperative keratitis in our large series of patients at 6 different military refractive centers.

In 1996, Schallhorn first reported on the safety, efficacy, and quality of vision after PRK in active duty Navy and Marine personnel.[17] In this study, we have collected information from both the Army and Navy tracking systems. One of the shortcomings of our work, as reported by Hammond et al previously, is that many of our patients have deployed overseas within the first few months after treatment.[18] For example, our patients from Fort Bragg, North Carolina currently have a 1-month follow-up of 80% and a 3-month follow-up of 61% (Barnes, unpublished data). We believe, however, that because most patients do not deploy for the first 3 months, our review of the data banks should be reasonably accurate. Also, our communications with the deployed ophthalmologists reveal no cases of infectious keratitis in patients who have been previously treated with PRK.

In conclusion, our study shows that infectious keratitis is very rare and appears early in the postoperative period. Preoperative antibiotics may be helpful in preventing this complication.

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Night Firing Range Performance following Photorefractive Keratectomy and Laser In Situ Keratomileusis

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Objective: To investigate the effect of laser refractive surgery on night weapons firing. Methods: Firing range performance was measured at baseline and postoperatively following photorefractive keratectomy and laser in situ keratomileusis. Subjects fired the M-16A2 rifle with night vision goggles (NVG) at starlight, and with iron sight (simulated dusk). Scores, before and after surgery, were compared for both conditions. Results: No subject was able to acquire the target using iron sight without correction before surgery. After surgery, the scores without correction (95.9 ± 4.7) matched the preoperative scores with correction (94.3 ± 4.0; p = 0.324). Uncorrected NVG scores after surgery (96.4 ± 3.1) exceeded the corrected scores before surgery (91.4 ± 10.2), but this trend was not statistically significant (p = 0.063). Conclusion: Night weapon firing with both the iron sight and the NVG sight improved after surgery. This study supports the operational benefits of refractive surgery in the military.

Introduction

Despite the proven safety and efficacy of laser refractive surgery, a variety of night vision difficulties such as glare, halos, starbursts, and reduced contrast sensitivity can potentially occur following the procedures.[1-5] Significant loss of contrast sensitivity or other night vision difficulty may have a negative impact on military operations, particularly those performed in low-light settings or through night vision goggles (NVG). In a previous study[6] we demonstrated an improvement in uncorrected NVG visual performance 3 months after photorefractive keratectomy (PRK) when compared to preoperative measurements. The practical significance of this finding on specific task performance, however, is largely speculative. In this study, we further investigate visual function under nighttime conditions following both PRK as well as laser in situ keratomileusis (LASIK) and evaluate the effect of refractive surgery on an important military task—the ability to fire an M-16A2 rifle under nighttime conditions.

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Subjects and Methods

This prospective study was conducted at the Center for Refractive Surgery, Walter Reed Army Medical Center, Washington, DC, between August 2002 and December 2003. All participants were 21 years of age or older with a manifest spherical equivalent less than –8.0 diopters (D) and astigmatism no >4.0 D. All participants demonstrated refractive stability over at least 12 months (no >0.5 D change in either the spherical or cylindrical portion of the manifest refraction) and had a best spectacle-corrected visual acuity of 20/20 or better. Subjects were excluded for current or previous eye disease or eye surgery, pregnancy, flight status, or any medical problems precluding refractive surgery. Subjects were recruited from a U.S. Special Operations detachment at Fort Belvoir, Virginia. All subjects had previous experience firing an M-16A2 rifle and with the use of NVGs, were available for the specified follow-up schedule, and had access to the night firing range at Fort Belvoir for baseline and postoperative testing. The study protocol was approved by the Institutional Review Board/Human Use Committee, Department of Clinical Investigation, Walter Reed Army Medical Center. All subjects enrolled into the study voluntarily agreed to participate and gave written informed consent.

Preoperative clinical examination included medical and ocular history, manifest and cycloplegic refraction, visual acuity, pupil size, corneal topography, keratometry, intraocular pressure, slit-lamp examination including assessment of corneal clarity, and fundoscopic examination. Subjects elected to have either PRK or LASIK after discussing risks and benefits of each procedure with the study team and their surgeon.

Surgical Technique

All treatments were performed using the LADARVision 4000 Excimer Laser System with Jupiter 2 software, version 5.11 (Alcon Surgical, Fort Worth, Texas). Preoperatively, 2.5% phenylephrine and 1% tropicamide were administered to the operative eyes to achieve pupil size at least 7 mm. Once the pupils were dilated adequately, 0.5% proparacaine hydrochloride ophthalmic solution was administered in the inferior fornix for topical anesthesia. If the manifest astigmatism was >0.75 D, the horizontal meridian was marked at the 3:00 and 9:00 o'clock limbus, with a sterile surgical marking pen, with the patient seated upright before positioning under the laser. The eyelids were draped with adhesive plastic drapes and gently retracted with a wire eyelid speculum. The operative eye was aligned with the laser system centered on the entrance pupil and the eye tracking system was engaged according to the manufacturer's guidelines before removing the epithelium (PRK) or cutting the flap (LASIK).

