Original article

Prospective comparison of chilled versus room temperature saline irrigation in alcohol-assisted photorefractive keratectomy

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Abstract

Introduction: Chilled saline is commonly used to irrigate the ocular surface after photorefractive keratectomy (PRK) and is often considered by the patients to be uncomfortable. Room temperature (non-chilled) saline may be a safe and less painful alternative. **Objectives:** To compare pain and visual outcomes after irrigating the ocular surface with chilled saline versus room temperature saline in alcohol assisted PRK. **Materials and methods:** In this prospective, single-masked, randomized, contralateral eye study, myopic eyes were treated with PRK. Immediately after laser ablation one eye was irrigated with chilled saline and the other with non-chilled saline. Primary outcomes measured were pain, haze, uncorrected (UCVA) and best-corrected (BCVA) visual acuities, and manifest refraction. **Results:** Each group comprised of 40 eyes. There was no significant difference in pain between the groups at any point during five days after surgery. At 6 months the mean UCVA was -0.08 logMAR ± .077 [SD] (20/17) and -0.07 ± .074 logMAR (20/17) in the chilled and non-chilled groups respectively ($p = .35$). Both groups achieved 95% UCVA of 20/20 or better. The manifest refraction spherical equivalent (MRSE) was -0.05 ± 0.21 D and -0.025 ± 0.27 D respectively ($p = .79$). There were no lines lost of BCVA and no haze observed. Similar outcomes were observed with regard to pain and vision in both groups. **Conclusion:** The use of room temperature saline irrigation during PRK appears to be safe and effective.

Keywords: photorefractive keratectomy, PRK, chilled saline, balanced salt solution, refractive surgery

Introduction

Chilled saline is commonly used to irrigate the ocular surface immediately after photorefractive keratectomy (PRK). This type of treatment, referred to as cold therapy, has been used to treat pain and swelling in musculoskeletal injuries for generations (Ernst & Fialka, 1994). Several studies suggest the use of chilled saline during PRK helps limit postoperative pain and prevent haze (Kitazawa et al, 1999; Nizuma et al, 1994; Stein et al, 1999; Tsubota et al, 1993); however, these early studies were performed using older-generation excimer lasers and surgical techniques. Since the mid-1990s, advances in laser technology and surface ablation techniques including the use of topical NSAIDs (Caldwell & Reilly, 2008), better bandage contact lenses (Cherry et al, 1994; Edwards et al, 2008; Engle

et al, 2005), prophylactic mitomycin C (Carones et al, 2002), and systemic vitamin C (Stojanovic et al, 2003) have significantly reduced postoperative pain and haze (Trattler & Barnes, 2008). The process of irrigating the ocular surface with chilled saline may be uncomfortable or even painful for the patient, and no modern studies have supported the necessity of this step as part of the PRK procedure. Our working hypothesis proposes that the use of chilled saline irrigation may be unnecessary given the technological advances of modern PRK. This prospective, single-masked, randomized, contralateral eye study compares outcomes of irrigating the ocular surface with chilled saline versus room temperature (non-chilled) saline in PRK.

Materials and methods
An Institutional Review Board approved the study and written consent was obtained from each patient. All patients included met the Food and Drug Administration guidelines for VISX CustomVue™ (Advanced Medical Optics, Santa Ana, CA) laser surgery. Patients with clinically significant lens opacities, previous corneal or intraocular surgery, keratoconus, unstable refraction, autoimmune disease, pregnancy or breastfeeding, or immunosuppressive therapy were excluded. Contact lenses were discontinued for at least one week for soft and for six weeks for rigid, gas-permeable lenses prior to screening. All patients had preoperative assessments including uncorrected visual acuity, best-corrected visual acuity, tonometry, slit lamp and dilated fundus examinations. Corneal topography and thickness were measured using the Pentacam LC topographer (OCULUS, Wetzlar, Germany). All eyes received at least five preoperative wavefront analyses with the VISX WaveScan™ aberrometer (Fourier Advanced Medical Optics, Santa Ana, CA). Contrast sensitivity was measured in controlled mesopic conditions at 3, 6, 12, and 18 cycles per degree using the Vectorvision CSV-1000E chart (Vectorvision, Greenville, Ohio).

