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Accelerated versus standard corneal collagen cross-linking in pediatric keratoconus patients: 24 months follow-up results

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ABSTRACT

Purpose: To compare the 24 month visual, refractive, topographic and aberrometric results of the accelerated and standard corneal collagen cross-linking (CXL) in pediatric keratoconus patients.

Methods: 87 eyes of 64 consecutive keratoconus patients under 18 years old with 24 month follow-up period following standard or accelerated CXL were included. 38 eyes received standard CXL (3 Mw/cm^2, 30 min), while 49 eyes had accelerated CXL (9 mW/cm^2, 10 min). Changes in the uncorrected (UCVA) and best corrected visual acuity (BCVA), spherical equivalent (SE), manifest astigmatism (MA), corneal topographic parameters, and corneal aberrations such as spherical aberration (SA), high order aberrations (HOAs), horizontal and vertical coma were evaluated. Corneal haze was graded and progression rate was assessed.

Results: The difference between baseline and 24 months postoperative UCVA, BCVA, SimK (keratometry)-1, SimK-2, Kmax, and the corneal aberrations were not significantly different between the two groups ($p > 0.05$ for all). The mean reduction in thinnest corneal pachymetry from baseline to 24 months after CXL was higher in accelerated CXL group ($p = 0.007$). The progression rate was 13.1% in standard and 16.3% in accelerated group ($p = 0.754$). There were no differences in the grade of corneal haze between the two groups ($p = 0.249$). No complications were observed in the both groups.

Conclusion: The 24 month results of accelerated and standard CXL revealed that, the efficacy and safety of accelerated CXL were the same with standard CXL in pediatric keratoconus patients. As being a rapid procedure, accelerated CXL appears to be more benefical for pediatric patients.

1. Introduction

Keratoconus is a progressive, bilateral and frequently asymmetric corneal ectasia characterized by localized corneal steepening and thinning, decreased visual acuity due to irregular astigmatism or corneal scarring [1]. Keratoconus generally begins at puberty and may progress up to 35–40 years of age [1,2]. Early onset of the disease is a negative prognostic factor due to its advanced stage at the time of diagnosis [3]. The need of corneal transplantation is seven-fold higher in pediatric keratoconus patients [3]. Therefore it is mandatory to stop or slow down the progression of the corneal ectasia in pediatric population rapidly and effectively.

Corneal cross-linking (CXL) is a procedure that alters the biomechanical properties of the corneal collagens by using the ultraviolet-A (UVA) and riboflavin (vitamin B2) [4]. It has been used in the treatment of corneal ectatic disorders including progressive keratoconus, pellucid marginal degeneration, and post-refractive corneal ectasia for years. Today, the standard CXL procedure includes 5.4 J/cm^2 energy with 3 mW/cm^2 intensity administered for 30 min [5]. Safety and efficacy of standard CXL in pediatric keratoconus patients have been well demonstrated [6]. The 5 year results of standard CXL treatment in pediatric keratoconus patients have shown stabilization of the visual acuity along with 2 diopters (D) decrease of the maximum keratometry (K-max) with a progression rate of 22% [6].

Accelerated CXL was introduced in clinical practice to shorten the treatment duration of the standard CXL procedure. It is based on the Bunsen-Roscoe law, which states that all photochemical reaction processes depend only on the total absorbed energy that is determined by radiant intensity and exposure time [7,8]. Accelerated CXL uses greater UVA irradiance intensity with lower total exposure time when

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compared to the standard protocol. Recent research indicates that the accelerated CXL protocol is as effective and safe as the standard CXL protocol in adult keratoconus patients [9–11]. In pediatric keratoconus patients only a few studies investigated the effects of the accelerated CXL, however none of them compared the efficacy and safety of this procedure with the standard CXL [12–15].

In this study we compared the 24 month visual, refractive, topographic, and aberrometric results of the accelerated and standard CXL procedures in pediatric keratoconus patients.

2. Methods

This single center retrospective study was conducted in compliance with the institutional and government review board regulations, informed consent regulations, and the Declaration of Helsinki. All consecutive keratoconus patients who were under the age of 18 and who underwent standard or accelerated CXL 24 months ago were included.

Our study comprised 87 eyes of 64 concecutive patients. All keratoconic eyes were diagnosed clinically; they had at least one clinical sign other than the topographic appearance of the map, which included; Munson's sign, scissors reflex during retinoscopy, corneal thinning, Fleischer's ring, Vogt's striae, increased visibility of the corneal nerves, and Rizzutti's sign. Exclusion criteria were as follows: age older than 18 years, corneal thickness less than 400 µm, presence of any central or paracentral corneal scar, history of herpetic keratitis, active ophthalmic inflammation or infection prior to CXL. Written informed consent was obtained from the parents of all patients.

All patients underwent a complete ophthalmological examination including spheric equivalent (SE), manifest astigmatic (MA) value, and uncorrected (UCVA) and best corrected visual acuity (BCVA) measurements, slit-lamp examination, intraocular pressure measurement, fundoscopic examination and topographical analysis of the cornea with the Sirius 3D rotating Scheimpflug camera and topography system (CSO, Italy) at baseline, six months, twelve and twenty-four months after CXL. Topographic corneal analysis included the measurement of simulated keratometry (Sim K)-1, Sim K-2, K-max, cylindrical (CYL) value, and corneal thickness at the thinnest point (thCT). The corneal aberrations including spherical aberration (SA), higher order aberrations (HOAs), horizontal and vertical coma were obtained from the topography device (at the 3 mm pupil diameter). Visual acuity was measured using the Snellen chart and were converted to the Logarithm of the Minimum Angle of Resolution (logMAR) for the statistical analysis.