PRK

PRK patients underwent epithelial removal using a rotary brush (Amoils Epithelial Scrubber, Innovative Excimer Solutions, Toronto, Canada). With the tracking system re-engaged, the previously applied reference marks were aligned with the horizontal reference on the laser system software. After ensuring proper patient fixation, engagement of the eye tracking system, and alignment of the reticules, the laser treatment was performed. Following laser ablation, the cornea was immediately irrigated with chilled balanced salt solution. Topical antibiotic, steroid eye, and nonsteroidal eye drops were administered and a bandage contact lens was placed over the cornea. The contact lens was left in place until complete re-epithelialization, in most cases by postoperative day 3 or 4. Postoperative analgesia included acetaminophen with codeine administered orally every 4 to 6 hours as needed and 0.1% topical diclofenac ophthalmic solution (Voltaren, Novartis Ophthalmics, Inc., Duluth, Georgia) up to four times per day for the first 3 days as needed. Topical ciprofloxacin (Ciloxan, Alcon Laboratories, Inc., Irvine, California) was administered four times per day for 1 week postoperatively, then discontinued. The patient was instructed to use topical 0.1% fluorometholone suspension (Allergan, Inc., Irvine, California) four times per day for 1 month, then three times per day for 2 weeks, twice a day for 2 weeks, and once a day for 2 weeks.

LASIK

After topical anesthesia and surgical preparation similar to PRK, LASIK patients received nasal-hinged flaps created with the Amadeus microkeratome (Allergan Surgical, Inc.). Microkeratome heads were selected to create a flap diameter of 9.5 mm and flap thickness of 160 μm. After ensuring proper patient fixation, engagement of the eye tracking system, and alignment of the reticules, the laser treatment was performed. Following laser ablation, the flap was carefully returned to its original position and the surgeon irrigated under the flap with balanced salt solution. Topical antibiotic, steroid, and nonsteroidal drops were administered at the conclusion of the case. Patients were examined 30 minutes postoperatively to ensure flap position and stability before being released home. Postoperatively, topical Ciloxan and prednisolone acetate 1% ophthalmic suspension (Pred Forte, Allergan, Inc.) were administered four times per day for 1 week and then discontinued.

Patients were examined postoperatively on day 1 and at 1 week, 1 month, and 3 months, 6 months, and 1 year. In addition, PRK patients were seen every 2 to 3 days until re-epithelialization was complete. Beyond the first postoperative week, examinations were similar to the preoperative evaluation and included visual acuity, manifest refraction, slit-lamp examination, corneal topography, and measurement of intraocular pressure.

Night Firing Range

Night firing was conducted under close supervision in the Night Vision Tunnel at Fort Belvoir, Virginia. Strict firing range protocols were followed at all times to ensure safety of the participants and range staff. All subjects were trained before baseline testing, and no further training was permitted before the 1-month or 3-month postoperative visit. Subjects were tested using their dominant eye only, both with and without correction. At each test interval, participants fired a total of 40 rounds:

20 rounds with an M-16A2 rifle using NVGs (AN/PVS-7D) and aiming light under starlight conditions (10 corrected and 10 uncorrected) and 20 rounds with iron sights under low light, or simulated dusk, conditions (10 corrected and 10 uncorrected). The 25M targets were collected and scored using a standardized grading system, with 100 being the highest possible score achieved by hitting the target with all 10 rounds. (Fig. 1) Before and after surgery, scores were compared for the iron sight and NVG sight. The paired t test was used to analyze the data. A $p < 0.05$ was considered to be statistically significant.

Results

Eighteen subjects ages 25 to 46 were included in this study. Refractive error ranged from -1.25 D to -7.13 D. Mean preoperative manifest spherical equivalent was -3.17 D. There were no significant adverse events reported for either PRK or LASIK patients. One LASIK patient was undercorrected and underwent enhancement at 1 year postoperatively. No PRK patients required enhancement.