The dominant eye of each enrolled patient was randomly assigned to either the chilled or non-chilled saline group, with the fellow eye receiving alternate treatment.

PRK was performed in the following manner. Patients received two drops of topical tetracaine 3-5 minutes before the procedure and two additional drops just prior to insertion of the eyelid speculum. No systemic sedation was utilized preoperatively or intraoperatively. The periocular region was prepped with 5% povidone iodine swabs and the lashes were draped with sterile adhesive plastic. The right eye was treated first and the left eye second for all patients, regardless of randomization. An adjustable eyelid speculum was placed and an 8 mm well was positioned on the epithelial surface centered over the pupil. A 20% ethanol solution was instilled and remained in contact for 30-40 seconds, followed by rinsing and then gentle debridement with a spatula. Laser ablation was carried out using Fourier v.5.10 software on the VISX Star S4 CustomVue™ laser creating a 6.5 mm optical zone and 8.00 mm transition zone. Mitomycin C was not used at any time during the study. Immediately after ablation, the ocular surfaces were cooled with 15 ml of either chilled (2.8 – 3.9 C) Balanced Salt Solution (BSS® Alcon Laboratories, Inc, Fort Worth, TX) or non-chilled (16 – 20 C) BSS over a period of 30-40 seconds. This was followed by one drop of gatifloxacin 0.4%, prednisolone acetate 1%, ketorolac tromethamine 0.4% and a bandage soft contact lens. Ketorolac tromethamine was continued 2 times a day for 3 days and then discontinued. Gatifloxacin and prednisolone acetate were continued four times a day for 1 week. Bandage contact lenses were removed once re-epithelialization was complete, typically on post-operative day four or five. Prednisolone acetate was continued twice a day until the one month visit and then the patients were switched to a weaker steroid to be used two times a day for month two, and once daily for post operative month three. All patients were instructed to use

preservative-free artificial tears at least four times per day for the duration of the study. All patients were prescribed hydrocodone/acetaminophen tablets to use as needed for severe pain.

All surgeries were performed in the morning. After surgery, patients were asked which eye was more uncomfortable during BSS irrigation. Patients then recorded subjective pain for each eye using the Ocular Pain Scale log every 12 hours for the first five days after surgery. The log consisted of numbers 0 – 10 with zero being "no pain" written at one end and ten being "worst pain imaginable" at the other. At each assessment period, patients were asked to circle the number that best represented the severity of pain they were experiencing. In addition, patients were interviewed concerning their use of oral pain medication during the first 3 days after surgery.

Corneal sub-epithelial haze was graded using the Fantes scale: grade 0 = clear; grade 0.5 = trace opacity only seen by indirect broad illumination; grade 1 = minimal density seen with difficulty with direct and diffuse illumination; grade 2 = mild haze visible with direct focal slit illumination; grade 3 = moderately dense opacity that partially obscures iris detail; and grade 4 = severely dense opacity that obscures intraocular structures (Fantes et al 1990).

Uncorrected visual acuity (UCVA), loss or gain of best-corrected visual acuity (BVCA), manifest refraction, higher order aberrations and contrast sensitivity were compared for each group. Visual outcome statistics were compiled for three and six-month postoperative visits. Wilcoxon signed rank tests were used to analyze ordinal data (e.g. pain and haze), and student t-tests were used for numerical data.

Results
Eighty-eight eyes of 44 patients were initially enrolled in the study, with 44 eyes enrolled in the chilled group and 44 eyes in the non-chilled group. 23 eyes were right eye dominant and 21 left eye dominant. The mean age was 31.8 years (range 22 to 46) with 68.8% men and 31.2% women. The mean pre-operative spherical

equivalent was -3.42 D (-0.25 to -6.25) in the chilled group and -3.43 D (-0.50 to -7.13) in the non-chilled group. There was no statistically significant difference in any preoperative characteristics between the two groups including amount of myopia and/or astigmatism, higher order aberrations and contrast sensitivity performance. Four patients discontinued the study due to noncompliance or relocation. Data were collected on 80 eyes of 40 patients.

