ORIGINAL ARTICLE

The Effectiveness of Corneal Cross-Linking in Stopping the Progression of Keratoconus

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SUMMARY

Objective.. Objective of the study was to prove the efficiency of corneal cross-linking (CXL) in stopping the progression of keratoconus.
Methods. In this study were included 58 eyes of patients with progressive keratoconus who underwent CXL according to the Dresden protocol in the years 2007-2009 at the Ophthalmic clinic FN Brno Bohunice. The eyes of patients were divided into four groups according to the change of maximum curvature of the cornea two years after CXL.
Results. Stabilization of maximum curvature of the cornea have been reported in 40 % of eyes, regression in 57 % of eyes by an average of 1,92D and disease progression in 3 % of eyes 2 years after CXL. The eyes with regression over 2D had significantly higher best-corrected visual acuity before and after the procedure compared to the group with stabilization. Spherical equivalent increased significantly in all groups, on average, in the group with stabilization of 0,54D, in the group with mild regression of 0,71D and in the group with a large regression of 2,09D. In the group with a large regression 100 % of eyes had stabilization or increase in SE. Our observations showed that, when a decrease in the patient keratometric values of cornea is present after CXL, it is comprehensive and applies to all parameters.
Conclusion. We have confirmed that corneal cross-linking stops the progression of the disease in 97 % of eyes two years after the procedure.

Key words: keratoconus, corneal cross-linking, riboflavin, UVA irradiation, maximum curvature of the cornea, effectivity of the treatment

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INTRODUCTION

More than fifteen years ago, the first study was published dealing with the possibility of using corneal cross-linking in the treatment of keratoconus. Within the context of the treatment of keratoconus, the period before this publication is known as the pre-CXL era (22, 19).
Conservative therapy of keratoconus is focused on the correction of the refractive error. This is most frequently a combination of myopia and irregular astigmatism. In the initial stages, correction by glasses or soft contact lenses (CL) is usually sufficient. The selection of suitable correction is important for improving the patient's vision, but especially for minimising trauma of the cornea in its tolerance limits (9, 13, 14, 21).
Transplant of the cornea is the most successful, most common and historically earliest introduced allogenic transplant in medicine. Despite new methods of treatment, for 10-20% of patients it is the only therapeutic option for regaining usable vision. The long-term results however most recently indicate that despite the envisaged advantages of lamellar techniques of transplantation, a graft following deep lamellar transplantation or endokeratoplasty in an equal indication and equal time period has a worse prognosis of survival than following penetrating keratoplasty. Upon transplantation of the cornea for keratoconus, the resulting vision is significantly better after a penetrating procedure than after deep anterior lamellar keratoplasty (DALK). After a corneal transplant, the majority of patients continue to require correction of the refractive error. In certain cases it is possible to correct this by methods of laser refractive surgery (2, 5, 4, 6, 7, 9, 12, 13, 25, 29, 30).
New methods of treatment also include implantation of rings made of polymethyl methacrylate into the periphery of the cornea, which leads to a flattening of the central part of the cornea and an arching in the place of the ring, thus bringing about a correction of myopia and astigmatism. The implantation of the ring in itself however does not influence the pathophysiological process of the disease (18, 20).
Over several observations of corneas following CXL, increased rigidity, a growth of the diameter of collagen fibres, lower susceptibility to edema, increased biochemical stability against lytic enzymes, heat, pepsin, mercaptoethanol and apoptosis of keratocytes was demonstrated in the anterior section of the corneal stroma. These changes reach to a depth of approximately 300 µm from the surface of the cornea, which was confirmed also by confocal microscopy. These facts merely confirm the significance of the introduction of CXL into the treatment of progressive keratoconus (15, 16, 23, 24, 26, 27, 32).

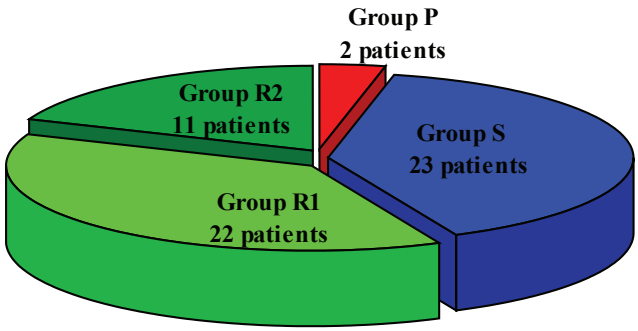
STUDY SAMPLE AND METHOD

The observed study sample comprised a total of 58 eyes of patients with an average age of 28.07 ± 9.78 years (range 13-55 years), who had under-

Table 1 Division of eyes of patients into groups according to success rate of corneal cross-linking (CXL).