Table I shows the mean scores with iron sights for the LASIK and PRK groups. Although there was no significant difference between preoperative and postoperative scores, both groups showed improvement postoperatively. Mean scores were higher postoperatively, without correction, compared to preoperative
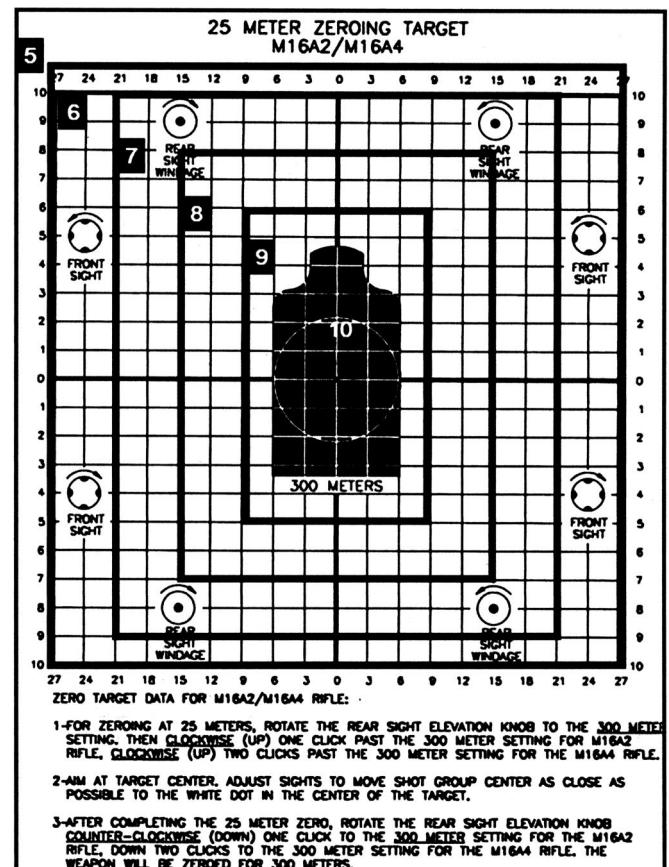

Fig. 1. Night firing range target with scoring system. Each session consisted of 10 rounds fired with an M-16A2 rifle from 25 meters. Score for each round was 0 (zero) if the target was missed altogether, and ranged from 5 (five) to 10 (ten) for hitting successively closer to the center of the target. Maximum score for 10 rounds was 100.

NIGHT FIRING RANGE SCORES WITH IRON SIGHTS BEFORE AND AFTER EXCIMER LASER KERATOREFRACTIVE SURGERY

	PRK		LASIK	
Iron Sights	Mean $\pm$ SD	p^a	Mean $\pm$ SD	p
Preoperative[b]	95.9 $\pm$ 4.0		92.7 $\pm$ 3.6	
1 month postoperative[c]	97.5 $\pm$ 3.1	0.362	93.7 $\pm$ 5.8	0.716
3 months postoperative	97.6 $\pm$ 2.8	0.368	95.7 $\pm$ 2.5	0.059

[a] Student's t test; comparison of preoperative to postoperative scores.
[b] Preoperative measurements done with best spectacle correction.
[c] Postoperative measurements done without correction.

scores with correction. No subjects were even able to acquire the target preoperatively without correction.

Table II shows the mean scores with NVGs for both groups. Preoperatively, the PRK group performed significantly better with the NVGs than the LASIK group, scoring 96.4 $\pm$ 2.7 (SD) compared to 86.3 $\pm$ 12.4 (p = 0.041), both with correction. However, at 1 month postoperatively, the LASIK group performed significantly better than they had previously, scoring 96.2 $\pm$ 2.2 (p = 0.046) without correction. Although the PRK group's performance improved postoperatively, there was no significant difference from their preoperative scores. At both 1 and 3 months postoperatively, there was also no significant difference in performance between the two groups (p > 0.2).

Discussion

In an earlier study, Subramanian et al.[6] demonstrated that there was no loss of best-corrected visual acuity with NVGs following PRK. Moreover, they demonstrated an increase in uncorrected visual acuity with NVGs at 3 months postoperatively compared to preoperative acuity. The previous study, however, did not evaluate the performance of specific tasks nor did it assess NVG performance following LASIK. The present study aimed to further investigate the effect of refractive surgery on night vision performance. Subjects were tested preoperatively and at 1 and 3 months postoperatively following PRK or LASIK to determine their contrast acuities and sensitivities, acuities with NVGs, and their performance at a firing range under nighttime conditions. This article reports the firing range results.

Analysis of night firing range scores suggests improved performance following PRK and LASIK. The subjects showed they could fire a weapon under nighttime conditions, both with NVGs and with iron sights, as well without correction after surgery as they could with correction before surgery. In fact, the LASIK group showed significant improvement 1 month after surgery.

Although all subjects were well experienced with the use of NVGs and with firing an M-16A2 rifle, they were all trained before testing. Despite this, the effects of learning cannot be ignored. Preoperatively, the LASIK group performed significantly worse with NVGs than the PRK group, suggesting that overall they may have been less experienced with the use of NVGs. Following surgery, the LASIK group showed a significant improvement. This may be due, in part, to learning effects. In addition, the return to preoperative performance at 3 months postoperatively, after 2 months without any practice, supports this theory. Nevertheless, neither the PRK group nor the LASIK group demonstrated any loss in performance following refractive surgery.