Pain
Both groups reported a significant increase in pain (chilled $p = .008$; non-chilled $p = .003$) from the time of surgery (0 hours) to 36 hours after surgery, with a gradual diminution over the next 36-48 hours (Fig. 1). There was no significant difference in pain between the chilled and non-chilled group at any point during the first five days after surgery, and most patients reported mild to moderate pain over the recording period. Although there was a trend for the chilled group to rate the irrigation step as more uncomfortable (mean 2.95 ± 0.78) at the time of surgery than the non-chilled group (mean 2.48 ± 0.64), this did not reach statistical significance ($p = .08$). Further sub-classification of pain into mild, moderate and severe did not reveal any statistically significant differences, although the chilled group had a trend toward more pain at the time of surgery (Figure 2).

Oral pain medication usage varied with most patients using hydrocodone/acetaminophen tablets, generally less than five doses, starting the day of surgery. Seven patients only used ibuprofen tablets and four patients did not use any oral pain medication (Table 1).

Haze
Two eyes in the chilled group had observable haze (one grade 0.5, and one grade 1) at 3 months. Neither eye had loss of BCVA or contrast sensitivity. These patients received no intervention for haze other than continued use of artificial tears, and steroid drops were tapered or discontinued per the study protocol. No haze was recorded in the non-chilled group at three months postoperatively. No haze was found in either group at the six-month postoperative visit,

including in the two eyes in the chilled group that previously had haze.

Visual acuity and refraction

The average UCVA at postoperative month six was 20/17 (logMAR -0.08 ± .077) in the chilled group and 20/17 (logMAR -0.07 ± .074) in the non-chilled group (Table 2). Thirty-eight (95%) eyes in each group achieved an UCVA of 20/20 or better and 40 (100%) eyes in each group achieved an UCVA of 20/25 or better. Neither group lost any lines of BCVA. Seven eyes in the chilled group and five eyes in the non-chilled group gained > 1 line of BCVA, but there was no significant difference ($p = .43$) between the groups. The manifest refraction spherical equivalent (MRSE) at six months was -0.05 ± 0.21 D in the chilled group and -0.025 ± 0.27 D in the non-chilled group ($p = .79$).

Secondary outcomes

Total higher order aberrations root mean square (HOA rms) with a > 6 mm pupil was measured with the VISX WaveScan™ aberrometer. No difference was found in the total HOA rms values between the two groups preoperatively ($p = .86$), at three-months ($p = .53$), or at six-months ($p = .77$) (Fig. 3). As expected, total HOA increased from preoperative to six-month measurements but the difference was not statistically significant (chilled $p = .15$, non-chilled $p = .09$). Contrast sensitivity using the Vectorvision CSV-1000E chart also demonstrated no significant difference between the two groups preoperatively ($p = .95$), at three-months ($p = .64$), or at six-months ($p = .36$).

High myopia

Ten (five eyes in each group) of the 80 eyes had a preoperative MRSE > - 6.00 D. Analysis of the group demonstrated no significant difference in outcomes from the eyes with low to moderate myopia. The high myopia group had no haze or lines lost of BCVA at six months. The six-month UCVA (chilled 20/17, non chilled 20/19, $p = .24$) and MRSE (chilled +0.10 ± 0.37, non-chilled +0.15 ± 0.57, $p = .86$) were also not significantly different between the chilled and non-chilled groups and from the eyes with low to moderate myopia.

