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Randomized Controlled Trial Comparing Transepithelial Corneal Cross-linking Using Iontophoresis with the Dresden Protocol in Progressive Keratoconus

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Purpose: To compare clinical outcomes of transepithelial corneal cross-linking using iontophoresis (T-ionto CL) and standard corneal cross-linking (standard CL) for the treatment of progressive keratoconus 12 months after the operation.

Design: Prospective randomized controlled clinical trial.

Participants: Thirty-four eyes of 25 participants with progressive keratoconus were randomized into T-ionto CL (22 eyes) or standard CL (12 eyes).

Methods: T-ionto CL was performed using an iontophoresis device with dextran-free 0.1% riboflavin-5-phosphate solution with enhancers and by irradiating the cornea with a 10 mW/cm^2 ultraviolet A device for 9 minutes. Standard CL was performed according to the Dresden protocol.

Main Outcome Measures: The primary outcome measure was stabilization of keratoconus after 12 months through analysis of maximum simulated keratometry readings (K_{max}, diopters). Other outcome measures were corrected distance visual acuity (CDVA, logarithm of the minimum angle of resolution [logMAR]), manifest spherical equivalent refraction (D), central corneal thickness (CCT, micrometers) and endothelial cell density (ECD). Follow-up examinations were arranged at 3 and 7 days and 1, 3, 6, and 12 months.

Results: Twelve months after T-ionto CL and standard CL, K_{max} on average flattened by -0.52 ± 1.30 D ($P = 0.06$) and -0.82 ± 1.20 D ($P = 0.04$), respectively. The mean change in CDVA was -0.10 ± 0.12 logMAR ($P = 0.003$) and -0.03 ± 0.06 logMAR ($P = 0.10$) after T-ionto CL and standard CL, respectively. The manifest spherical equivalent refraction changed on average by $+0.71\pm1.44$ D ($P = 0.03$) and $+0.21\pm0.76$ D ($P = 0.38$), respectively. The CCT and ECD measures did not change significantly in any group at 12 months. Significant differences in the outcome measures between treatments were found in the first week postoperatively. No complications occurred in the T-ionto CL group; 1 eye (8%) had sterile corneal infiltrates, which did not affect the final visual acuity, in the standard CL group.

Conclusions: Significant visual and refractive improvements were found 12 months after T-ionto CL, though the average improvement in corneal topography readings was slightly lower than the Dresden protocol in the same period. *Ophthalmology 2017;■:1–9 © 2017 by the American Academy of Ophthalmology*

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Over the past decade, riboflavin/ultraviolet A (UVA) corneal cross-linking has become an established treatment option for improving the biomechanical stability of the weakened cornea in eyes with progressive keratoconus. In general, treatment efficacy has been assessed in clinical studies by comparing postoperative corneal topography with baseline measurements over at least 12 months after treatment.[1–8]

As emerging techniques are at surgeons' disposal, it is of high clinical significance to assess their safety and efficacy in comparison with the gold standard (i.e., the Dresden protocol) and make the results readily available to clinicians. Transepithelial corneal cross-linking is gaining increasing interest among corneal specialists; several approaches, which differ by type of riboflavin solution and UVA irradiation used for the treatment, have been developed and are still under investigation for comparing the results with the gold-standard protocol for stabilization of progressive keratoconus.

Iontophoresis is a noninvasive technique used to deliver the charged dextran-free 0.1% riboflavin-5-phosphate hypotonic solution with ethylenediaminetetraacetic acid and trometamol transcorneally by repulsive electromotive force using a small electrical charge applied to an iontophoretic chamber. The clinical outcomes from both uncontrolled and controlled studies[9–13] have shown that the procedure is safe and improves visual performance, with stable or decreased maximum simulated keratometry readings (K_{max}), during 12 months of follow-up.

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The present randomized controlled trial (RCT) with identifier code NCT02117999 was designed to compare the treatment of progressive keratoconus by transepithelial corneal cross-linking using iontophoresis (T-ionto CL) with the standard corneal cross-linking (standard CL) protocol at 12 months. In this article, we present the 12-month clinical outcomes in the complete cohort of participants.

Methods

Study Design

This is a prospective, unmasked RCT conducted at the clinical trials center of the Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Fondazione G.B. Bietti (Rome, Italy). The aim of the study was to assess the efficacy of T-ionto CL (study group) in the treatment of progressive keratoconus in comparison with standard CL (control group). The primary outcome measure of the study was K_{max} at 12 months. Approval was obtained from the Istituti Fisioterapici Ospitalieri (IFO)-IRCCS Ethical Committee (Rome, Italy) and the conduct of the study adhered to ethical principles that have their origin in the Declaration of Helsinki (7th revision, 2013) and the Convention of Oviedo (April 4, 1997). After full explanation of the protocol, written informed consent was obtained from all participants before enrollment in the study.

The trial was registered with the U.S. National Institutes of Health registry with identifier code NCT02117999 (https://clinicaltrials.gov/ct2/show/NCT02117999).