Group	Criterion for grouping – success rate of procedure	Number of eyes	Average age ± standard deviation	Age range (years)
P	Progression (growth MAX > 1D)	2	-	27 and 42
S	Stabilisation (change MAX -1 to +1D)	23	28.22 ± 8.75	17 – 45
R1	Regression (reduction MAX 1-1.9D)	22	25.36 ± 8.76	13 – 43
R2	Regression (reduction MAX > 1.9)	11	32.00 ± 12.75	17 – 55

(MAX – maximum curvature of cornea)



Graph 1 Division of eyes according to success rate of CXL

gone corneal cross-linking with an isotonic solution of riboflavin and abrasion of the corneal epithelium according to the Dresden protocol (Riboflavin 0.1% + 20% Dextran T500, IROC UV-X 1000) at the Ophthalmology Clinic at the Brno Bohunice University Hospital in the period from 2007 to November 2009.

The basic indication criteria were diagnosis of keratoconus with demonstrated progression maximally for the period of the last year, minimum corneal thickness of 400 μm measured by an Orbscan II instrument, and that the patient had sufficient best corrected vision with glasses or contact lenses. The observation period in this analysis was 24 months. All the patients, and in the case of minors their legal representative, were regularly instructed with regard to the risks of the procedure, its course and postoperative care, and signed a declaration of informed consent.

We wished to divide the study sample into four groups (P, S, R1 and R2) according to the difference in maximum curvature of the cornea before the procedure and after two years. Since we recorded an increase of maximum curvature by more than 1D in only two eyes (3%), it was not possible to create a statistically relevant group (P) from this number. Twenty three eyes with a value of difference from -1D to +1D were classified into the group with stabilisation (S). 22 eyes with a reduction of the value between 1D – 1.9D were classified in the group with slight regression (R1) and we included 11 eyes in the group with a large regression (R2) (table 1 and graph 1). The parameters evaluated in these groups were best corrected visual acuity (BCVA) on ETRDS optotypes, spherical equivalent (SE), corneal thickness measured by ultrasound method (UZV CCT) on a Nidek UP-1000 instrument and keratometric values measured by an Orbscan II instrument.

The statistical analysis was performed by the program STATISTICA version 12.2 in licence of Masaryk University (=MU) and the program Microsoft Office Excel 2007. With regard to the unconfirmed normal dispersion of values, non-parametric methods (Wilcoxon pair test) were used for the data analysis. The statistical significance of the tests was assessed on the level of significance $\alpha = 0.05$.

RESULTS

Upon a comparison of best corrected visual acuity (BCVA) in the groups of eyes divided according to the success of the procedure (S, R1, R2), no statistically significant increase was confirmed. Upon a comparison of the percentage of eyes with an improvement of BCVA, the increase was the largest (73%) in the R2 group. Upon a comparison between the groups, the eyes in the group with the largest regression before the procedure had worse best corrected visual acuity than in the group with stabilisation, and this difference became further pronounced to the detriment of the R2 group after 2 years. The complete results are presented in table 2.

Upon a comparison of spherical equivalent (SE) in the groups, a statistically highly significant increase of negative SE was confirmed 2 years after CXL. In the group with stabilisation, the increase was on average by 0.54D, in the group with slight regression by 0.71D and in the group with large regression by 2.09D. In the group with large regression 100% of eyes had stabilisation or increase of SE. Upon a comparison of the SE values between the groups, there was a statistically significant difference before the procedure between the S and R2 groups, and between R1 and R2 to the detriment of the R2 group. At the time of two years after CXL this significance was lost, from which it ensues that the eyes in the group with large regression (R2) surprisingly had significantly the lowest negative SE before the procedure, but 2 years after CXL this had increased to the degree that the difference between the groups had disappeared. The complete data is presented in table 3.

Upon a comparison of the values of corneal thickness measured by the ultrasound method, no significant difference was recorded between CXL and 2 years after CXL either within the individual groups of eyes or between the groups. On the basis of these results, no influence of corneal thickness measured by ultrasound method was demonstrated on the success of CXL (table 4).

Upon a comparison of the keratometric values in all groups, a statistically significant reduction was recorded in comparison between the status before CXL and 2 years after, with the exception of the values Sim K and MIN in the group with stabilisation.

Upon a comparison of the values of minimum curvature of the cornea and irregularity of the cornea in the 3mm zone, no significant difference was recorded between the groups either be-

Table 2 Best corrected visual acuity (BCVA) in groups of patients divided according to success rate of CXL (number of letters).

