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Corneal crosslinking (CXL) with 18-mW/cm^2 irradiance and 5.4-J/cm^2 radiant exposure—early postoperative safety

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Abstract

Purpose To investigate safety of accelerated corneal crosslinking during the first postoperative month.

Methods In this retrospective study, 76 eyes of 60 patients with verified progressive keratectasia were enrolled in this study and followed for 1 month after accelerated CXL (18 mW/cm^2 for 5 min, radiant exposure 5.4 J/cm^2) (A-CXL(5*18)). Preoperatively, objective refraction, slit lamp inspection, and corneal tomography were performed. Early postoperative slit lamp examinations were performed on days 1 and 4. At 1 month, objective refraction, slit lamp inspection, and corneal tomography were performed.

Results Gender distribution was m:f = 55:21, OD:OS was 40:36, and the average age was 26.5 ± 8.6 years at surgery. Only 71 of the 76 eyes completed the 1-month follow-up, indicating a dropout rate of 6.6%. In 7.0% ($n = 5$), sterile infiltrates were observed; 5.6% of eyes ($n = 4$) showed delayed epithelial healing (> 4 days) in 2.8% ($n = 2$); an infection occurred and in 1 eye (1.4%), a stromal scar was detected; no other complications, neither a loss of two or more Snellen lines at 1 month postoperatively, were observed. As a risk factor for sterile infiltrates, thin preoperative pachymetry could be identified ($p = 0.027$).

Conclusions This study revealed no difference in early postoperative safety between CXL using 18 mW/cm^2 and standard corneal CXL. Thinner preoperative pachymetry could be identified predicting a higher rate of postoperative sterile infiltrates.

Keywords Corneal crosslinking · Keratokonus · Keratectasia · Accelerated crosslinking · 18 mW · Sterile infiltrate

Introduction

Corneal crosslinking (CXL) by means of riboflavin and UVA light was experimentally proposed in 1996 to halt the progression of primary and secondary keratectasia by improving the biomechanical and biochemical properties of the cornea [1, 2]. Current literature reports a failure rate of approximately 3 to 10% and a complication rate of 1 to 10% [3–6].

During the last years, the original Dresden protocol for CXL has been modified by several approaches, in particular increasing the irradiance by up to 30 mW/cm^2 [7, 8] or changing the riboflavin solution [9] with the goal to shorten the treatment time. Previous clinical data showed that increasing the irradiance seems to be effective [10–12], without describing the prevalence of early postoperative complications, such as sterile infiltrates, delayed epithelial healing, infection, stromal scares, or corneal melting. Anecdotally, it is said that higher irradiance might cause a stronger inflammatory reaction of the eye.

The aim of this paper is to evaluate the early postoperative complications of CXL using an irradiance of 18 mW/cm^2 with the conventional radiant exposure of 5.4 J/cm^2.

Patients and methods

Study group and protocol

Seventy-six eyes of 60 patients with progressive keratectasia who received A-CXL(5*18) between March 2013 and

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December 2014 at the Klinikum rechts der Isar, Technische Universität München were enrolled in this study. Progression of the keratectasia was verified by repeated Scheimpflug images (Pentacam HR 70700, Oculus, Wetzlar, Germany) over at least 6 months, and progression was accepted if the increase in K_{max} exceeded 1 diopter which equals 3 standard deviations [13]. Eyes with maximal K-readings less than 70.0D were included, whereas eyes with previous ocular surgery other than LASIK, penetrating trauma, glaucoma, aphakia, corneal scars that may interfere with Scheimpflug photography, history of recurrent erosions, pregnancy, breast feeding, and eyes with ocular pathology other than keratectasia were excluded. We differentiated between the diagnoses post-LASIK ectasia ($n = 3$), keratoconus ($n = 51$), PMD-like ectasia ($n = 15$), or classical PMD ($n = 2$), based on the appearance of the Scheimpflug image, the eccentricity of the maximum posterior elevation, and the thinnest pachymetry. An eccentricity of the maximum posterior elevation of more than 2.8 mm determined a PMD; an eccentricity of 1.5–2.8 mm a PMD-like ectasia. More central maximum posterior elevation indicated the diagnosis of a keratoconus. Eyes without a definable maximum posterior elevation were only assigned based on pachymetry and the appearance of the Scheimpflug image.

Patients were examined preoperatively, early postoperatively on days 1 and 4, and 1 month after CXL. Every examination, except the early postoperative, consisted of slit lamp inspection, objective refraction, and Scheimpflug imaging. Patients using rigid contact lenses were asked not to use their lenses 2 weeks prior to CXL and during the postoperative course.

