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14. ABSTRACT The purpose of this study was to determine if topical cyclosporine A, when added to the standard post-operative regimen, leads to a reduction in the formation of haze and better visual acuity outcomes in patients after photorefractive keratectomy. This randomized, controlled trial took 120 patients and randomized each to have one eye receive the standard regimen and the fellow eye receive the standard regimen with the addition of topical cyclosporine A twice daily for 6 months. Patients were followed for 1 year after surgery and, at each visit, had uncorrected visual acuity, best corrected visual acuity, slit lamp haze, and pentacam haze measured. Data were then analyzed using a paired T-test in Microsoft excel to determine significance. There were no statistically significant differences in any of the metrics measured in this study at any of the follow-up visits with the exception of the average time it took patients to reach 20/40 (legal to drive) vision. Eyes that received cyclosporine in addition to the standard regimen reached 20/40 on average at 1.8 weeks post-op, while eyes that received only the standard regimen took 1.9 weeks (p=0.04). While this is statistically significant, it is unlikely clinically significant with only 0.1 week difference on average between the 2 groups. This finding is important in that it demonstrates that the addition of topical cyclosporine (which some refractive surgeons often employ in their post-operative regimens) to our standard post-operative regimen does not improve visual outcomes out to 12 months after surgery and also does not decrease corneal haze. This is especially important because it provides evidence that topical cyclosporine does not provide a clinically significant advantage worth the additional cost of the medication.						
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Medical Report

Evaluation of Topical Cyclosporine in Preventing the Development of Corneal Haze after Photorefractive Keratectomy

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Purpose: The risk of haze following photorefractive keratectomy (PRK) is commonly mitigated with steroids, but they are associated with many side effects. Specific targeting of the pro-inflammatory mediators using topical cyclosporine A (CsA) may achieve similar results with fewer side effects. The purpose of this study is to examine the efficacy of topical cyclosporine A (CsA) following PRK in regards to visual outcomes and the development of corneal haze.

Methods: This is a randomized, controlled trial which took place at the Joint Warfighter Refractive Surgery Center, Lackland AFB, TX. 120 patients received standard PRK and were randomized to receive either cyclosporine in one eye or the other. They were then evaluated post-operatively to determine visual acuity and also had slit-lamp evaluation for haze formation, and objective haze measurement using Pentacam technology.

Results: There was no significant difference between those getting csa and those getting control with the exception of time to reach 20/40 visual acuity.

Conclusions: When used in addition to topical steroids, topical cyclosporine A does not significantly help reduce corneal haze and does not provide any clinically significant difference in visual outcomes.

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INTRODUCTION

Despite ongoing improvements in refractive surgery techniques and instrumentation, optimization of corneal wound healing and the prevention of post-operative haze remain essential to providing the best visual outcome for patients after surgery. Even in the setting of an otherwise flawless procedure, mild corneal haze can cause postoperative quality of vision complaints and in more severe cases impact final visual acuity.¹

Two widely accepted medications are currently used to decrease the incidence of haze: mitomycin C and steroids. Mitomycin C is a cell cycle regulator and inhibits cellular proliferation by arresting the cell cycle between the G and S₁ phases.² The purpose of this treatment is to prevent haze by slowing fibroblast proliferation and concomitant fibrotic scar deposition at the corneal wound site. Unfortunately, mitomycin C also inhibits epithelial, stromal, and endothelial replication and can lead to vascular endothelial injury and secondary tissue necrosis.³ Due to these side effects, steroids are often preferred over mitomycin C for the prevention of post-surgical haze. Steroids prevent haze by a different mechanism: they inhibit inflammatory mediators by down regulating phospholipase A2 which in turn blocks the cell signaling cascades that lead to corneal inflammation and phagocyte activation.⁴ However, topical steroids have their own side effects such as delayed wound healing, increased risk of infection, posterior subcapsular cataracts, ocular hypertension, and glaucoma.^{5,6}

Because of the side effect profiles of these two common medications, refractive surgeons have long been interested in finding a medication which prevents haze and has a better safety profile than steroids or mitomycin C. A host of medications have been examined, including NSAIDS,^{5,7,8} anti-VEGF and anti TNF- α compounds⁹, nicergoline and β -glucan,¹⁰ and IL1-ra.¹¹ Many refractive surgeons anecdotally use topical cyclosporine A (CsA), which is FDA approved

for the treatment of dry eye, for haze prevention. It is important to note that the addition of CsA to the standard regimen creates an additional cost in both the military and civilian setting.