Participants

Patients with a confirmed diagnosis of progressive keratoconus were invited to participate in this study. Keratoconus was deemed to be progressive if there was an increase of at least 1 diopter (D) in the K_{max} derived by computerized Placido disk corneal topography over the 12 months preceding the operation. Diagnosis was made by 2 corneal specialists (M.L. and S.S.). Exclusion criteria included a minimum corneal thickness less than 400 μm, a K_{max} steeper than 61 D, any corneal scarring, previous refractive or other corneal or ocular surgery, and other ocular disorders (e.g., cataract, glaucoma, herpetic keratitis). Patients who were pregnant or breastfeeding at the time of enrollment were also excluded. Only patients aged between 18 and 46 years were included in the study. Baseline characteristics of all participants were given in a previous publication.[9]

Randomization

Eligible patients were randomized after enrollment, with an allocation ratio of 2:1, into either the study or control group using a computer-generated randomization plan with block randomization. Two different blocks were created, which included eyes with K_{max} steeper or flatter than 54 D to randomize patients with comparable baseline K_{max} values in either group. If both eyes of a patient qualified for participation in the study, each eye was randomized independently. Second eyes were treated no earlier than 2 months after the first eyes.

Assessments

Contact lens wearers were instructed to discontinue their use for a minimum of 3 weeks before the preoperative eye examination. In addition, we asked participants to discontinue the use of contact lens during follow-up to minimize measurement bias of the primary outcome measure.

Participants underwent ophthalmic examinations at baseline and 3 and 7 days and 1, 3, 6, and 12 months after treatment. Each examination included combined Placido disk corneal topography and anterior segment optical coherence tomography (Visante; Carl Zeiss Meditec Inc., Dublin, CA) for measuring K_{max} (D), which was the primary outcome measure of the study, and central corneal thickness (CCT; micrometers). The secondary outcome measures included slit-lamp examination of the anterior segment of the eye, as previously described[9,14,15]; uncorrected distance visual acuity (UDVA; logarithm of the minimum angle of resolution [logMAR] units) and corrected distance visual acuity (CDVA, logMAR units), obtained using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at 4 meters; contrast sensitivity function (CSF; log units) evaluated using the Pelli-Robson chart; manifest refraction (expressed as spherical equivalent; D); and endothelial cell density (ECD; cells per square millimeter) measured by noncontact specular microscopy (Perseus; CSO, Florence, Italy). Intraocular pressure (IOP) measurements were collected with a Goldmann applanation tonometer (Haag-Streit AG, Koeniza, Swizterland) preoperatively and 6 and 12 months postoperatively.

All data were acquired and analyzed in an unmasked manner. To improve the reliability of topography measurements, a minimum of 3 acquisitions were performed for each eye at each time interval. If the value varied more than 10% between the scans, then another scan was obtained. The best scan was then selected for analysis.

To exclude infection, document epithelial healing, and provide general postoperative care, all patients were assessed also on day 1 after treatment in addition to the described follow-up schedule.

Treatments

For each participant, corneal cross-linking was performed within 4 weeks of the baseline examination. All treatments were performed by an experienced corneal specialist (M.L.) under topical anesthesia; anesthetic eye drops (oxybuprocaine hydrochloride 0.4% [Novesina]; Novartis Farma S.p.A., Varese, Italy) were instilled 3 times over a 10-minute period before treatment.

Before iontophoresis, a sterile Biopore membrane attached to a plastic cylinder (Millicell, cod. PICM01250; Merck SpA, Milan, Italy) was pressed against the central cornea to remove the precorneal mucin layer.[9] Corneal soaking with dextran-free ethylenediaminetetraacetic acid and trometamol-enriched 0.1% riboflavin-5-phosphate hypotonic solution (Ricrolin +; Sooft Italia SpA, Italy) was performed using a commercial iontophoresis device (Iontophor CXL; Sooft Italia SpA, Fermo, Italy). The passive electrode was applied to the forefront of the eye to be treated. The active electrode, a bath tube made of plastic, was applied to the corneal surface. After suctioning the tube to the corneal epithelium, the tube was filled with riboflavin solution. The current intensity was set at 1.0 mA for 5 minutes. After iontophoresis, the corneal surface was gently washed with chilled 0.9% chloride sodium solution. Based on the manufacturer's instruction at the time of this RCT, corneal UVA irradiation was applied using a 10 mW/cm^2 device (370±8 nm; Vega 10 mW; CSO) for 9 minutes (total energy density: 5.4 J/cm^2). One drop of chilled 0.9% chloride sodium solution was applied over the corneal epithelium every 3 minutes during irradiation; no riboflavin drop was applied over the corneal surface so as to avoid dissipating the incoming UVA energy for effective stromal cross-linking.

The control group received corneal cross-linking according to the standard Dresden protocol.[5,6] The central 10-mm corneal epithelium was removed using an Amoils brush (Innovative Excimer Solutions Inc., Toronto, Canada). A solution containing 20% dextran-enriched 0.1% riboflavin (Ricrolin; Sooft Italia SpA) was instilled every 3 minutes for 30 minutes before UVA