We set as our primary outcome measure a comparison between the postoperative firing range scores without glasses to the preoperative scores with the best spectacle correction. This scenario reflects the operational goals of the Warfighter Refractive Eye Surgery Program. The Warfighter Refractive Eye Surgery Program was developed as a military readiness program to enhance soldiers' ability to deploy into a field environment or combat theater without the need for optical correction.[7] Before refractive surgery, the best option for the ametropic soldier (one with refractive error) was to wear glasses. Contact lenses are not authorized. Glasses have numerous drawbacks, not the least of which is the potential to get lost, broken, scratched, or fogged. Even without these difficulties, glasses are often incompatible with military equipment such as gas masks, helmet-mounted displays, and targeting devices. Night operations in particular pose a challenge to the spectacle-dependent soldier. In addition to incompatibility with NVGs, reflections from the surface of the glasses may signal the location of the soldier to enemy combatants, thus placing the soldier at higher risk. Because of this, many opt to go without correction they would need for optimal vision. Clearly, the best soldier is the emmetrope (free from refractive error) or near emmetrope who can function without corrective lenses. Refractive surgery makes this possible.

NIGHT FIRING RANGE SCORES THROUGH NVGS WITH AIMING LIGHT BEFORE AND AFTER EXCIMER LASER KERATOREFRACTIVE SURGERY

	PRK		LASIK	
NVG	Mean $\pm$ SD	p^a	Mean $\pm$ SD	p
Preoperative[b]	96.4 $\pm$ 2.7		86.3 $\pm$ 12.4	
1 month postoperative[c]	96.5 $\pm$ 3.7	0.973	96.2 $\pm$ 2.2	0.046
3 months postoperative	90.0 $\pm$ 8.9	0.19	88.6 $\pm$ 8.5	0.665

[a] Student's t test; comparison of preoperative to postoperative scores.
[b] Preoperative measurements done with best spectacle correction.
[c] Postoperative measurements done without correction.

A potential drawback to this study is the small sample size. The original sample size of 25 PRK and 25 LASIK patients was designed to provide sufficient statistical power to reveal within and between subject differences in the following visual performance and optical measures: high- and low-contrast visual acuity, large and small letter contrast sensitivity, glare testing, forward light scatter, refractive error, pupil size, corneal haze, corneal curvatures, corneal thickness, corneal topographic indices, wavefront aberrations, NVG performance (resolution, letter visual acuity and contrast sensitivity), and night firing performance. However, because of the high operational tempo with the current global war on terrorism, we stopped enrolling new subjects due to inability to establish good follow-up. Many soldiers were deploying and redeploying at a rate that made compliance with the protocol schedule impossible. We therefore elected to limit the data analysis to the night firing range scores. Although the sample size was too small to fully analyze the visual performance as originally intended, the number of subjects was sufficient to demonstrate a statistically significant improvement in night firing performance. A larger sample size would be necessary to determine whether quantitative relationships exist between performance measures (e.g., visual acuity, contrast sensitivity) and preoperative variables (e.g., corneal properties, refractive status, luminance level, pupil size, or refractive error) and to identify significant factors that may be predictive of visual and operational performance.

Conclusions

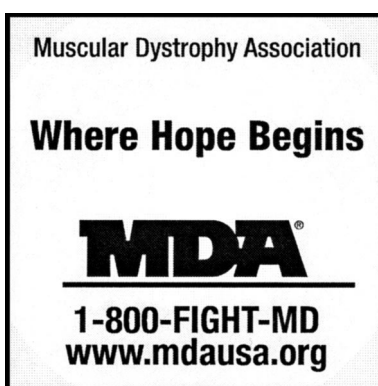This study was aimed to determine the effect of refractive surgery on night vision performance, more specifically the effect on the soldier's ability to perform tasks under conditions they may experience in the field. We conclude that the ability to fire a rifle under nighttime conditions without the need for optical correction is enhanced following both LASIK and PRK. This study supports the operational benefits of refractive surgery in the military.

Acknowledgments

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TECHNICAL REPORT

Anterior Segment Measurements Using Digital Photography: A Simple Technique

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ABSTRACT

Purpose. The purpose of this study is to describe a simple method of measuring anterior segment lesions from digital slit lamp images and confirm reliability of the technique.

Methods. Ten reference photos were taken of a PD ruler, refocusing on the ruler for each photo. Using Adobe Photoshop, the number of pixels per millimeter squared (area) and 1 mm (linear) were recorded for each photo. An Excel spreadsheet was set up to convert pixels to millimeters and millimeters squared. Interrater reliability was determined by two observers who independently calculated the area of 69 epithelial defects. A Bland and Altman plot was used to demonstrate the agreement between the two doctors.

