Original article

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Corneal iontophoresis and cross linking: a preliminary report of our experience

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Abstract

Purpose. To evaluate the effect induced by UVA radiation with corneal iontophoresis and cross-linking.

Material and Methods. From February 2013 to August 2014 we saw 15 eyes of 15 patients, age range 19-38 years (10 women and 5 men) keratoconus stage 1-2. Vision evaluation was carried out with ETDRS scale and Topography and Pachymetry. To evaluate line of demarcation with the confocal microscope and corneal optical coherence tomography (OCT) and the pain with the Faces Pain Scale.

Results. At 6 months there was a stabilization of vision and topography, with a slight improvement at 1 year of vision of 1 line and of the Km of 0.5 diopters.

The *in vivo* microscopic examination with the confocal microscope showed that the line of demarcation was not particularly evident, it was irregular and when present was more evident at 150-200 μ depth, there was a keratinocyte activation in the anterior stroma with slight oedema.

There were also superficial epithelial alterations present and only slight involvement of the subepithelial nervous plexus, there were no alterations of the endothelium.

The Faces Pain Scale the pain score was 2±1. We have to stress the usefulness of Corneal optical coherence tomography (OCT) also pre and post iontophoretic treatment.

Conclusions. Further, larger studies and longer follow-ups are needed, recent studies have shown the absorption of riboflavin with iontophoresis is 50% with respect to the classic technique, the percentage of riboflavin in the anterior 2/3 of the corneal stroma would be, however, efficacious to provide good results. ***Clin Ter 2015; 166(4):e254-256. doi: 10.7417/CT.2015.1869***

Key words: *Iontophoresis, Cross-linking, keratoconus*

Introduction

The method of cross-linking (CLX) of the corneal collagen used today consists in the photo-polymerization of the stromal fibres by means of the combined action of a photosensitizing substance (riboflavin-vitamin B2) that undergoes ultraviolet light irradiation at 370 nm for 30 min, increasing rigidity and resistance to keratectasia.

CLX increases the molecular bridges between the corneal stromal collagen fibrils by a photochemical effect induced by UVA radiation. The CLX technique has had the following evolution since 2006:

- Classic epi-off technique (variables: minimal PTK or PRK);
- Transepithelial epi-on technique (conflicting results, both with and without enhancer);
- Iontophoresis 30 min 3 mW, 9 min 10 mW.

Moreover, to favour absorption various artifices are used:

mini-incisions, rings, in the stromal bed (micro-keratome, femtolaser, microscheper or epithelium disruptors).

The major disadvantage of the transepithelial technique is the poor passage of riboflavin through the corneal epithelium, this has been demonstrated both *in vivo* and *in vitro*. Riboflavin is a hydrophilic macromolecule, does not penetrate the epithelium intact (1), the epithelium absorbs the UVA radiation (2). On an animal model *in vitro* transepithelial CXL has been shown to not be efficacious (3). Further *in vivo* studies have shown that the presence of an intact basal epithelial layer acts as a barrier against riboflavin absorption in the corneal stroma.

Iontophoresis (from *iòntos*=ion and *phòresis* = transport) is the transport of ions unidirectionally with a low intensity electric field.

Polarized drugs are applied to the electrodes according to their polarity: positive polarity drugs are applied to the positive electrode, negative polarity drugs to the negative electrode, while the other pole is placed in a zone bordering that to be treated.

This can attain concentrations notably superior (up to 50-100 times) with respect to passive permeation.

The need for this new technique is due to the attempt to unite the advantages of the 2 techniques:

- Epi-on has fewer complications;
- Reduce the time for execution and improve patient compliance;
- Save time for the clinician;
- Ionophoresis gives a greater penetration of riboflavin, favoured by a dipole 1 corresponding suction ring and the other on the forehead, the negative charge of riboflavin encourages penetration.

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There is an electrical generator with an intensity of 1 mA connected to 1 electrode for the ionic exchange (new Vega 10 mW) with 5 min of imbibition and 9 min of treatment.

In ocular iontophoresis, treatment is carried out by applying two electrodes on the patient connected to a DC generator. The principle electrode (- pole, cathode) is inside a rubber ring that is applied to the cornea to be treated; the other electrode (+ pole, anode) consists of a patch placed on the patient's forehead.

The penetration of riboflavin in human corneas of cadavers using the 3 techniques: *a*) epi-off; *b*) epi-on; and *c)* iontophoresis 3 mW and 10 mW was analyzed as well as the anteroposterior penetration using a femtolaser examination of the 150 micron anterior, intermediate and posterior strips in the permeation order of → epi-off, → iontophoresis, → epi-on (4, 5).

The permeation was measured by photo spectrometry.

Iontophoresis uses the movement of ions in an electric field. The total flux of the molecules during iontophoresis takes place according to 3 mechanisms of transport:

– The contribution of the Passive Flux (Jp) is less with respect to the other two;
– Electromigration (EM) depends on molecular weight (Mw);
– Electro-osmosis (EO) is independent of Mw.

The intensity that is delivered by the generator for iontophoresis is of 1 mA/min (5 min of treatment). The current supplied is continuous and supplied by a battery. The duration of the treatment is automatically monitored by a suitable software program for the generator. After 5 min treatment, iontophoresis is automatically stopped (6).

