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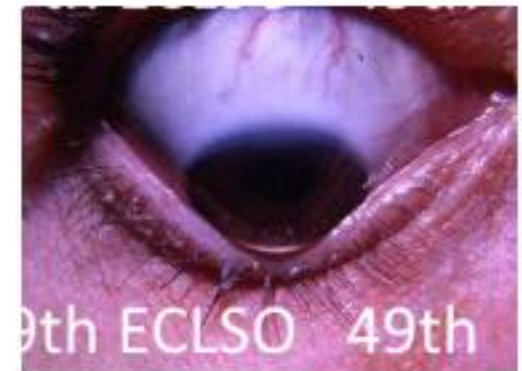
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# Comparative results between “Epi-off” conventional and accelerated corneal collagen cross-linking for progressive keratoconus in pediatric patients



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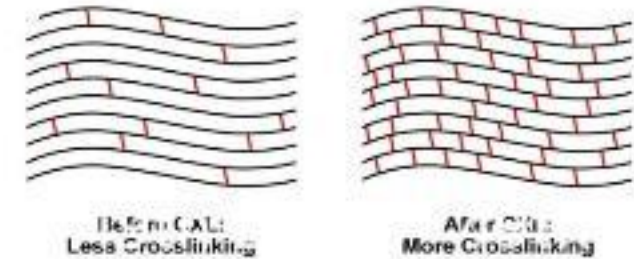
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I do not have any potential conflict of interest

# Introduction

- Keratoconus (KC) is a degenerative corneal disorder characterized by corneal thinning, conical protrusion, irregular astigmatism and visual impairment [1].
- Classically, the **onset** of the disease is in the **second decade of life** when the cornea presents **biomechanical instability** [1].
- This may conduct to a rapid deterioration in younger patients and in the same time affect life quality.
- It was demonstrated by several studies that KC in **pediatric patients** presents a **higher and faster rate of progression compared to adults** [2,3,4,5,6,7,8].
- 
- That is why it is a must **treating KC** in pediatric patients **as early as possible** and not waiting until patients develop a more advanced stage demanding corneal graft surgery [9].

# Introduction



- In the 1990s, **Wollensak et al** [10] introduced corneal collagen cross-linking (**CXL**) technique as a modern therapeutical option in adults KC that can halt the progression.
- CXL is a technique that uses the photochemical reaction between the ultraviolet A (UVA) light and riboflavin within the corneal stroma. The **final effect is the formation of chemical bonds between collagen fibrils strengthening the cornea**[11,12]
- Taking into consideration the poor prognosis of corneal transplantation in children than in adults, a treatment to stop the progression could be beneficial! [13].
- Some studies showed the **efficiency of CXL** in pediatric patients with KC [2].

## Purpose

- to analyze the results in terms of **efficacy** and **safety** of conventional and accelerated “epi-off” CXL procedure in pediatric patients with progressive KC up to 4 years following the procedure.

## Methods

- A retrospective, observational single center study was performed at the Oculens Private Clinic in Cluj-Napoca, Romania
- Two groups of pediatric patients with progressive KC:
- S-CXL group- 37 eyes of 37 patients-CXL “epi-off” “conventional
- A-CXL group - 27 eyes of 27 patients -CXL “epi-off” “accelerated

# Methods

## Inclusion criteria:

- age younger than 18 years
- males and females
- progressive KCN of different stages (according to the Krumreich classification)
- an average corneal thickness of at least 400  $\mu\text{m}$  at the thinnest corneal point
- Progression of KC was defined as an increase in steep K values at the apex of KC of 1 diopter (D) in 1 year
- In cases with KC stage III and IV the CXL procedure was done at once without waiting the KC progression.

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# Methods

## Exclusion criteria

- previously intracorneal ring placement
- herpetic keratitis in the past
- corneal pachymetry  $<400\mu$
- central corneal scar or Vogt striae



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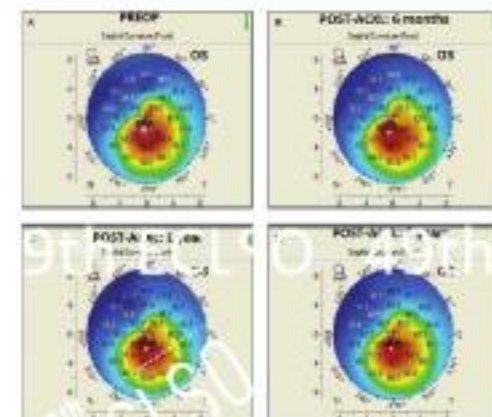
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# Methods

## Ocular exam

- UCVA and BCVA
- refractometry (manifest and cycloplegic)
- keratometry (Topcon autorefract-kerato-meter, KR 8900)
- slit lamp exam (Slit Lamp BX 900, Haag-Streit AG)
- eye fundus examination
- intra-ocular pressure by applanation tonometry,
- ultrasonic pachymetry (Sonomed 300P Pachymeter)
- corneal tomography (Pentacam® HR Premium; Oculus Optikgerate GmbH, Wetzlar, Germany)
- endothelial cell counting (Konan SP-9000, Hyogo, Japan)
- patients were asked for stopping the wear of soft contact lens 2 weeks and for rigid gas permeable for 1 month before the ocular examination or surgery.



