IONTOPHORESIS

IONTOPHORESIS (from iòntos=ion and phòresis = to move across, ions moving across) consists in the one way movement of charged molecules throughout the tissue that needs to be treated, thanks to a low intensity electrical field applied.

Several drugs can be transported within the tissue that needs to be treated.

Polarized drugs are applied onto the electrodes, based on their polarity: positively charged molecules are applied on the positive electrode, while negatively charged molecules are applied on the negative electrode. On either cases, the other electrode is applied nearby the area that will be treated.

It allows to reach concentrations superior than those obtained using passive permeation (up to 50-100 folds)
HOW IONTOPHORESIS WORKS

- Delivery Electrode
- Power Supply
- Applied Formulation
- Counter Electrode

= Active ingredient
In 1905, Leduc investigated the transdermal transport of strychnine (+) using iontophoresis.
IONTOPHORESIS

- Iontophoresis represents today the most commonly used technique for the introduction of a drug through the epidermis.

- It allows to directly treat the area affected by pain from rheumatic pathologies (arthritis, sciatic, low back pain, etc.) and also by other pathologies such as cellulites, fat deposits, etc, obtaining a rapid therapeutic effect.

- The intake of drugs orally is avoided, thus minimizing any systemic side effects.

- Acyclovir
APPLICATIONS IN DERMATOLOGY AND OPHTHALMOLOGY

**Lidosite Lidocaine patch**  
(Vyteris)

**Iontopatch Dexamethasone**  
(Teikoku Pharma)

**Ionsys Fentanyl patch**  
(Incline therapeutics)

**Eyegate Trans-scleral device**  
(Eyegate Pharma)  
Phase III
Iontophoresis in ophtalmology has been investigated for few years now, and several publications have been presented. For example, the work of Frucht-Pery et al. on the transcorneal administration of dexamethasone or the studies performed in the US by the Company Eye-Gate.
Results: 1 to 20 of 180


20 free full-text articles in PubMed Central
Ocular iontophoresis of EGP-437 (dexamethasone phosph) [Clin Ophthalmol, 2011]
Recent advances in ophthalmic drug delivery, [Ophthalmic Res, 2010]
Effective electrophoretic mobilities and charges of anti-VEGF proteins [J Pharm Biomed Anal, 2011]
121. Fundamental and experimental studies on iontophoresis of vitamin B2 (FMN & FAU).
   PMID: 13751115 [PubMed-indexed for MEDLINE]
   Related citations

122. Behavior of hydrogen ion concentration in iontophoresis with unbuffered iodide solutions and with natural and synthetic spring-water products from Bad Hall iodine mineral springs (Upper Austria).
   POMMER H.
   PMID: 13339652 [PubMed-indexed for MEDLINE]
   Related citations

123. Influence of iontophoresis on the permeability of the excised cornea.
   DYSON C.
   PMID: 15369359 [PubMed-indexed for MEDLINE]
   Related citations
- 17 patients undergoing PKP
- Administration of methylprednisolone (MP), 62.5 mg/ml using the Eyegate system, by applying 1.5 mA electrical current for 4 minutes
- 1 application/day for 3 days

- No significant side effects were observed
FACTORS AFFECTING IONTOPHORESIS

\[ J_{\text{TOT}} = \left( \frac{I}{AF} \right) \frac{u_{\text{drug}}}{\sum_i u_i} + \frac{v_{\text{A}+}}{c_{\text{drug}}} \]

Main factors are

- Physico-chemical properties of molecules:
  - Molecular dimensions
  - Charge
  - Concentration ($C_{\text{drug}}$)

- Drug delivery system characteristics:
  - Diluents
  - Buffers (competitive ions, $C_i$)

- Current intensity ($I$)

- Treatment time
SPECIFICITY OF APPLICATIONS THROUGH THE CORNEA

- Corneal epithelium is a natural barrier to the penetration of macromolecules
  - Up to 150 kDa for the sclera vs 1 kDa for the cornea

- Cornea is sensitive to electrical currents
  - 5 mA/cm² for the sclera vs 1 mA/cm² for the cornea
  - Cornea contains nervous fibres

3 ways to enhance stromal penetration

- Removal of the epithelium (RICROLIN®): long treatment time, painful and possible side effects
- Use of enhancers (RICROLIN® TE): long treatment time
- IONTOPHORESIS
RIBOFLAVIN: THE PERFECT CANDIDATE

✓ low molecular weight (376,36 Da + Ph⁻)

✓ Negatively charged at physiological pH

✓ Highly soluble in water
Treatment in ocular iontophoresis is done through the application of two electrodes connected to a power generator.