Cyclosporine A (CsA) is an autoimmune regulatory molecule which has a narrower anti-inflammatory target scope than steroids. CsA inhibits calcineurin, which in turn more blocks T helper cells and Th2 cells from producing the downstream cytokines and chemokines that activate CD4 and CD8 cells.¹² Although toxicity exists when the medication is taken orally,¹³ during topical delivery to the cornea, almost none of the drug penetrates either intraocularly or into the bloodstream.¹⁴ The drug does not inhibit corneal wound healing¹⁵ and has not been associated with any serious drug related events, though an ocular burning sensation is common.¹⁴

In the post-refractive surgery setting, some surgeons experiment with shorter steroid tapers and long postoperative courses of CsA to decrease the amount of time that patients are subjected to steroids and their potential side effects. Steroids are necessary because they are the standard of care, but some surgeons note that steroids may also bridge the gap that exists between the time that CsA is started and the time that it reaches its maximum effect, which usually occurs in four weeks but could be as long as two to six months for full immunomodulation.^{16,17}

To provide evidence for CsA after refractive surgery, many studies examining the drug after laser in-situ keratomileusis (LASIK) have been undertaken that demonstrate improvement in corneal sensitivity,¹⁸ refractive predictability,¹⁹ and the time needed for visual recovery.²⁰ One recent study by Hessert et al also examined CsA in the post-photorefractive keratectomy (PRK) setting.²¹ They did not demonstrate any difference in visual recovery, final visual acuity, patient symptoms, or postoperative cytokine composition of the tear film between the group that received CsA bilaterally and the group that did not. Unfortunately, the study did not assess

postoperative haze and did not measure patient compliance with treatment during their three month trial.

This study was designed to evaluate if CsA, when added to our standard post-operative regimen, contributes to decreased corneal haze after PRK. A six month treatment period (twice the length of the Hessert study)²¹ was employed, consistent with the six month period during which patients continued to show improvement for dry eye in its clinical trials.^{16,17} This study evaluated the difference between two eyes of the same patient: one eye receiving a standard post-PRK regimen (steroids) and the other receiving the standard regimen plus topical cyclosporine A (0.05%). We examined if topical cyclosporine provides an added benefit to steroids with regards to post-operative visual acuity (uncorrected or best-corrected), time to recover uncorrected 20/40 distance vision, slit-lamp corneal haze, and Pentacam corneal haze.

METHODS

Approval for this prospective, randomized, controlled study was granted by the Wilford Hall Medical Center (now Wilford Hall Ambulatory Surgery Center) Institutional Review Board. After a power analysis was performed, one hundred twenty patients undergoing PRK at the Joint Warfighter Refractive Surgery Center (JWRSC) in Lackland Air Force Base, TX were recruited, and informed consent was obtained. Enrollment criteria included patients undergoing bilateral primary PRK treatments for spherical and spherocylindrical myopia (age ≥ 21) at the date of pre-operative evaluation. Per our standard protocol, patients with the following characteristics were excluded: unstable refraction, ocular hypertension, glaucoma, previous ocular surgery, systemic diseases that could alter the wound-healing process (e.g. connective tissue disease or diabetes mellitus), pregnancy, use of systemic corticosteroids, abnormal ophthalmic examination, and topographic evidence of keratoconus or warpage from contact

lenses. Systemic medications were permitted unless they were known to affect the cornea. Soft contact lenses were removed at least thirty days and hard contact lenses at least one month per decade of wear prior to treatment. Topical eye medications were stopped one week prior to surgery.

Patients underwent PRK using either an Allegretto Wave[®] Eye-Q 400 Hz Wavefront Optimized laser treatment or VISX[™] CustomVue[™] STAR S4 IR[™] Wavefront Guided laser treatment. Ablation patterns included a 6.5mm optical zone with a blend zone extending to 8mm on the VISX[™] and 9mm on the Allegretto[®]; a bandage soft contact lens was placed at conclusion of the treatment. All eyes received standard postoperative management during the first week including topical moxifloxacin 0.5% and fluoromethalone 0.1% four times daily, frequent preservative-free artificial tears, oral vitamin C, and oral oxycodone/acetaminophen 5/325mg every 4 hours as needed; tetracaine 0.5% was used as a rescue medication for breakthrough pain only. Steroid drops were tapered over 1-3 months post-surgically depending on the amount of refractive error treated.

