Efficacy of transepithelial corneal cross-linking using iontophoresis

Experimental studies on eye-bank donor eyes

and

Preliminary results on the clinical trial NCT02117999

Marco Lombardo, MD, PhD
Senior Researcher IRCCS Fondazione G.B. Bietti
CEO Vision Engineering Italy srl
1 – In vitro studies on CXL using iontophoresis

1.1 Corneal diffusion
1.2 UV-A corneal absorbance
1.3 Corneal biomechanics

2 – Randomized Clinical Trial: preliminary results at 3 months follow-up

3 – Conclusions
Controversial data have been reported on the effect of transepithelial corneal CXL to slow down progressive keratoconus in patients.

The studies on riboflavin diffusion through the corneal epithelium and on the effect of TE-CXL have been carried out using conventional dextran-enriched solutions.

Dextran-enriched solutions are not adequate to claim that riboflavin cannot diffuse through the intact corneal epithelium.
Transepithelial corneal CXL

**PROS**

1) No complications related to epithelial removal (pain, haze, infection)

2) Fast visual rehabilitation (socially important)

**CONS**

1) Controversial data on former TE-CXL techniques:
   - inadequate permeation of riboflavin in the stroma
   - low or limited cross-linking effect
In laboratory studies*, **iontophoresis** has been shown to deliver riboflavin (dextran-free, hypotonic solution) efficiently through the intact epithelium and to improve the mechanical stiffness of the stroma after rapid UV irradiation.

Iontophoresis

Iontophoresis for corneal CXL is a noninvasive technique in which a weak electric current (1 mA for 5 minutes) is used to enhance the penetration of riboflavin-5-phosphate into the stroma.

Safety of iontophoresis

Current densities of up to 4 mA/cm² for 10 minutes through the sclera of rabbits have been shown to cause no alterations to eye function or structure.

Currents of up to 3 mA for 20 min or 1.5 mA for 40 min, used for trans-scleral iontophoresis, in human subjects caused no significant alterations in the ophthalmic assessments nor given rise to clinical symptomatology.
Purpose

We aimed to evaluate both the **diffusion of riboflavin in the stroma** and the **corneal stiffening effect in human eye globes** in response to rapid* UV-A transepithelial corneal cross-linking using iontophoresis (**T-ionto CXL**) in comparison with **standard CXL**.

*T-ionto CXL* was performed using 10 mW/cm² UV-A lamp

Methods

N=4 eye globes were treated with T-ionto CXL and N=4 eyes with standard CXL.

A purpose-designed instrument, ie, the Ocular Biomechanics Modulator (OBM), combined to a Scheimpflug camera, was used to perform the experiments.
Densitometry 1

Results

Average changes of corneal light backscattering, with respect to baseline measurements, in specimens that underwent T-onto CXL.

A) Baseline
B) After iontophoresis
C) 5 min after T-onto CXL

Scheimpflug images

A
B
C
Densitometry 2

A) Average changes (±SD; vertical bars) of corneal light backscattering, with respect to baseline measurements, in specimens that underwent **T-iontop CXL**.

B) Average changes (±SD) of corneal light backscattering, with respect to baseline measurements, in specimens that underwent **Standard CXL**.

**Iontophoresis is effective to deliver riboflavin efficiently in the stroma**
Corneal absorbance (280-700 nm) before (blue) and after (red) stromal soaking with 20% dextran-0.1% riboflavin.
Corneal absorbance (280-700 nm) before (blue), after (green) corneal soaking with dextran free 0.1% riboflavin and after de-epithelialization (black).
After T-ionto CXL
The Young’s modulus on average increased 1.8 times (from $1.6 \pm 1.0$ to $2.9 \pm 1.6$ MPa).

After standard CXL
The Young’s modulus on average increased 1.9 times (from $1.3 \pm 0.9$ to $2.5 \pm 1.4$ MPa).

After both CXL procedures, stress-strain loading curves of the anterior cornea were steeper than preoperatively.

The area inside the loading and unloading curves (hysteresis) was found to be smaller than preoperatively.
TE-CXL with IONTOPHORESIS vs Standard CXL

Same effectiveness as the standard procedure but...

NO RISK OF HAZE
NO RISK OF INFECTION
FASTER VISUAL REHABILITATION
A RCT is ongoing at the IRCCS Fondazione G.B. Bietti, Rome, Italy

**Clinical Trial NCT02117999**

Randomized clinical trial comparing transepithelial corneal cross-linking using iontophoresis and standard corneal cross-linking for the treatment of keratoconus

PI: Dr. Marco Lombardo
At 3-months follow-up, both CXL procedures halted keratoconus progression.

5 and 4 cases underwent T-ionto CXL and Standard CXL respectively. Average age 28.0 and 28.8 years respectively. Progressive keratoconus showing Kapex >1 D over 1 year follow-up.
BCVA improved after T-ionto CXL in all cases

T-ionto CXL: from 41 preop (20/40) to 52 at 3-months (20/25)
Standard CXL: from 54 preop to 53 at 3-months
Conclusions

IN LABORATORY:
1) Iontophoresis was shown to deliver efficiently riboflavin through the epithelium.

2) After T-Ionto CXL, the corneal tissue became stiffer than preoperatively.

The results of T-Ionto CXL were mostly comparable to those obtained with standard CXL

IN CLINIC:
3) The preliminary results on patients treated by T-Ionto CXL are demonstrating that the procedure is effective to halt keratoconus progression, while improving the corneal optical performance and vision function.

Marco Lombardo can be reached at mlombardo@visioeng.it