BCVA (number of letters)	Number of eyes	Average	Standard deviation	Range of values	Increase Number (%)	Stabilisation Number (%)	Reduction Number (%)	p value in group
S before	22	45.05	11.30	15-59	-	-	-	-
R1 before	21	42.71	8.27	23-55	-	-	-	-
R2 before	11	35.64	12.22	15-55	-	-	-	-
S 2Y	22	49.00	9.84	21-60	15 (68%)	3 (14%)	4 (18%)	0.05
R1 2Y	21	44.73	8.66	25-55	12 (57%)	3 (14%)	6 (29%)	0.19
R2 2Y	11	39.09	8.57	28-50	8 (73%)	1 (9%)	2 (18%)	0.10

(S – group with stabilisation of maximum curvature of the cornea, R1 – group with regression of 1 to 1.9D, R2 – group with regression of more than 2D, before – before procedure, 2Y – 2 years after procedure)
Note: in two patients it was not possible to determine BCVA with glasses lenses reliably due to high astigmatism, the significance is determined from the pair values

fore or 2 years after CXL. There was a statistically significant difference between the S and R2 groups between the preoperative values of simulated keratometry, maximum curvature of the cornea and irregularity of the cornea in the 5mm zone, where the eyes in the group with large regression had higher values before the procedure, but this significant difference disappeared after 2 years.
Upon a comparison of the average values of all keratometric parameters before the procedure, the highest values were in the group with the largest regression.
From these comparisons it ensues that the eyes in the R2 group showed the largest reduction of all keratometric values, not only the values of maximum curvature of the cornea as the selection criterion upon dividing into the groups P, S, R1 and R2. When a reduction of keratometric values takes place after CXL, this is complex and relates to all parameters.
We recorded progression of the disease, as an increase in maximum curvature of the cornea by more than 1D, in 2 patients (3%). These were men aged 27 and 42 years, with stage 2 keratoconus according to the Amsler – Krumeich scale. They did not have a positive family anamnesis, were not being treated and did not have either general diseases or ophthalmological diseases in their anamnesis. In the younger patient, despite the increase in the value of maximum curvature of the cornea by 1.5D at the limit thickness of the cornea (420 μm before the procedure) and the increase in

Table 3 Spherical equivalent (SE) in groups of patients divided according to success rate of CXL (D).

SE (D)	Number of eyes	Average	Standard deviation	Range of values	Increase Number (%)	Stabilisation Number (%)	Reduction Number (%)	p value in group
S before	23	-5.03	4.55	-19.25 to -0.25	-	-	-	-
R1 before	22	-5.52	3.51	-13.75 to -0.25	-	-	-	-
R2 before	11	-8.14	2.97	-12.00 to -2.25	-	-	-	-
S 2Y	23	-4.49	4.17	-17.00 to 0.50	16 (70%)	1 (4%)	6 (26%)	$p < 0.01$
R1 2Y	22	-4.81	3.25	-13.00 to 0.50	18 (83%)	1 (5%)	3 (14%)	$p < 0.01$
R2 2Y	11	-6.05	3.11	-10.75 to 0.75	9 (82%)	2 (18%)	0 (0%)	$p < 0.01$

(S – group with stabilisation of maximum curvature of the cornea, R1 – group with regression of 1 to 1.9D, R2 – group with regression of more than 2D, before – before procedure, 2Y – 2 years after procedure)

Table 4 Thickness of cornea measured by ultrasound method (UZV CCT) in groups of patients divided according to success rate of CXL (μm)

UZV CCT (μm)	Number of eyes	Average	Standard deviation	Range of values	p value in group	Stabilisation Number (%)	Reduction Number (%)	p value in group
S before	23	466.96	36.40	420 – 544	-	-	-	-
R1 before	22	473.23	36.90	417 – 560	-	-	-	-
R2 before	11	467.18	39.73	430 – 552	-	-	-	-
S 2Y	20	470.90	50.52	415 – 600	0.79	3 (14%)	4 (18%)	0.05
R1 2Y	18	458.33	37.51	412 – 536	0.19	3 (14%)	6 (29%)	0.19
R2 2Y	8	456.50	34.72	402 – 501	0.26	1 (9%)	2 (18%)	0.10

(S – group with stabilisation of maximum curvature of the cornea, R1 – group with regression of 1 to 1.9D, R2 – group with regression of more than 2D, before – before procedure, 2Y – 2 years after procedure)
Note: for technical reasons it was not possible to determine the given parameter in all patients two years after the procedure, the significance is determined from the pair values

negative SE by 0.75D to -7.00D after two years, there was an improvement of BCVA by 4 letters. The older patient, despite pachymetry of 520 µm before the procedure had high SE (-15.75D), which was reduced after 2 years by -3.25D. Six months after the procedure the increase in maximum curvature of the cornea in this patient was by as much as 13.4D (from 45.50D to 58.90D), with a subsequent reduction to 51.70D two years after CXL. However, in this patient there was a pronounced deterioration of best corrected visual acuity by 8 letters.