Each patient was randomized to additionally receive topical cyclosporine A 0.05% (Restasis, Allergan) in either the right or left eye twice daily for six months. Patients who had significant dry eyes not controlled effectively by artificial tears and ointments were permitted to restart Restasis (in both eyes) for the treatment of dry eyes after completing the treatment portion (6 months) of this study. This study was not masked; medications were labeled and packaged in the standard fashion by the manufacturer.

At post-operative visits on days 1 and 4, uncorrected visual acuity (UCVA), and best corrected visual acuity (BCVA) were measured and patients completed a satisfaction survey. This survey provided further comparisons of patients' interpretations of vision in both eyes, monitoring for potential side effects, and overall satisfaction (both in each eye individually and

overall). At 1, 2, 3, 4, 6, 9, and 12 months postoperatively, patients' UCVA and BCVA were again measured, they completed the same survey, and any corneal haze present was quantified subjectively by an ophthalmologist and objectively with a Pentacam (OCULUS®, Dutenhofen, Germany). Subjective corneal haze was defined as follows: 0-totally clear; 0.5-faint corneal opacity seen only by oblique indirect illumination; 1-opacity of minimal density seen with difficulty with direct and diffuse illumination; 2-easily visible opacity; 3-denser opacity that significantly decreases the visualization of intraocular structures (such as the iris and retina); 4-opaque cornea. Pentacam haze was measured using the highest densitometry value on their scans; this was taken only in patients noted to have corneal haze on slit lamp examination. Patients that were not noted to have slit lamp haze had '0' input for their densitometry. In the event that haze developed and became severe enough to cause a significant decrease in the patient's vision, patients were offered further treatment for their corneal haze.

Other variables analyzed included epithelial healing time (measured in days) and time to recovery of 20/40 vision. Data were analyzed using a paired t-test in Microsoft Excel and were reviewed by the Medical Wing Contract Statistician.

RESULTS

One hundred twenty patients were enrolled in the study. Of these, 111 were included in the statistical analysis. Patients were removed for not reporting for surgery (1), opting for monovision (2), applying cyclosporine to both eyes (2), stopping cyclosporine after one week (1), and moving prior to adequate data collection at one month (3). The mean age for patients included in the analysis was 37.6 years and 68% of the patients were female. The average spherical equivalent in treatment eyes was -2.90 and -3.37 in control eyes ($p=0.37$). There was no significant difference ($p=0.52$) in epithelial healing time between the treatment and control

eyes with treatment eyes healing in an average of 4.54 +/-1.21 days and control eyes healing in an average of 4.56 +/- 1.15 days. There was a significant difference (n=111, p=0.04) in the time to recovery of 20/40 (legal driving) visual acuity with treatment eyes taking an average of 1.8 weeks (SD=1.6) and control eyes taking an average 1.9 weeks (SD=1.6). Seventy seven percent of treatment eyes and 73% of control eyes were 20/40 or better at 1 week with only 3% of treatment and control eyes taking 2 months to reach 20/40.

Uncorrected distance visual acuity at 1 month was not significantly different (n=111, p=0.70) with an average in treatment eyes of 20/28 (48.1 letters correct, SD=7.0) and an average in control eyes of 20/28 (48.4 letters correct, SD=7.3). There was no significant difference (n=111, p=0.94) in best-corrected distance visual acuity at 1 month with both groups averaging 20/20 (treatment eyes 56.1 letters correct, SD=3.1; control eyes 56.1 letters correct, SD=3.7). No treatment eyes showed slit-lamp corneal haze at 1 month and only 2 control eyes showed trace corneal haze at 1 month; this was not statistically significant (n=111, p=0.16). This was also the case for Pentacam haze at one month with p=0.32.

Uncorrected distance visual acuity at 3 months was not significantly different (n=104, p=0.44) with an average in treatment eyes of 20/20 (54.8 letters correct, SD=5.2) and an average in control eyes of 20/20 (54.3 letters correct, SD=6.4). There was no significant difference (n=104, p=0.12) in best-corrected distance visual acuity at 3 months with both groups averaging 20/17 (treatment eyes 59.2 letters correct, SD=3.1; control eyes 58.7 letters correct, SD=3.4). Five treatment eyes showed slit-lamp corneal haze at 3 months (mean=0.04, SD=0.18); 5 control eyes also showed corneal haze at 3 months (mean=0.03, SD=0.14); the difference was not statistically significant (n=104, p=0.48). Three of the patients showed bilateral haze at 3 months. There was no significant difference in Pentacam haze at 3 months (n=102, p=0.42)