Significant visual loss was defined as a loss of 3 or more Snellen lines of BCVA. After CXL treatment corneal haze was evaluated and graded at the slit lamp biomicroscopy on a scale from 1 to 4. Grading of corneal haze was as follows [16]:

0 + = Clear cornea

1 + = Focal areas of corneal clouding or reticulation

2 + = Diffuse mild stromal clouding or reticulation

3 + = Diffuse stromal clouding or reticulation obscuring view of iris details

4 + = Focal or diffuse areas of dense stromal haze obscuring iris detail.

Progression was defined by an increase of the K-max readings of the anterior corneal surface, within 3.00 mm from the apex, of at least 1.00 D in corneal topographies 24 months after all CXL procedures [17].

2.1. Surgical technique

All procedures were performed in an operating room under sterile conditions under topical anaesthesia with proxymetacaine hydrochloride 0.5% eyedrops (Alcaine, Alcon Laboratories Inc) or general anaesthesia. In both standard and accelerated CXL procedures, corneal epithelium was removed mechanically with a crescent knife at an intended 8.5 mm zone after loosening the epithelium with a 20% alcohol solution applied for 20 s over the cornea within an 8.5 mm alcohol well. After epithelial removal, residual corneal thickness was measured with an ultrasonic pachymeter (PalmScan AP-2000-Ultima, Micro Medical Devices, USA). Riboflavin drops were applied to the center of cornea every 3 min for 30 min until the cornea had swollen to > 400 µm and aqueous stained yellow. Isotonic (0.1% riboflavin in 20% dextran T500 solution, Meran, BNM Inc., Istanbul, Turkey) riboflavin was used in all eyes. The UVA irradiation was applied using a commercially available UVA system (Meran Tıp, BNM Inc., Istanbul, Turkey). In the standard procedure before the UVA treatment, the intended 3 mW/cm^2 surface irradiance (5.4 J/cm^2 surface dosage after 30 min) was calibrated using a UVA meter (UVA-365, Lutron Electronic). In the accelerated procedure 9 mW/cm^2 irradiance was applied for 10 min (5.4 J/cm2 surface dosage after 10 min). During both procedures, the riboflavin solution was applied for every 2 min to ensure saturation and balanced salt solution (BSS®) was applied for every minute to moisten the cornea. Ultrasonic pachymetry was obtained for 2 times (15 and 30 min) in the standard CXL procedure, and once (5 min) in the accelerated CXL procedure after the start of riboflavin drops. A silicone hydrogel bandage contact lens (Acuvue Oasis, Johnson&Johnson Vision Care) was applied at the end of the surgery until full reepithelization of the cornea. Postoperative treatment included ofloxacin (Exocin, Allergan Inc.) eye drops q.i.d.for 1 week, fluorometholone eye drops (FML, Allergan Inc.) q.i.d. on a tapering schedule for 1 month, and artificial tears q.i.d. for 6 months.

2.2. Statistical analysis

All data was collected in an unmasked fashion and analyzed using the SPSS software (version 21; International Business Machines Co, Armonk, NY). Significance of the difference between preoperative and postoperative 6 months, 12 months and 24 months after both CXL procedures were analyzed with the repeated measures analysis of variance (ANOVA) and Bonferroni posttest. Significance of the difference between preoperative and postoperative 24 months after CXL was compared between the two groups with independent samples *t*-test Percentages of progression in both groups were compared with chi-square test/Fisher's exact-test When the significance level was less than or equal to the priori alpha level ($p \leq 0.05$).

3. Results

Thirty-eight eyes of 29 patients received standard CXL, while 49 eyes of 35 patients received accelerated CXL. In standard CXL group there were 8 (27.5%) females and 21 (72.5%) males with a mean age of 15 ± 0.30 (11–17) years. In accelerated CXL group, there were 10 (28.5%) females and 25 (71.5%) males. Their mean age was 14.92 ± 0.34 (10–17) years. There were no significant differences between the groups in terms of age and gender ($p = 0.896$, $p = 0.519$, respectively). As seen in Table 1, there were no statistically significant differences between the preoperative visual, refractive, topographic, and aberrometric measurements between the two groups ($p > 0.05$ for all).

Twenty-four months after standard CXL, the mean UCVA and BCVA improved from 0.84 ± 0.4 and 0.32 ± 0.2 logMAR to 0.73 ± 0.5 and 0.30 ± 0.3 logMAR, respectively, but the differences were not statistically significant ($p = 0.623$, $p = 0.213$, respectively). In eyes which received accelerated CXL, the mean UCVA improved significantly from 0.70 ± 0.4 logMAR to 0.50 ± 0.4 logMAR ($p = 0.023$), while the mean BCVA remained stable 24 months after the treatment ($p = 0.374$). As shown in Table 2, the intergroup difference for the mean UCVA and BCVA were insignificant ($p = 0.252$ and $p = 0.32$, respectively). The mean SE and MA did not show any significant differences during the follow-up period in standard and accelerated groups ($p = 0.466$ and $p = 0.054$ for SE, $p = 0.309$ and $p = 0.371$ for MA, respectively), (Table 2). The mean simK-1, simK-2, K-max and CYL