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# Methods



The cross-linking procedure:

- in the operating room
- the “epi-off” CXL technique was used for conventional and accelerated procedure
- during the procedure a single 3.0 ml of the riboflavin 0,1% - dextran 20% solution was opened, and the power of the UVA illuminator ( Peschke Meditrade GmbH, Huenenberg, Switzerland CXL system) was verified
- **topical anesthesia** (alkaline solution) was done 15-20 minutes before cross-linking.
- **corneal de-epithelization** on a **9 mm diameter optical zone** was performed, followed by the instillation of one drop of alkaline solution and **instillation of riboflavin 0.1%** every **3 minutes** for **30** minutes prior to irradiation
- pachymetry was done after the corneal epithelium was removed to ascertain that corneal depth was more than 400 $\mu$
- the optical zone was further exposed to UVA light and riboflavin was applied every 3 minutes for a period of 30 minutes, using a power of **3 mW/cm<sup>2</sup>** for **conventional (standard) CXL** (Dresden protocol) and under a power of **9mW/cm<sup>2</sup>** for **accelerated CXL**- 10 minutes
- care was directed to **secure limbus** from inadvertent UV exposure
- the cornea surface was irrigated with balanced salt solution after irradiation.

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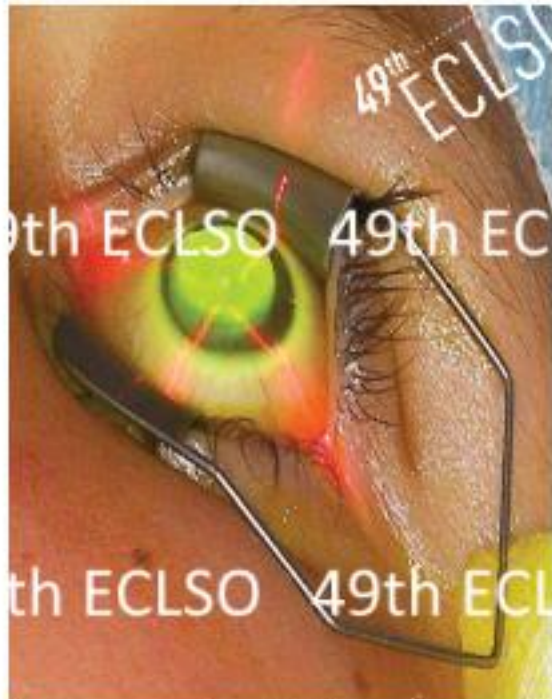
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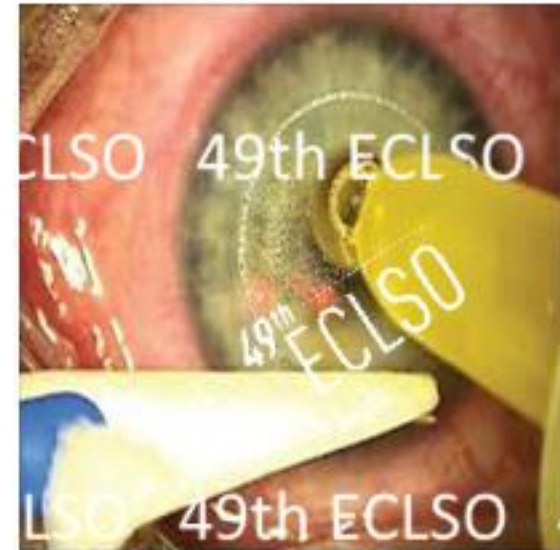
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•removal of the corneal  
epithelium 9mm of  
diameter;



corneal irradiation of central 9mm  
through the CMBX linker +  
instillation of riboflavine 0,1%  
every 3min – 30min;



Instillation of riboflavine 0,1% every  
3 min for 30min before the  
irradiation