Upon an observation of selected characteristics of the eyes in the individual groups, we determined that in the group with stabilisation 52% of patients had 1 keratoconus according to the Amsler-Krumeich scale, whilst in the entire study sample only 38% of patients had this stage. There was a higher percentage representation of women in the eyes of patients with stabilisation (24% to 34%). In the other observed characteristics we did not determine any differences (age, biomicroscopic symptom of keratoconus, presence of atopy, wearing of hard contact lenses).

DISCUSSION

Koller (10) in his study defined also an increase of maximum curvature of the cornea by 1D as a complication, and at the same time defined a reduction of the value by more than 1D as regression. He recorded progression of the disease in 7.6% of eyes, stabilisation in 55.2% of eyes and regression in 37.1% of eyes 1 year after CXL. Upon a comparison of selected characteristics of these groups, he determined that in the group with progression of the disease, there were significantly more women in comparison with the overall study sample.

In another study, Koller et al. (11) observed a study sample of 155 eyes after CXL, and described flattening of the cornea by more than 2D in 13% of eyes, stabilisation of maximum curvature of the cornea in 60.3% of eyes and recorded progression in 2% of eyes.

Wollensak et al. (31), in the first published study dealing with corneal cross-linking, describe the regression of the value of the maximum curvature of the cornea one year after CXL in 70% of eyes by an average of 2.01D, they recorded stabilisation in 22% and progression in 5% of eyes.

Raiskup et al. (24) in a 6-year observation of 241 eyes of 130 patients after CXL recorded a failure of treatment in only 2 patients with neurodermatitis, and the progression of the disease was at the time of worsening of the clinical picture of neurodermatitis. In both patients, CXL was subsequently repeated without complications. In a further analysis of the study sample, they describe a reduction of the maximum curvature of the cornea by an average of 1.91D in 54% of eyes at a follow-up examination after two years, as well as stabilisation in 35% of eyes.

Agrawal et al. (1) recorded a reduction of the maximum curvature of the cornea in 54% of eyes by an average of 2.47D and stabilisation in 38% of eyes, whilst Asri et al. (3) described a reduction by more than 2D in 21.3% of eyes. Hersh et al. (8) recorded a reduction by more than 2D in 31% of eyes and an increase by more than 2D in 4.2% of eyes. The results of the published works correspond with our present and past published findings (28). A summary of the results of the compared studies with our current results is presented in table 5.

CONCLUSION

We recorded the failure of treatment in 3% of eyes. Stabilisation of the maximum curvature of the cornea was achieved in 40% of eyes, regression up to 2D in 38% of eyes and we recorded a reduction by more than 2D in 19% of eyes 2 years after CXL. Patients with regression of more than 2D had worse best corrected visual acuity before the procedure in comparison with the other groups, and 2 years after CXL this difference was still more pronounced. In the group with large regression there was also the lowest spherical equivalent before the procedure and the most pronounced reduction of all keratometric values, not only the values of maximum curvature of the cornea.

On the basis of the results, we can state that corneal cross-linking is an effective procedure for stopping the progression of the disease in 97% of eyes 2 years after CXL. Long-term and continual observation of patients following CXL is essential for an assessment of the overall effect of the course of the disease.

Table 5 Comparison of success rate of CXL with published studies

Author 1 (year of publication)	Observation period (years)	% of eyes with regression (definition)	% of eyes with stabilisation	% of eyes with progression
Koller (10) (2009)	1	37.1%	55.2% (± 1D)	7.6%
Koller et al. (11) (2011)	-	13% by more than 2D	60.3% (± 1D)	2%
Wollensak et al. (31) (2003)	1	70% (average by 2.01D)	22%	5%
Raiskup et al. (24) (2008)	2	54% (average by 1.91D)	35% (± 0.5D)	-
Agrawal et al. (3) (2009)	1	54% (average by 2.47D)	38%	-
Asri et al. (3) (2011)	1	21.3% by more than 2D	-	-
Hersh et al. (8) (2011)	1	31.0% by more than 2D	-	4.2% by more than 2D
Strmeňová et al. (2014)	2	57% (average by 1.92D)	40% (± 1D)	3%

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