Discussion

Studies supporting the use of chilled saline irrigation in PRK to prevent pain and corneal haze are primarily from the 1990s and are based on out-dated laser technology and surgical
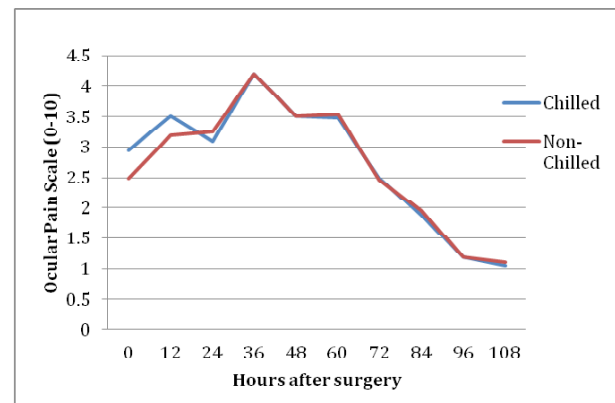

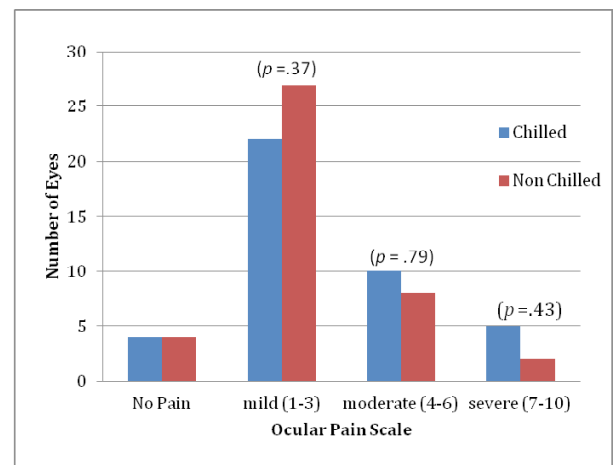**Figure 1: Average ocular pain during the first 5 days after surgery.**

Figure 2: Pain at the time of irrigation divided into categories of mild, moderate, and severe.
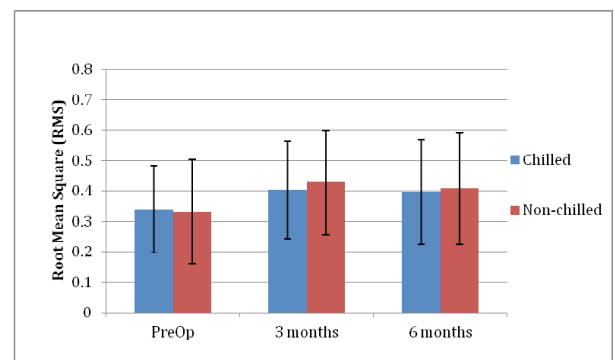

Figure 3: Comparison of pre and postoperative higher-order aberrations (HOA) between the chilled and non-chilled groups

Table 1: Number of patients using pain kills

Number of Narcotic Tablets	First Day to Use Pain Pills		
(e.g. oxycodone/acetaminophen, hydrocodone/acetaminophen)	Day 1	Day 2	Day 3
< 5 tablets	12	3	3
5 - 10 tablets	3	2	0
10 - 15 tablets	5	1	0
Ibuprofen only (< 5 tablets)	6	0	1
No pain medications = 4 patients			

Table 2: Six-months post operative data

Parameter	Chilled (n=40)	Non chilled (n=40)	P value
SE refraction (D)			
Mean ± SD	-0.05 ± 0.21	-0.025 ± 0.27	0.79
Range	-0.50 to + 0.38	-0.75 to + 0.88	
Sphere (D)			
Mean ± SD	-0.11 ± 0.23	-0.12 ± 0.31	0.89
Range	-0.50 to +0.25	-0.50 to +0.75	
Cylinder			
Mean ± SD	+0.19 ± 0.26	+0.24 ± 0.32	0.78
Range	0.00 to +0.75	0.00 to +1.25	
UCVA			
Mean logMAR ± SD	-0.08 ± .077	-0.07 ± .074	0.35
Snellen equivalent	≈ 20/17	≈ 20/17	
20/15 or better, n (%)	26 (65%)	22 (55%)	
20/20 or better, n (%)	38 (95%)	38 (95%)	
20/25 or better, n (%)	40 (100%)	40 (100%)	
BCVA			
No change	33	35	
Lines lost	0	0	
Gained ≥1 line	7	5	0.43
SE = spherical equivalent; UCVA= uncorrected visual acuity; BCVA = best corrected visual acuity			