The main electrode (-) is contained in a rubber ring that is applied on top of the cornea that needs to be treated; the other electrode (+) is a patch that is positioned on the patient forehead.
Current flux (low intensity) between the two electrodes allows a specific formulation of riboflavin (RICROLIN®+), specifically formulated for iontophoresis application, to rapidly penetrate the corneal stroma, through the intact epithelium (no removal of the epithelium).
CORNEAL IONTOPHORESIS

Current intensity that originates from the iontophoresis generator is 1 A/min (5 min treatment).
The supplied current is continuous and battery powered.
Treatment duration is automatically monitored by a software within the generator.
When the 5 min treatment are reached, the iontophoresis is automatically stopped.
IONTOPHORESIS: PLUS

- Total corneal impregnation in 5’ with EPI-ON technique. **Total procedure lasts just 14 minutes.**

- Safe, no side effects
  **NON RISK OF HAZE, INFECTION**

- More reproducible stromal Riboflavin concentration

- Increased patients (and ophthalmologists!) compliance
CORNEAL IONTOPHORESIS

IONTOPHORESIS CURRENT GENERATOR

IONTOPHORESIS SOLUTION

IONTOPHORESIS APPLICATOR
IONTOPHORESIS: PRE-CLINICAL STUDY
EFFECTS OF UVA CXL IN HUMAN CORNEAS AFTER IONTHOPHOREESIS AND HYPOTONIC RIBOFLAVIN SOLUTION: AN EX VIVO STUDY

Rita Mencucci
University of Florence
Department of Anatomy, Histology and Forensic Medicine
**Control group:** not treated corneas (n=3)

**Group 1:** 5 min riboflavin imbibition iontophoresis + 3mW/cm² x 30 min irradiation (n=5)

**Group 2:** 5 min riboflavin imbibition iontophoresis + 10 mW/cm² x 9 min irradiation (n=5)

**Group 3:** 5 min riboflavin imbibition iontophoresis (n=5)

Iontophoresis 1 mA x 5 min

All the specimens were analyzed 48 h after treatment
Fig. 1 - Haematoxylin eosin staining shows no endothelial damage in the treated groups
It works?
Group 2 CTL

Group 3

TUNEL: keratocyte apoptosis

EFFECTIVE APOPTOSIS
CONCLUSIONS

• Future researches will focus upon evaluation of the most effective UV irradiation power combining iontophoresis 1mA/cm² and CXL

• From our preliminary report the power of 10mW/cm² 9 min irradiation time could be considered safe and effective

• Combining iontophoresis and CXL represents an exciting new frontier in ophthalmic pharmacotherapeutics
Crosslinking via iontophoresis
A new approach

F. Malecaze
Toulouse, France
METHODS / TREATMENT GROUPS

Rabbits Groups \((n=100)\)

- **Iontophoresis CXL (Epi-on):**
  - Ricrolin®+ for 5 min
  - UVA 3 mW for 30 min \((n=20)\)
  - or UVA 10 mW for 9 min \((n=20)\)

- **Conventional CXL (Epi-off):**
  - Ricrolin® for 30 min
  - UVA 3 mW for 30 min \((n=20)\)

- **Several controls groups** \((n=40)\)
Rabbits treated eyes were processed

- Immediately for riboflavin diffusion analysis

- 2 weeks after the CXL for structural analysis of cornea
DIFFUSION OF RIBOFLAVIN TWO-PHOTON RESULTS
EFFECTS ON CORNEAL STRUCTURE
TWO-PHOTON RESULTS
Second Harmonic Generation

Untreated controls  Conventional-CXL  Iontophoresis-CXL

Collagen fibers more stacked and more linear
Riboflavin delivery by iontophoresis into corneal stroma is 2 times lower than EPI-OFF conventional application; the diffusion in more homogeneous in IONTO samples.

However, this amount is sufficient for an efficient crosslink of the two third anterior of the stroma, similar to the one induced by conventional crosslinking.
Corneal cross-linking: Intrastromal riboflavin concentration in iontophoresis-assisted imbibition versus traditional and transepithelial techniques.

Mastropasqua L, Nubile M, Calianno R, Mattei PA, Pedrotti E, Salgari N, Mastropasqua R, Lanzini M.

Abstract

**PURPOSE:** The present study aimed at determining differences in riboflavin concentration in the anterior, intermediate and posterior stroma after three corneal cross-linking imbibition techniques (standard Epi-off, Epi-on and Iontophoresis-assisted administration) of 0.1% riboflavin.