Results. Interrater reliability was excellent as measured by an intraclass correlation coefficient (ICC 2,1) = 0.99. From the Bland and Altman plot it was determined that in 95% of cases, the area of the epithelial defect measured by provider 2 may be as much as 1.17 mm² less than or 1.09 mm² greater than that measured by provider 1.

Conclusion. This simple method, which allows accurate measurements from digital images using common off-the-shelf software, is a valuable tool for clinical documentation as well as for research purposes.
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Key Words: digital imaging, computer, slit lamp, ocular pathology, epithelial healing, image processing

Digital images have been used as a measurement tool clinically or in research for a number of innovative applications, including the measurement of retinal vessel diameter,[1] conjunctival vessel diameter,[2] exposed surface area of the eye,[3] radial keratotomy clear zone diameter,[4] pupil size,[5] corneal "white-to-white diameter" diameter,[6] as well as epithelial defects[7,8] and other surface lesions and ocular pathology. A variety of methods, including the use of expensive or proprietary software, have been reported in the literature.[1,5,7] We describe an easy method of measuring anterior segment lesions (using an epithelial defect as an example) from digital slit lamp images using image processing software such as Adobe Photoshop or Photoshop Elements and demonstrate reliability of the technique.

METHODS

Hardware and Software

All images where taken with a Sony DKC-5000 digital photo camera on a Haag-Streit BQ 900 slit lamp imported into a Macintosh G3 computer running Adobe Photoshop version 5.0. Images where saved at quality level 10 in Joint Photographic Experts Group (JPEG) format and transferred to a Dell Dimension 8400 desktop where photos were opened in Adobe Photoshop version 7.0.

Calibration

Measuring the surface area involves counting the number of pixels in a digital picture and converting pixel numbers to area. This technique can be used with both Adobe Photoshop and Photoshop Elements. Calibrating the number of pixels per millimeter squared can be obtained by taking a reference picture of a millimeter ruler. Both the ruler and the object being measured must be taken at the same magnification. To count the number of pixels in

a square millimeter, open the file that contains the picture of a millimeter ruler. Choose the rectangle marquee from the tool bar. Place the edge of the cursor at the edge of a millimeter mark. Left click on the mouse and then hold down on the shift key before you start to drag the cursor. This will keep the marquee square as the cursor is dragged from one millimeter mark to the next. Release the mouse button to outline a 1-mm area. Then click on "Image" under the menu bar and scroll down to the histogram option; the histogram function will count the number of pixels outlined in the millimeter square (Fig. 1).

To measure the numbers of pixels between points, use the measure tool from the tool bar. If the measure tool is not present, click and hold on the eyedrop tool. A list of other tools will appear; pick the measure tool (icon is a small ruler) from the list. Click and drag using the measure tool between two points. The distance in pixels can be read on the status bar under D1. If the reading is not in pixels, go to "Edit" on the menu options, scroll down to preferences, then pick units and rulers from the options listed. A preference window will pop open. Go to the ruler setting, which is under the unit type, and choose pixels. Now all readings with the measurement tool will be taken in pixels. Once the ratio of pixels per millimeter and millimeter squared is known, a spreadsheet can be created to automatically calculate distance and area.

Measuring Lesions

Open the file that contains the picture of the ocular lesion that needs to be measured. In this example, a corneal abrasion will be used. From the tool bar, click on the lasso icon, and then click and hold the left mouse button down as the object is traced. When the mouse button is released, the traced object will then be outlined with a flashing line. Click on "Image" under the menu bar and scroll down to the histogram option. A window will open with information on the outlined area including the number of pixels (Fig. 2).

If the area has distinct borders and is uniform in color, the magic wand tool can be used to outline the borders. The tolerance on the magic wand can be adjusted from zero to 255 to select colors that are similar. A low tolerance value selects colors that are similar and a high value selects a broader range of colors. A value of 35 works well in outlining fluorescein-stained epithelial defects.

If the object that needs to be traced is round or elliptical, the marquee tool can be used to trace the borders. In each case, use the histogram window to count the number of pixels in the outlined area.

To measure distance, click on the measuring tool. Place the crosshairs at the starting point, click and hold; drag the crosshairs to the end point that is being measured and then release. By holding down the shift key, the line being drawn can be forced perfectly vertical or horizontal. On the top of the screen is information on the line made. D1 is the number of pixels in that line (Fig. 3).

