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Nationwide reduction in the number of corneal transplantations for keratoconus following the implementation of cross-linking

Daniel A. Godefrooij, Renze Gans, Saskia M. Imhof and Robert P. L. Wisse

Department of Ophthalmology, Utrecht Cornea Research Group, University Medical Center Utrecht, Utrecht, The Netherlands

ABSTRACT.

Purpose: **Keratoconus is characterized by corneal ectasia and irregular astigmatism, which can lead to diminished vision and corneal scarring. Approximately 10–20% of patients with keratoconus eventually require a corneal transplant. Corneal cross-linking (CXL) is a relatively new treatment that may help prevent the need for corneal transplantation. Here, we investigated whether the introduction of CXL has reduced the number of corneal transplants performed annually.**

Methods: **Data regarding the transplantation procedures performed in patients under the age of 50 years were extracted from the Dutch National Organ Transplant Registry. The number of corneal transplants performed prior to (i.e. in 2005 through 2007) and following the introduction of CXL (i.e. in 2012 through 2014) were compared. Furthermore, a trend analysis on annual keratoplasties over time was performed.**

Results: **Approximately 25% fewer corneal transplants were performed in the 3-year period following the introduction of CXL compared to the 3-year period prior to the introduction of CXL (201 versus 269 transplants, respectively; $p = 0.005$). Age, gender and visual acuity were similar between the patient groups in the two time periods. Trend analysis also demonstrated a significant decrease in the amount of corneal transplants ($p = 0.001$).**

Conclusion: **Significantly fewer corneal transplants were performed for treating keratoconus following the nationwide introduction of CXL. This reduction suggests that corneal cross-linking can significantly reduce the need for corneal transplantation.**

Key words: corneal transplantation – cross-linking – keratoconus – keratoplasty

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Introduction

Keratoconus is a corneal disease characterized by a gradual thinning of the central and peripheral corneal stroma, resulting in corneal protrusion and reduced visual acuity (Rabinowitz 1998; Prakash et al. 2016). Optical correction with either rigid contact lenses or spectacles is usually sufficient to counteract the reduced visual acuity in mild cases of keratoconus. However, if keratoconus progresses, these visual aids are often insufficient for maintaining adequate visual acuity; ultimately, 10–20% of patients require corneal transplantation (Davidson et al. 2014).

In 2003, Wollensak et al. introduced corneal cross-linking (CXL) as a potential treatment for keratoconus. Corneal cross-linking uses riboflavin-containing eye drops and UV-A radiation to strengthen the corneal collagen in the stroma and increase the cornea's rigidity (Ashwin & McDonnell 2010). The effectiveness of using cross-linking to slow and in some cases, halt the progression of keratoconus has been demonstrated in randomized controlled trials, suggesting that CXL may help prevent the need for corneal transplantation in patients with keratoconus (Spoerl et al. 2007; Caporossi et al. 2010; Hersh et al. 2011; O'Brart et al. 2011; Wittig-Silva et al. 2014).

In the Netherlands, corneal cross-linking was first performed near the end of 2007. In the years following its introduction, CXL has been used increasingly more often in expert treatment centres. Corneal cross-linking is now a well-established treatment for keratoconus in the Netherlands.

In a recent study performed on a local scale, Sandvik et al. (2015) suggested that the introduction of CXL was the principal underlying factor responsible for the recent reduction in keratoplasties for treating keratoconus. This finding prompted us to investigate whether the introduction of CXL has reduced the number of corneal transplantation surgeries performed in patients with keratoconus throughout the Netherlands.

Materials and Methods

Data regarding corneal grafting procedures performed in the Netherlands from 2005 through 2014 were extracted from the Dutch National Organ

Transplant Registry (NOTR). The NOTR database is hosted by the Dutch Transplantation Foundation (*Nederlandse Transplantatie Stichting*) and contains information regarding all patients who underwent keratoplasty for keratoconus in the Netherlands. Dutch corneal surgeons are required to complete both a pretreatment form and a surgical form, and participation in the NOTR is required in order to receive donor corneas, leading to near perfect registration. The NOTR database was anonymized with respect to the patients and surgeons and then provided to the researchers. Permission to extract the anonymized data was granted by the NOTR scientific council (the Dutch Cornea Workgroup, a subcommittee of the Dutch Ophthalmic Society). The study was designed and performed in accordance with the tenets of the Declaration of Helsinki with respect to medical research involving human subjects.