**DESIGN:** Experimental laboratory investigation of human cadaver corneas not suitable for transplantation.

**METHODS:** 10 corneas underwent imbibition with Epi-on (n=3), Epi-off (n=3), Iontophoresis (n=3) and saline exposure (control; n=1). Femtosecond laser was used to produce three 8mm discs of the superficial (0-150µm), intermediate (150-300µm) and deep stroma (>300µm). Riboflavin concentration was measured with High-Performance Liquid Chromatography. The main outcome measure was riboflavin concentration at the three evaluated depths.

**RESULTS:** The overall stromal concentration of riboflavin was 34.1±7.1 µg/g in Epi-off, 7.2±3.7 µg/g in Epi-on and 15.0±5.1 µg/g in Iontophoresis. The mean riboflavin content in the superficial slice in the Epi-off group was about two-fold greater than that of the Iontophoresis group (50.5±5.3 µg/g and 23.6±2.5 µg/g, respectively) and four-fold greater than that of the Epi-on group (11.7±3.3 µg/g). Similar differences among the three groups were observed for the intermediate and posterior stromal slices, presenting an evident reduction of riboflavin concentration with increasing depth in all groups. Slight depth-dependent decrease in riboflavin concentration was statistically significant (General Linear Model (GLM); F1,8=62.265, p=0.001), as was the group-dependent variation (GLM; F2,6=20.266, p=0.002) and the slice depth-group interaction (GLM; F2,6=10.004, p=0.002).

**CONCLUSIONS:** Corneal cross-linking transepithelial Iontophoresis imbibition yielded greater and deeper riboflavin saturation with respect to conventional Epi-on, while maintaining the advantages of avoiding epithelial removal and shorter procedure-time, but did not reach concentrations obtained with standard Epi-off.
Comparative Stress Strain Measurements Of Human Corneas After Transepithelial UV-A Induced Cross-linking: Impregnation With Iontophoresis, Different Riboflavin Solutions And Irradiance Power.

R. Vinciguerra, MD, E. Spoerl, PhD,
M.R. Romano, MD, PhD, G. Guerra, PhD,
P. Rosetta, MD, P. Vinciguerra, MD, C. Costagliola, MD
<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Standard epi off</th>
<th>Ionto 3 mW</th>
<th>Ionto 10 mW</th>
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<tbody>
<tr>
<td>Number</td>
<td>4</td>
<td>4</td>
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<tr>
<td>Impregnation</td>
<td>Ricrolin</td>
<td>Ricrolin</td>
<td>Ricrolin + solution</td>
<td>Ricrolin + solution</td>
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<tr>
<td>Impregnation Time</td>
<td>30 min</td>
<td>30 min</td>
<td>30 min</td>
<td>10 min</td>
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<tr>
<td>Irradiation Power</td>
<td>0 mW/cm²</td>
<td>3 mW/cm²</td>
<td>10 mW/cm²</td>
<td>10 mW/cm²</td>
</tr>
<tr>
<td>Irradiation Time</td>
<td>0 min</td>
<td>30 min</td>
<td>9 min</td>
<td>9 min</td>
</tr>
<tr>
<td>Iontophoresis</td>
<td>NO</td>
<td>NO</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>removal epithelium</td>
<td>YES</td>
<td>YES</td>
<td>NO</td>
<td>NO</td>
</tr>
</tbody>
</table>
Stress Strain analysis
Stress strain results showed a maximal effect in the iontophoresis group with 10 mW compared to other transepithelial techniques.

Due to the small number of corneas from the epi off group we are not able to say if it is as effective as standard treatment.

Preliminary isthological analysis did not show severe alterations of endothelial and epithelial cells in the IONTO group compared to control.
Same effectiveness as standard procedure but...
NO HAZE
NO RISK OF INFECTION
Transepithelial corneal collagen cross-linking by iontophoresis of riboflavin

Guzel Bikbova\textsuperscript{1,2} and Mukharram Bikbov\textsuperscript{1}

\textsuperscript{1}Ufa Eye Research Institute, Ufa, Russia
\textsuperscript{2}Department of Ophthalmology and Visual Science, Chiba University Graduate School of Medicine, Chiba, Japan
### Risultati