Reliability

Ten reference photos were taken refocusing on the PD ruler for each photo. The number of pixels per millimeter squared (area) and 1 mm (linear) were recorded for each photo using the previously mentioned method. Descriptive statistics in Microsoft Excel
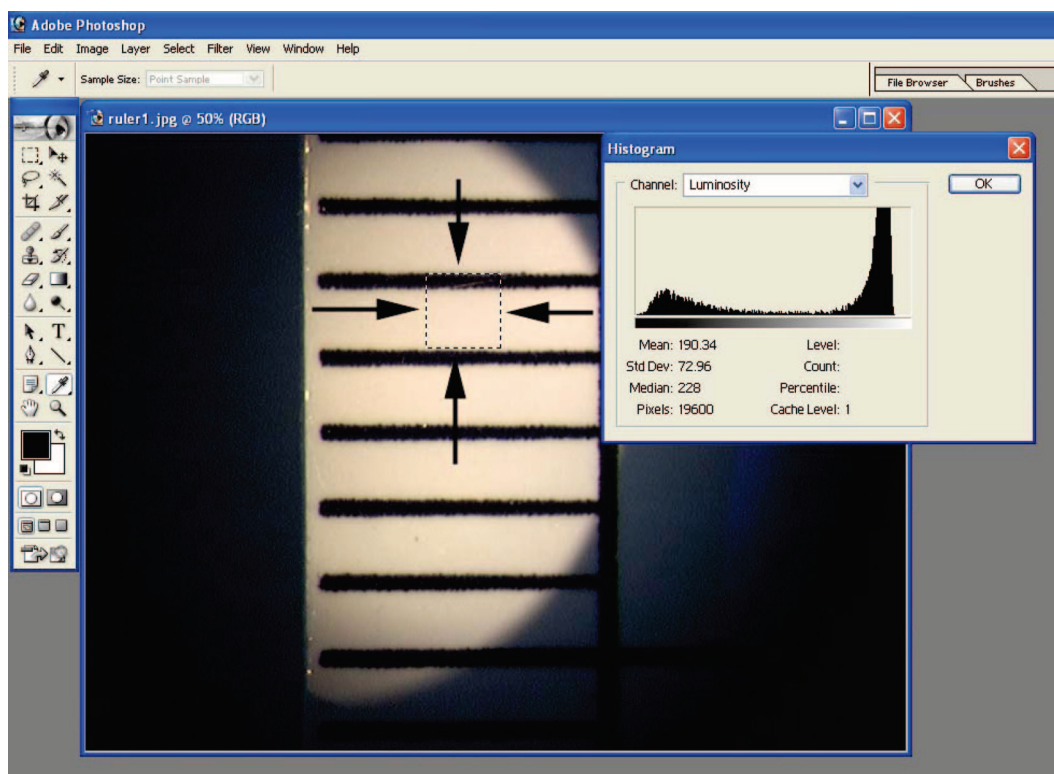

FIGURE 1.