technique. The authors suggest that the cooling process may decrease pain by reducing inflammation and chemical mediators, such as prostaglandins (Kitazawa et al, 1999; Nizuma et al, 1994). Risk of corneal haze may be decreased by limiting thermal tissue damage and inhibiting the cytokine cascade that leads to keratocyte activation and fibroblast formation (Kitazawa et al, 1999; Stein et al, 1999). These initial reports and subsequent use patterns have perpetuated this practice and there is little or no current published evidence to validate early claims. Historically, surgeons and patients in our centers have often observed the process of using chilled saline irrigation after the laser ablation to be a subjectively uncomfortable, albeit brief, part of standard PRK procedure. Our current study helps demonstrate the safety and efficacy of using room temperature saline as an alternative to chilled saline in an effort to limit postoperative pain or corneal haze.

Although not statistically significant, there was a trend for the chilled group to experience more moderate to severe pain than the non-chilled group at the time of surgery. In retrospect, we did not design the study to specifically determine whether the irrigation step itself was more painful in one eye or the other, but rather compared the patient's perception of pain for the overall surgical procedure. As most surgeons know,

there is often a subjective difference in the amount of sensation or discomfort experienced in fellow eyes of the same patient at the same surgical event, despite identical anesthesia (Bartfield et al 1998). Treatment with bandage contact lenses, preservative free lubricants, topical corticosteroids and NSAIDs and PRN oral pain medications did not eliminate the pain, which increased for both groups in the first 36 hours after surgery. The use of oral analgesics (NSAIDs, narcotics, combination agents) was not controlled or standardized, however, since the study design was a contralateral eye study, and oral analgesics act systemically, both the chilled BSS and non-chilled BSS groups would likely be equally affected. Our study did not consider the use of dilute topical proparacaine which has been touted by some to be safe and effective for treating post-PRK pain (Shahinian et al, 1997), but also has been associated with toxicity in other reports (Kim et al, 1997; Moreira et al, 1999).

Visual outcomes were excellent in both groups and there were no complications. No statistically significant differences were noted in visual acuity, refractive outcome, higher order aberrations, or in contrast sensitivity between the groups. Visually significant haze did not occur. This was somewhat expected because the number of patients in the study was relatively low, and their treatment was low to moderate myopia. A study with more patients and higher myopic treatments would better assess haze.

No prophylactic mitomycin C but only a fairly conservative topical steroid regimen was used in our study, and this was consistent with our current standard of care. A recent retrospective series had similar visual outcomes and no haze although it is not specified whether the saline irrigation used after the PRK was chilled (Bababeygy et al, 2011). Given the low incidence of haze expected with modern PRK , it would be very difficult to prospectively and conclusively determine whether chilling the corneal surface helps prevent haze.

The question of the value of cooling the ocular surface after PRK ablation is still open. Ocular surface temperatures in the ambient environment have been measured in the 29 – 32 C range (Betney et al, 1997) and in as high as 37 - 53 C after excimer laser ablation in human and rabbit models (Nizuma et al, 1994; Betney et al, 1997; Kitazawa et al, 1997; Burns et al, 1988). Direct temperature measurements of the ocular surface were not measured in our study, but it is likely that both groups had significant cooling due to irrigation. Room temperature, or non-chilled saline, at 16 to 20 C, may provide sufficient cooling to have a similar effect to chilled saline; however the relationship of effect is unclear.

Conclusion

This study questions the generally-accepted practice of using chilled saline to irrigate the corneal surface following excimer laser ablation during PRK. The use of non-chilled or room temperature saline irrigation appears to be equally effective and perhaps offers a more comfortable and convenient option for patients and surgeons. Similar outcomes were observed with regard to subjective pain, and excellent safety and visual results were achieved in both groups.

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