Uncorrected distance visual acuity at 6 months was not significantly different (n=99, p=0.16) with an average in treatment eyes of 20/18 (57.6 letters correct, SD=4.3) and an average in control eyes of 20/18 (56.8 letters correct, SD=6.2). There was no significant difference (n=99, p=0.87) in best-corrected distance visual acuity at 6 months with both groups averaging 20/17 (60.0 letters correct, SD=2.9 for treatment eyes, 60.1 letters correct, SD=3.0 for control eyes). Five treatment eyes showed slit-lamp corneal haze at 6 months (mean=0.06, SD=0.27) and 5 control eyes showed corneal haze at 6 months (mean=0.04, SD=0.18); there was no significant difference noted (n=99, p=0.55). Again, 3 patients demonstrated bilateral haze. There was no significant difference in Pentacam haze at 6 months (n=97, p=0.08).

Uncorrected distance visual acuity at 12 months was not significantly different (n=78, p=0.06) with an average in treatment eyes of 20/18 (57.8 letters correct, SD=3.9) and an average in control eyes of 20/18 (56.9 letters correct, SD=5.7). There was no significant difference (n=78, p=0.71) in best-corrected distance visual acuity at 12 months with both groups averaging 20/17 (treatment eyes=59.8 letters correct, SD=3.0 and control eyes mean=59.7 letters correct, SD=3.2). Four treatment eyes showed slit-lamp corneal haze at 12 months (mean=0.03, SD=0.11) and 3 control eyes showed corneal haze at 12 months (mean=0.02, SD=0.10); there was no significant difference noted (n=78, p=0.32). Again, 3 patients showed bilateral haze (all patients had trace haze). There was also no significant difference noted in Pentacam haze at 12 months (n=76, p=0.34).

DISCUSSION

Consistent with prior studies, there was no evidence of delayed epithelial healing in eyes receiving topical cyclosporine. There was a statistically significant difference in the time to recovery of 20/40 visual acuity, with treatment eyes reaching that mark in an average of 1.8

weeks and control eyes 1.9 weeks. While this is statistically significant, it is unlikely clinically significant with a mean difference of only 0.1 weeks. The 20/40 mark is important because this vision is that which is required (in at least one eye) for driving (in the state of Texas). It could be extrapolated that 20/40 vision, then, is that vision at which a troop may be able to return to duty, in at least some form. Averaging around 2 weeks in both treatment and control eyes is consistent with the amount of leave that is typically taken for recovery after photorefractive keratectomy.

For the patient population followed in this study there were no significant differences in uncorrected or best corrected visual acuity at 1, 3, 6 and 12 months after photorefractive keratectomy. Additionally, there was no significant difference in slit-lamp or Pentacam haze at 1, 3, 6 and 12 months after surgery. This is especially important in the case of Pentacam haze, as the data was collected in a manner that would maximize the chances that a statistically significant difference could be found (haze eyes had true densitometry input, while non-haze eyes had '0' input instead of the average corneal densitometry which would be in the low 20s). These findings are important because they demonstrate that the addition of topical cyclosporine (which some refractive surgeons often employ in their post-operative regimens) to our standard post-operative regimen does not improve visual outcomes out to 12 months after surgery and also does not decrease corneal haze. This is especially important because it provides evidence that topical cyclosporine does not provide a clinically significant advantage worth the additional cost of the medication.

There are a few limitations to this present study. The first is that a number of patients were unable to complete the study (n at the start was 111, by month 12 n=78), which lowered the power for the later data analyses. Also, determining the maximal densitometry for the Pentacam haze required manual review of multiple scans for each eye with haze (at multiple levels of the cornea) which creates a situation where the true highest value may be missed.

One potential direction for future studies would be analyzing mapped slit lamp haze and comparing them to a real densitometry map of the cornea on the Pentacam to determine the correlation between the 2 measurements as well as the densitometry values for differing degrees of corneal haze. Another study could examine the efficacy of topical cyclosporine in addition to the standard regimen (vs. the standard regimen) in eyes that have higher refractive errors, as these eyes are at an increased risk for the development of corneal haze.

CONCLUSION

Topical cyclosporine (in addition to the standard post-operative regimen) is not worth the additional cost as it does not convey any clinical benefit over the standard post-operative regimen in regards to visual acuity (both uncorrected and best corrected) or in the development of corneal haze after photorefractive keratectomy.

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