The number of pixels per millimeter squared is displayed in the histogram box. Pixels: 19,600. The square marquee tool was used to outline a square millimeter while holding down the shift key to force a 1:1 aspect ratio of the box.
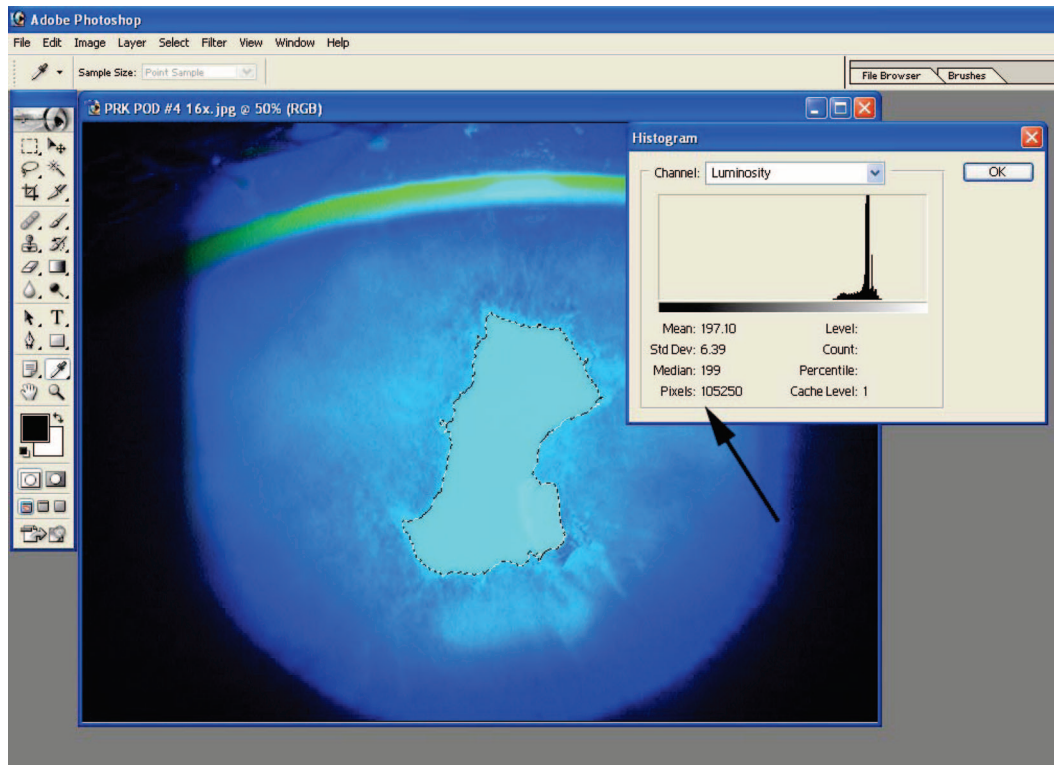
FIGURE 2.
The epithelial defect was outlined using the lasso tool. The histogram window displays the total number of pixels in the highlighted area. Pixels: 105,250.
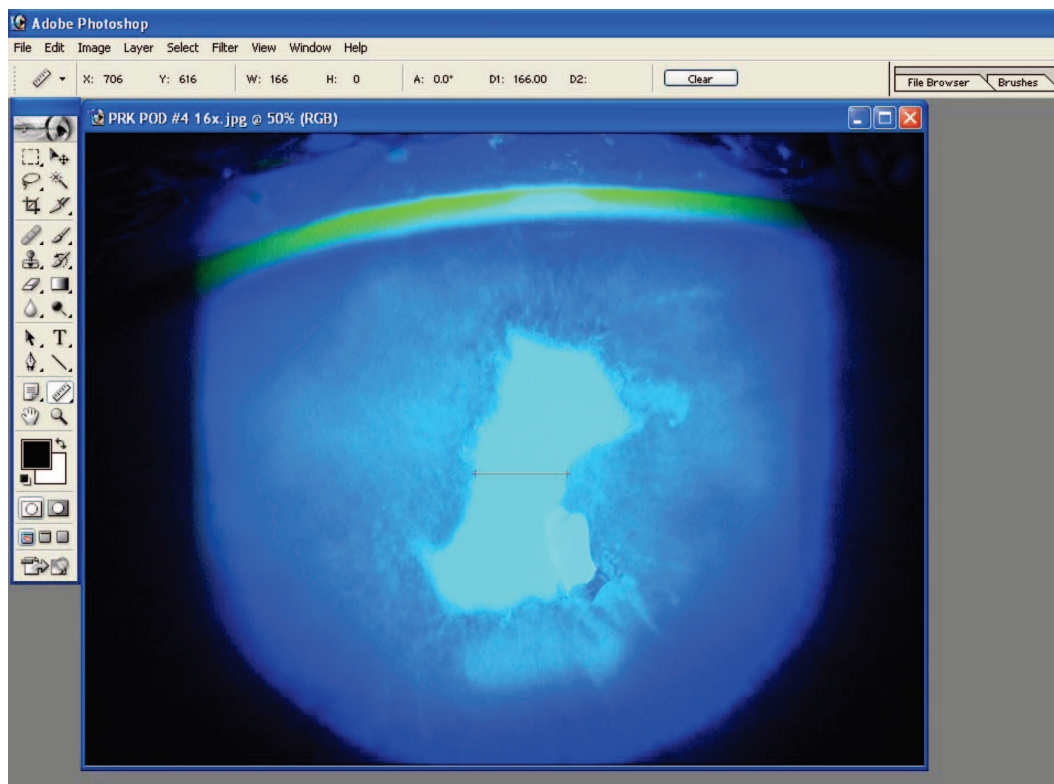

FIGURE 3.
Linear distance is obtained with the measure tool. The number of pixels between the two points being measured on the epithelial defect is listed below the menu at D1: 166 pixels.

were used to calculate mean, standard deviation, and confidence interval from the reference data.

Interrater reliability was measured by comparing results from two separate observers who independently calculated the area of 69 epithelial defects, which were secondary to photorefractive keratectomy (PRK) on various postoperative days. Reliability is described using the intraclass correlation coefficient (ICC) based on the two-way random-effects analysis of variance for a single measurement, ICC (2, 1). Reliability was analyzed using Statistical Package for the Social Sciences (SPSS) for Windows (version 13.0; Chicago, IL). Differences between raters are presented graphically using the Bland and Altman plot.

RESULTS

Using the 10 reference photos, the average number of pixels in 1 mm was calculated as 138 with a standard deviation of 0.5. A 95% confidence level was calculated at plus or minus 0.32 pixels. The average number of pixels in a square millimeter was 19,588 with a standard deviation of 579. The 95% confidence interval was plus or minus 378 pixels. The confidence interval was calculated in Microsoft Excel by using the confidence function along with the descriptive statistics data obtained from the reference photos.