Treatment

Topical anesthesia of the cornea was obtained using proparacaine drops applied every 3 min for 15 min. After insertion of a lid speculum, a corneal abrasion with a diameter of 9 mm was performed using a blunt hockey knife, followed by the instillation of 0.1% riboflavin in aqueous 20% dextran every 4 min for 30 min. In case of corneal pachymetry of less than 400 μm before irradiation ($n = 4$), hypoosmolar 0.1% riboflavin drops were applied until the thinnest pachymetry was above 400 μm. Eyes were then inspected by mobile slit lamp to ensure that the riboflavin had diffused into the anterior chamber. Afterwards, the eye was irradiated for 5 min with an irradiance of 18 mW/cm^2 at 365 nm (CCL-365 vario, Peschke Meditrade, Huenenberg, Switzerland) leading to a total energy of 5.4 J/cm^2 applied to the cornea. During irradiation, 0.1% riboflavin drops were applied every 2 min. At the end of the procedure, a bandage lens soaked in levofloxacine was applied and the eye was patched. The patient was asked to use antibiotic drops (Oftaquix (levofloxacine), Santen GmbH, Munich, Germany) five times a day for 3 days. After epithelial healing, topical dexamethasone (Monodex, Thea Pharma GmbH, Berlin, Germany) was applied three times a day, afterwards tapered off gradually over 3 weeks.

Postoperative follow-up

At the early postoperative visits, the patients were examined for sterile infiltrates, delayed epithelial healing, infection, herpes reactivation, and corneal decompensation. Manifestation of stromal haze as well as level of conjunctival injection were not collected as different physicians performed the individual examinations. New stromal scars, corneal melting, or a loss of two or more Snellen lines were checked at the 1-month examination. Sterile infiltrates were treated with dexamathasone (Monodex, Thea Pharma GmbH, Berlin, Germany) eye drops at least five times a day and infections with moxifloxacine (Vigamox, Alcon Pharma GmbH, Freiburg, Germany) and polymyxin B, neomycin, and gramicidin (Polyspectran, Alcon Pharma GmbH, Freiburg, Germany) eye drops. In patients with delayed epithelial healing, we left the bandage lens in place and extended the antibiotic application until epithelial closure was achieved.

Numerical evaluation

Means and standard deviations of preoperative Scheimpflug imaging parameters (thinnest corneal thickness, K_{max}, maximum posterior elevation (PE), eccentricity of PE, Q_{ant}, KI, and ISV), demographic data as digital variables (gender, side, and diagnosis), and the defined complications were calculated using MS Excel (Microsoft, Redmond, WA). Comparison of parameters between groups was performed using the Mann-Whitney U test. Correlations and their significance were tested using Spearman's rank correlation test. All calculations were performed with WinSTAT® for Excel (R. Finch Software, 2015). Statistical significance was accepted if $p < 0.05$.

Results

The average age of the patients was 26.5 ± 8.6 (15–46) years and there were more men than women affected (f:m = 21:55). Forty right and 36 left eyes were treated. The demographic data of study group is listed in Table 1. Table 2 shows the data obtained preoperatively from the Scheimpflug imaging. Fifty-six eyes showed a maximum posterior elevation on the posterior elevation map with an average amplitude of 54.04 ± 17.6 μm and an eccentricity of 1.20 ± 0.59 mm.

Of the 76 eyes, only 71 eyes completed the 1-month follow-up (dropout rate 6.6%). In the early postoperative and 1-month postoperative examinations, five sterile infiltrates (Fig. 1), one stromal scar, two infections, and no cornea with melting or endothelial decompensation were observed

Table 1 Demographic data

Parameters	Value (patients)
Patients	60
One-month follow-up	
Dropout	4 (6.6%)
Included	56 (93.4%)
Eyes	76
One-month follow-up	
Dropout	5 (6.6%)
Included	71 (93.4%)
Age (years)	
Mean	26.5 ± 8.6
Range	15–46
Gender (mean)	f:m = 32:25
Gender	
Female	21
Male	55
Eye	
OD	40
OS	36
Diagnosis	
Keratoconus	51
–	(f:m = 13:38)
PMD-like	15
–	(f:m = 3:12)
PMD	2
–	(f:m = 0:2)
Post-LASIK ectasia	3
–	(f:m = 3:0)

(Table 3). No eye showed a vision loss of two Snellen lines or more, and four eyes showed a delayed epithelial healing of more than 4 days. Apart from thin preoperative corneas being significant correlated with the development of sterile infiltrates ($p = 0.027$), no risk factors (including age, gender, diagnosis) could be identified for the development of complications.