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# Methods

- topical **steroids** and **antibiotics** and were instilled at the end of procedure
- postoperative **bandage soft contact lens** for 3-4 days
- after the procedure:-topical antibiotics (ciprofloxacin eye drops) 4x/day for 3 days
  - steroids (fluorometholone acetate 0.1%) 4x/day for 4 weeks
  - artificial tears 2x/day for 2 to 3 months
- anterior segment biomicroscope at day 1, at 4 days, 1 month, 6 months, 1 year and each year up to 4 years.
- statistical analyses : t student test

# Results

	S-CXL		A-CXL		P
Mean age	16.43±1.281	range: 12 and 18 years	16.77±1.527	range: 12 and 18 years	0.702
Male	24		20		0.632
Stage of KC I	24.3%		37.0%		
II	54.1%		37.0%		
III	18.9%		22.2%		
IV	2.7%		3.7%		
history of rubbing		58.6%			
atopy		20 eyes (12.8%)			
VKC		10 eyes (6.4%)			
Rigid CL		4 (1.32%)			
Family history of KCN		10%			



# Results K1 (K flat)

K1 (D)	S-CXL	p	A-CXL	p	P both
49th ECLSO	49th ECLSO	49th ECLSO	49th ECLSO	49th ECLSO	49th ECLSO
Baseline	47.41±3.39		46.97 ±4.17		0.801
1 y	46.76±3.59	0.0098	46.33±4.48	0.037	0.897
2 y	46.14± 3.55	0.010	45.77±4.25	0.045	0.512
3 y	45.65±±3.64	0.030	45.24±4.23	0.03	0.487
4 y	45.36±3.62	0.004	44.97±4.24	0.048	0.514

# Results K2 (K steep)

K2 (D)	CXL	p	A-CXL	p	P both groups
ECLSO	49th ECLSO	49th ECLSO	49th ECLSO	49th ECLSO	49th ECLSO
Baseline	51.98±4.11		50.55 ±4.10		0.200
1 y	51.49±4.60	0.0045	49.93±4.64	0.0072	0.1411
2 y	51.20±4.58	0.033	49.52±4.26	0.0051	0.1984
3 y	50.83±4.65	0.007	49.05±4.18	0.0101	0.0986
4 y	50.21±4.81	0.0078	48.75±4.13	0.0287	0.1122

# Results Kavg (mean K)

K avg	p	A-CXL	p	P both groups
Baseline	49.68±3.56	48.79±3.86		0.438
1 y	49.13±3.83	48.13 ±4.26	0.0071	0.0096
2 y	48.67±3.84	47.63±4.11	0.0094	0.012
3 y	48.24±3.98	47.15±4.09	0.0051	0.0399
4 y	47.79±3.98	46.86±4.11	0.0099	0.0356

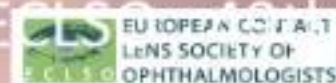


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# Results -mean cylinder

Mean Cyl	S-CXL	p	A-CXL	p	P both groups
Baseline	-4.98±2.80		-4.37±2.45		
1 y	-4.73±2.78	0.032	-4.12±2.35	0.044	0.4176
2 y	-4.49±2.55	0.0041	-3.89±2.58	0.0088	0.4002
3 y	-4.27±2.61	0.022	-3.70±2.48	0.0079	0.3966
4 y	-4.11±2.59	0.0091	-3.57±2.51	0.0143	0.4029

# Results SE

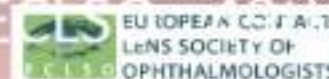
SE (D)	S-CXL	p	A-CXL	p	P both
49th ECLSO	49th ECLSO	49th ECLSO	49th ECLSO	49th ECLSO	49th ECLSO
Baseline	-6.90±4.31		-5.73±4.55 D		
1 y	-6.34±4.31	0.047	-5.30±4.59	0.0313	0.3561
2 y	-6.28 ± 4.33	0.036	-5.23±4.19	0.0075	0.3561
3 y	-6.23±4.24	0.017	-5.16±4.26	0.0072	0.3247
4 y	-6.18± 4.25	0.0087	-5.15±4.26	0.016	0.346

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# Results UCVA logMar

UCVA	S-CXL	p	A-CXL	p
Baseline	0.8 ±0.23		0.77±0.25	
1 y	0.7±0.24	0.0091	0.74 ±0.24	0.0123
2 y	0.69±0.23	0.042	0.69±0.25	0.0244
3 y	0.66±0.23	0.0085	0.65 ±0.24	0.02
4 y	0.65 ±0.24	0.072	0.63 ±0.25	0.0039