To demonstrate interrater reliability, separate providers calculated the area of different epithelial defects and the results were compared. Reliability between raters, as measured by the ICC (2, 1), was 0.99, signifying a very strong relationship between the two providers' measurements. The ICC represents the strength of the relationship between two variables but does not provide information about their agreement. One method for establishing agreement between the providers' measurements is demonstrated in a Bland Altman plot[9] (Fig. 4), a plot of the difference between the measurements against the mean of the measurements. The mean difference was -0.04 mm^2. The limits of agreement are -1.17 mm^2 and 1.09 mm^2. Thus, in approximately 95% of cases, the area of the epithelial defect measured by provider 2 may be as much as 1.17 mm^2 less than or 1.09 mm^2 greater than that measured by provider 1. This analysis assumes that the distribution of the differences is equivalent across all means. In this case, however, as the mean increases, so does the difference between the measurements.
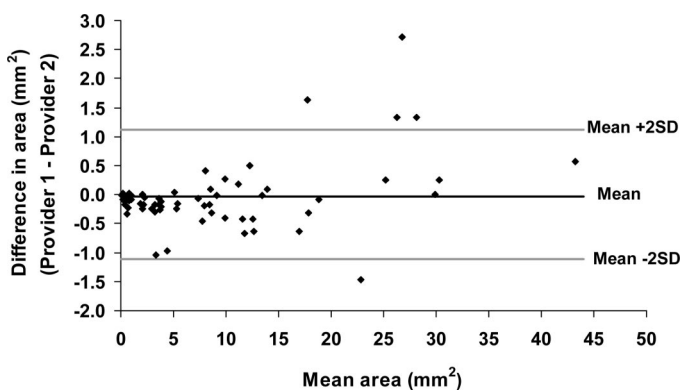

FIGURE 4.

Bland and Altman plot of the area of epithelial defect. Differences between providers are plotted against the average of the defect area. The mean of the rater differences and limits of agreement (± 2 standard deviations) are designated on the graph.

DISCUSSION

This method is a practical and inexpensive way to obtain accurate quantitative measurements with digital photography. Although approximations can be made with a slit lamp, this technique has its disadvantages. Eye movements can make it difficult to line up the slit lamp beam. In addition, size of asymmetric lesions may be difficult to calculate using simple geometric formulas. In a study by Mekerji et al., they compared manual measurement of epithelial defects using a slit lamp with measurement using image analysis software.[7] Although they found no significant difference between the two methods, the image analysis software was more accurate. In that study, they used Image Pro Plus software from Media Cybernetics, which costs over $3000, and thus they used the slit lamp technique as a less expensive alternative. The method we have outlined is an inexpensive measurement technique that can be done without having to purchase expensive imaging software. Adobe Photoshop Elements version 3.0 and Photoshop CS2 cost approximately $88.94 and $548.99, respectively.

The method described is applicable to most computer systems as long as the reference photos and the ocular images are consistently obtained, saved, and opened in the same way. This will provide a more accurate pixels-to-millimeter ratio. For most pictures, using the 10 or 16 magnification on the slit lamp is sufficient. However, the photograph of both the ruler and the ocular lesion must be taken at the same magnification. Focus must be obtained by adjusting the distance of the slit lamp to the image. This ensures each image is captured at the same plane of focus. An autofocusing system on the camera must not be used with this method.

Files can be saved as JPEG or Tag(ged) Image File Format (TIFF). Saving files as JPEG compresses the image. Although this can affect the image quality if pictures are opened and resaved repeatedly, it does not appear to affect the number of pixels of the object that is measured. This was tested by opening and saving the same photo 10 times with low- and high-quality JPEG compression. There were no changes in the ratio of pixels to millimeters in any of the resaved photos. Saving files as a TIFF image eliminates concerns of image compression; however, saved TIFF photos will require more memory for storage.

When measuring epithelial defects, fluorescein stain facilitates visualization of the defect. The cobalt blue filter enhances the defect's border through fluorescence. If the defect is small, not enough fluoresced light is reflected back to the camera and the borders may be difficult to distinguish. In this circumstance, taking the picture in white light may yield better results. The fluorescein, however, may still afford good border contrast without the use of a cobalt filter. To isolate the fluorescence, one may consider using a pair of interference filters, which includes a yellow barrier filter that is placed in front of the camera's sensor.

This simple method, which allows precise measurements from digital images using common off-the-shelf software, is a valuable tool for clinical documentation as well as research purposes. Although this example used a corneal abrasion, this same technique can be used to measure other ocular lesions. Using imaging processing software such as Adobe Photoshop or Photoshop Elements, doctors and trained staff can accurately measure the surface area of a lesion, which can be accurately compared with subsequent photographs for change in size.

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