Materials and Methods

From February 2013 to August 2014 we saw 15 eyes of 15 patients, age range 19-38 years (10 women and 5 men) keratoconus stage 1-2, in 1 case CLX TE was carried out and then Perforating keratoplasty. The patients underwent 5 min of iontophoresis and 9 min of UVA radiation(C.B.M. X-Linker Vega 10 mW®; CSO, Florence, Italy) and cross linking (Iontofor CXL®; SOOFT Italia S.p.A., Montegiorgio, Italy).

It was performed in vivo microscopy with Confoscan 4 (Nidek®). It is the assessment of pain with Faces Pain Scale (Scale 0-10).The line of demarcation has been evaluated with the OCT (Spectralis Heidelberg Engineering®, Inc., Carlsbad, CA).

Results

At 6 months there was a stabilization of vision and topography, with a slight improvement at 1 year of vision of 1 line and of the Km of 0.5 diopters; vision evaluation was carried out with ETDRS scale and Topography (OPD 10000 III Nidek®) and Pachymetry (Oculus Optikgerate, Wetzlar®, Germany).

The *in vivo* microscopic examination with the confocal microscope showed that the line of demarcation was not particularly evident, it was irregular and when present was more evident at 180-240 μ depth, there was a keratinocyte activation in the anterior stroma with slight oedema (Fig. 1 and 2).

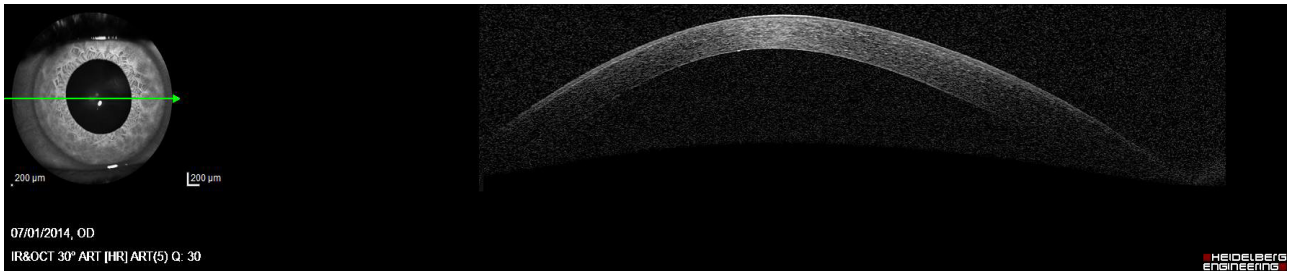

Fig. 1. OCT Pre - CLX Iontophoresis. Not line of demarcation.

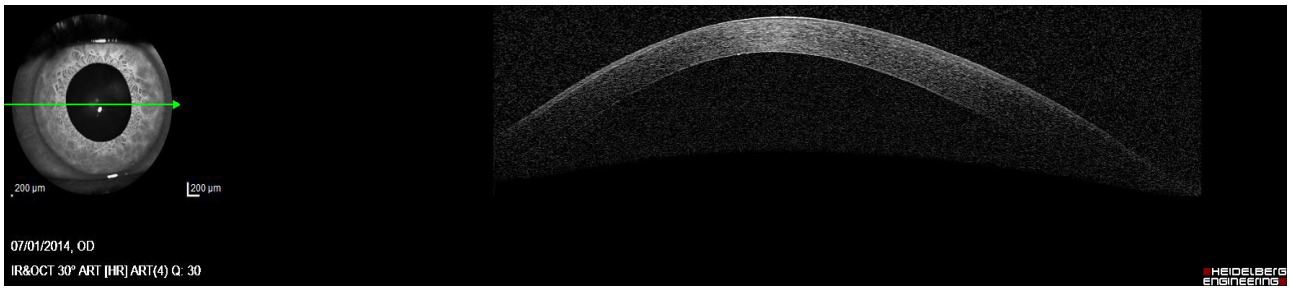

Fig. 2. OCT 1 month Post - CLX Iontophoresis . Line of demarcation was not particulary evident, was irregular.

There were also superficial epithelial alterations present and only slight involvement of the subepithelial nervous plexus, there were no alterations of the endothelium.

The patients complained of slight pain in the first 24-48 h. The evaluation of the pain was carried out with a subjective evaluation test: the Faces Pain Scale (scale 0-10) , the pain score was 2±1.

Discussion

We have to stress the usefulness of Corneal optical coherence tomography (OCT) also pre and post iontophoretic treatment. The corneal stromal demarcation line was identified in 10 eyes (66 %) by both examiners.

Using *in vivo* studies Malhotra et al. and Vinciguerra et al. evaluated the penetration of vitamin B2 in the anterior stroma, in the epi-off group the passive impregnation was homogeneous, a hyper-reflective band appeared at about 80 μ, in the iontophoresis group the hyper-reflective band was less homogeneous with a dissolving effect up to 200 microns (7, 8).

These are preliminary results with evaluations at 1 year, a more in-depth topographic, aberrometric and biomechanical evaluation (rigidity and hysteresis, CORVIS and ORA Ocular Response Analyzer) would be interesting.

Further, larger studies and longer follow-ups are needed, recent studies have shown the absorption of riboflavin with iontophoresis is 50% with respect to the classic technique, the percentage of riboflavin in the anterior 2/3 of the corneal stroma would be, however, efficacious to provide good results.

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