#### Risultati visivi e refrattivi

<table>
<thead>
<tr>
<th></th>
<th>Mean ± SD</th>
<th>1 week</th>
<th>1 month</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
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</thead>
<tbody>
<tr>
<td>UDVA (LogMar)</td>
<td>0.61 ± 0.44</td>
<td>0.52 ± 0.42</td>
<td>0.48 ± 0.38</td>
<td>0.51 ± 0.29</td>
<td>0.49 ± 0.31</td>
<td>0.48 ± 0.41</td>
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<tr>
<td>CDVA (LogMar)</td>
<td>0.34 ± 0.29</td>
<td>0.26 ± 0.25</td>
<td>0.30 ± 0.31</td>
<td>0.29 ± 0.22</td>
<td>0.28 ± 0.28</td>
<td>0.29 ± 0.25</td>
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<tr>
<td>Cheratometria (D)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>K1</td>
<td>44.6 ± 1.12</td>
<td>45.06 ± 2.11</td>
<td>44.02 ± 1.19</td>
<td>43.98 ± 1.97</td>
<td>42.38 ± 1.75</td>
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</tr>
<tr>
<td>K2</td>
<td>47.02 ± 2.33</td>
<td>47.12 ± 1.89</td>
<td>46.61 ± 2.63</td>
<td>46.74 ± 2.12</td>
<td>45.76 ± 2.01</td>
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</tr>
<tr>
<td>Av</td>
<td>46.47 ± 1.03</td>
<td>46.98 ± 1.85</td>
<td>46.2 ± 1.99</td>
<td>46.21 ± 1.79</td>
<td>44.19 ± 1.16</td>
<td>44.12 ± 1.12</td>
</tr>
<tr>
<td>Astigmatismo (D)</td>
<td>3.44 ± 0.48</td>
<td>3.36 ± 0.42</td>
<td>3.47 ± 1.12</td>
<td>3.12 ± 0.95</td>
<td>2.87 ± 0.67</td>
<td>2.95 ± 0.23</td>
</tr>
</tbody>
</table>

UDVA = acuità visiva non corretta, CDVA = acuità visiva corretta  
K 1 = potere diottrico corneale del meridiano più piatto (nell'area dei 3 mm centrali)  
K 2 = potere diottrico corneale del meridiano più curvo (nell'area dei 3 mm centrali)  
Δv = potere diottrico corneale medio (nell'area dei 3 mm centrali)  
D = diottrie
“One year transepithelial corneal collagen cross-linking by iontophoresis for progressive keratoconus in pediatric patients: results”

Dr Lapenna, Bari, Italy

11 eyes of 7 pediatric patients
Progressive keratoconus (stage II and III according to Amsler-Krumeich classification)

- Improvement in UCVA and BCVA
- Kmax regression 0.7 D
- No endothelial damage
“Riboflavin iontophoresis cross-linking 6 month follow-up with SD OCT: a pilot study”

dr. Capello, Treviso, Italy

18 eye of 18 patients affected by progressive keratoconus (I-III stage according to Krumeich classification)

- Improvement in BSCVA
- Kave stabilization
- Reduction in corneal astigmatism
IONTOPHORETIC PROCEDURE

1. Apply the «plaster» (positive electrode) on the patient’s forehead, after having cleansed it.
2. Connect the vacuum syringe to the luer lock (1) connector and verify that the stop clamp (2) is in the “open” position.
3. Position the **iontophoresis applicator (IONTOFOR® CXL)** onto the cornea to be treated, after having applied the speculum.
4. Check the correct position by looking throughout the center of the applicator: the cornea and the applicator must be concentric to one another.

5. Make a slight suction with the syringe of about 1 mL and close the **stop clamp (2)**.
6. Verify that the applicator is secured to the cornea. If not, repeat steps 3 to 5.

7. Aspirate with a syringe the RICROLIN®+ solution from the vial, and fill the applicator until the solution reaches the level above the grid (negative electrode).
8. Make sure that the electrode’s grid is always covered with the riboflavin solution for the entire duration of the procedure, thus to obtain a regular flow of the electrical current.

9. Verify that the generator is in the "OFF" position prior to connect the cables of the electrodes to the generator itself.
10. Connect the cable of the **negative electrode (4)** to the **current generator “I-ON® CXL”** and connect the plaster’s cable (positive return electrode) to the power generator.
11. Turn on the power generator, select 1 mA and press **START**. The procedure takes about 5 minutes.
12. After the electrophoretic procedure, remove the remaining RICROLIN®+ through the tube (5) by syringe connected to the yellow luer lock (8), open the stop clamp thus to allow the air to enter the vacuum’s ring (6).
12. Remove the applicator from the cornea and disconnect the power generator from the applicator and from the return electrode.

13. Rinse the eye with saline solution.

14. Proceed with the irradiation using the emitting **UV-A VEGA® 10 mW or equivalent (9 min)** according to the procedure’s guidelines.

15. Dispose of the applicator, the return electrode and the vacuum syringe in accordance with the standard procedures of the healthcare facility.