# Results -BCVA logMar

BCVA	S-CXL	p	A-CXL	p
49 <sup>th</sup> ECLSO	49 <sup>th</sup> ECLSO	49 <sup>th</sup> ECLSO	49 <sup>th</sup> ECLSO	49 <sup>th</sup> ECLSO
Baseline	0.57 ±0.20		0.54 ± 0.21	
1 y	0.50±0.19	0.005	0.51 ±0.22	0.0066
2 y	0.47 ±0.20	0.033	0.50±0.20	0.0109
3 y	0.46 ± 0.21	0.0061	0.49 ± 0.21	0.0077
4 y	0.45 ±0.20	0.0009	0.44 ± 0.21	p=0.0098

# Discussions

- The **major concern** is the **faster progression** of the disease in the pediatric patients.
- Chatsis and Hafezi [2] showed that 88% of KC in pediatric patients had a **progression** from the initial visit, suggesting that it may be inappropriate to wait for signals of progression as we consider in adults to offer treatment. [14]
- It is already known that **biomechanical stiffness** of the cornea is **inversely related to age** and children with KC are eye rubbers, mainly those who present vernal keratoconjunctivitis[14]. Corneal collagen crosslinking has been used in adult patients with KCN in order to halt the progression of the illness.
- Management of **vernal conjunctivitis** in pediatric patients with KCN is of prime importance as constant eye rubbing can "nullify" the effect of CXL.[14]

# Discussions

- In our study :- reduction in **K1** in S-CXL group by 2.05D and in A-CXL by 2.00D
- - reduction in **K2** in S-CXL group by 1.77 D and in A-CXL by 1.80D
- Arora et al. [21] applied standard CXL in 15 eyes from 15 pediatric patients with moderate in one eye and advanced keratoconus in the other one. **Mean change in apical K** ( $1.01 \pm 2.40$  D) was also significant ( $p=.004$ ).
- 
- In a prospective, international study Vindiguerra et al. [17] showed a **significant reduction** ( $p < 0.05$ ) in **keratometry** in the steepest and flattest meridian.



- In a prospective nonrandomized phase II open trial, Caporrossi et al [19] revealed after 3 years post **CXL statistically significant improvement in K readings and asymmetry index parameters.**
- Panos et al [9] in a retrospective study on 59 eyes from 42 children showed after 3 years of follow up period **a significant K max reduction after 24 months** and lost significance at 36 months.
- In their study Zotta et al [23] showed a **stabilization of K flat and K steep in all cases through follow-up.**

# Discussions

- Magli et al [26] demonstrated that in the “epi-off” CXL group there was a **significant improvement** at 12 months for **K max** (-1.11D,  $p=0.01$ ), **K min** (-3.2D,  $p=0.001$ ) and **mean K** (-1.47D,  $p=0.01$ ).
- Caporossi et al [27] revealed a statistically significant **improvement in K readings** and asymmetry index values.



## Discussions

- In our study **SE** and **mean cylinder** decreased significantly statistic in both groups at 4 years ( $p=0.0091/p=0.0143$ )
- Ozgurhan et al [28] demonstrated **that mean spherical and cylindrical refraction were not significantly changed** ( $p>0.0001$  for both), but at one year there was a statistically significant

# Discussions

- Similar results were shown by Shetty and al[31] who demonstrated an **improvement in cylindrical refraction** from  $-3.63 \pm 1.82D$  to  $-2.80 \pm 1.48D$  at 2 years ( $p=0.008$ ).
- The conclusion of Zotta et al [23] study was that **after conventional “epi-off” CXL procedure** there is a **stabilization** of the topographic cylinder ( $p<0.05$ ).
- Shetty et al. [31] demonstrated a **decrease in SE** from baseline  $-2.80 \pm 1.48D$  to  $-3.75 \pm 3.49 D$  ( $p<0.001$ ).

# Discussions

- In our study: postoperative **UCVA and BCVA** were statistically significantly **lower** than baseline (logMar) ( $p < 0.001$ )
- Caporossi et al. [26] demonstrated that functional data at 36 months had an **increase of +0.18 and +0.16 Snellen lines** for UCVA and BCVA, respectively in the thicker group (corneal thickness  $> 450 \mu$ ).
- Vinciguerra et al. [17] showed a mean logMAR baseline UCVA and BCVA of  $0.79 \pm 0.21$  and  $0.39 \pm 0.10$ , respectively. Mean UCVA and BCVA at 2 years were  $0.58 \pm 0.18$  and  $0.20 \pm 0.09$ , respectively.
- Mazzotta et al [25] showed **an improvement in UCVA and BCVA from 0.45 to 0.23 logMar ( $p = 0.0001$ ) and from 0.14 to 0.1 logMar ( $p = 0.019$ ) respectively.**

# Conclusions

- “Epi-off” conventional and accelerated corneal collagen cross-linking was found to be safe and effective in the first year with similar effect after 4 years in pediatric keratoconus patients in terms of functional and topographic outcomes.

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- Thank you!