Table 2 Data obtained from preoperative Scheimpflug imaging

Parameters	Preoperative values
K_{max} (*D*)	52.83 ± 6.71
KI	1.20 ± 0.089
Q anterior	− 0.64 ± 0.42
ISV	76.19 ± 27.07
Maximum posterior elevation	56 (of 76) eyes 73.7%
Eccentricity of PE (mean) (mm)	1.20 ± 0.59
Amplitude (mean) (μm)	54.04 ± 17.6
Thinnest pachymetry (μm)	473.95 ± 37.5

D = diopter

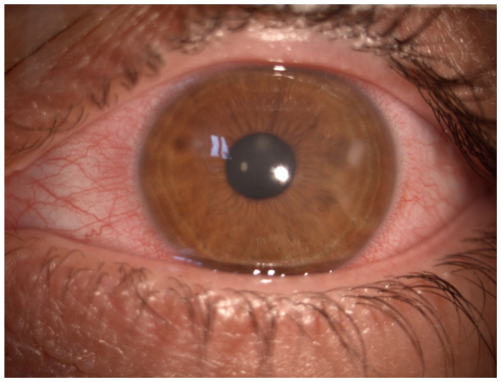

Fig. 1 Sterile infiltrate

Discussion

The major findings of this study are as follows:

(1) From 71 eyes receiving A-CXL with an irradiance of 18 mW/cm^2, sterile infiltrates occurred in five eyes (7%), four eyes (6%) suffered from delayed epithelial healing, and two eyes (3%) showed a bacterial infection at the early postoperative examination. No other complications occurred.
(2) One month postoperatively, one eye (2%) had developed early stage stromal scar and in none of the eyes, a corneal melting neither a loss of two or more Snellen lines occurred.
(3) Thin preoperative pachymetry was correlated with the occurrence of sterile infiltrates.

Little literature about the incidence of complications after CXL exists; mostly single cases are reported. Koller and coworkers examined a larger cohort in 2009 [13], which was treated with an irradiance of 3 mW/cm^2. They experienced sterile infiltrates in 7.6% and stromal scares in 2.9%, which is comparable to our findings. The average epithelial healing time was 3.28 days. Out of organizational reasons in our clinic, we were not able to see every patient at days 2, 3, and 4, but only four eyes (6%) showed a healing time longer than 4 days.

Kymionis et al. and Gatzioufas et al. reported no postoperative complications for very small cohorts with an irradiance of 9 and 18 mW/cm^2, respectively [14, 15].

Table 3 Postoperative observations

Complications	*n*
Stromal scar	1
Sterile infiltrate	5
Infection	2
Endothelial decompensation	0
Melting	0
Delayed epithelial healing	4
Vision loss (≥ 2 Snellen lines)	0

This study suggests that irradiances up to 18 mW/cm^2 do not lead to a higher early postoperative complication rate. Based on Poissons statistics, the zero incidence of a complication indicates a complication rate of less than 5%, only in group sizes bigger than 66. This post hoc analysis indicates a minimal sample size of 67.

Thin preoperative pachymetry was correlated with the occurrence of sterile infiltrates what was described in other studies before [16]. Raiskup et al. considered preoperative high k value and thin pachymetry being predicting factors for the development of permanent corneal haze [17]. Those or other correlation could not be found in our study. Cerman et al. found a higher incidence of sterile infiltrates using epi-off procedure and higher irradiance [18]. The increase of radiant exposure from 5.4 up to 7.2 J/cm^2 in the 30-mW/cm^2 group in their study limits the comparability to the here presented data. Our results did not show such tendency.

The efficacy of A-CXL is discussed controversial and cannot be judged in our study as the 1-month data allows no prognosis about the efficacy. Some newer publications from different groups seem to support the fact that A-CXL has less potential in corneal flattening than conventional crosslinking [10, 19, 20]. A reasonable explanation might be the oxygen dependency of CXL [21, 22]. The availability of oxygen remains equal, but the consumption is increased using higher irradiances. This theory is supported by the fact that the demarcation line is more shallow [23, 24] using higher irradiances. Biomechanical measurements revealed similar observations. A reduced stiffening effect is reported by Seiler and Hammer using higher irradiances [25, 26].

The relatively high dropout rate and changing observers should be announced as limiting factors of this study. The dropout rate is due to a high proportion of foreign patients, which were followed abroad, and follow-up data was not available. According to that, one of the patients with assumed infectious keratitis could not be followed up in our clinic. This patient was treated prophylactically with antibiotics, even though the diagnosis could not be verified.

In summary, accelerated CXL up to an irradiance of 18 mW/cm^2 seems to be as safe as conventional CXL. However, long-term follow-up is still missing to prove efficacy.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria, educational grants, participation in speakers' bureaus, membership, employment, consultancies, stock ownership or other equity interest, and expert testimony or patent-licensing arrangements) or non-financial interest (such as personal or professional relationships, affiliations, knowledge, or beliefs) in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (name the institution/committee) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Ethical approval For this type of study, formal consent is not required.

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