The following data were extracted from the NOTR database: diagnosis, presence or absence of corneal hydrops, age at the time of transplantation, gender, preoperative best-corrected visual acuity (BCVA), and preoperative keratometry results. Best-corrected visual acuity (BCVA) was measured either with spectacles or contact lenses and was used in our subsequent analyses. The preoperative keratometry result was noted as the average keratometry value and was measured using either Javal, corneal topography, automated refraction, or an unknown method (in which case the surgeon selected 'other' in the pretreatment form). Only patients who were under 50 years of age were included; 50 years of age was selected as the cut-off because this is the highest age at which CXL is performed and thus would have the best chance of detecting any effects of the introduction of CXL. Two 3-year time periods were selected and compared. The 'pre-CXL' period was from January 2005 through December 2007. The 'with-CXL' period was a 3-year period following the introduction of CXL and was from January 2012 through December 2014.

All ophthalmologists participating in the Dutch Cornea Workgroup or centres potentially performing CXL were contacted and asked to share the yearly amount of performed cross-linking procedures for keratoconus. All centres responded and the data of eight centres performing CXL during the study period were included in this study: Erasmus University Medical Center, Eye Hospital Rotterdam, Gelre Hospital Apeldoorn, Leiden Universitary Medical Center, Maastricht University Medical Center, Radboud Univerity Medical Center, University Medical Center Groningen/HanzeKliniek Groningen, and University Medical Center Utrecht.

Statistical analysis

All summary data are presented as percentage, range or mean with standard deviation (SD). Age, gender and BCVA values were compared between the two time periods using the independent samples *t*-test. The annual size of the Dutch population under the age of 50 was based on numbers obtained from the Dutch Bureau of Statistics and were averaged for each time period (CBS 2014). The two-proportion *Z*-test was used to analyse the differences between the pre-CXL and with-CXL periods. Poisson regression was used to analyse the trend in the annual amount of corneal transplants over time during the whole study period. The β-value refers to the slope of the regression line, with negative values indicating a decrease in the annual amount of corneal transplants. Differences with a p-value < 0.05 were considered to be statistically significant. The data were analysed using SPSS, version 21.0 (IBM, Armonk, NY, USA).

Results

The average annual population of people in the Netherlands <50 years of age was 10 895 112 and 10 552 445 in the pre-CXL and with-CXL periods, respectively (CBS 2014). A total number of 1364 cross-linking treatments was performed in the Netherlands in the period September 2007 through December 2014. The distribution of cross-linking treatments per year is displayed in Fig. 1.

In the 3-year pre-CXL period, a total of 269 corneal transplants were performed; in contrast, in the 3-year with-CXL period, a total of 201 corneal transplants were performed. This 25% difference in the number of corneal transplants performed in the two time periods was statistically significant ($p = 0.005$). The trend analysis also demonstrated a significant decrease in the amount of corneal transplants ($p = 0.001$, $\beta = -0.034$).

The baseline characteristics of the patients in the two groups were similar with respect to age, gender and visual acuity (Table 1). The mean ($\pm$SD) keratometry values in the pre-CXL and with-CLX groups were 54.6 ± 6.9 and 61.6 ± 9.6, respectively. However, it should be noted that the keratometry readings were not available in the records of 69% and 61% of patients in the pre-CXL and with-CXL groups, respectively. Age and gender were reported for all patients in both groups, and BCVA was reported in 91% and 93% of the patients in the pre-CXL and with-CXL groups, respectively.

Discussion

Our analyses reveal that significantly fewer corneal transplantation surgeries were performed in the Netherlands for

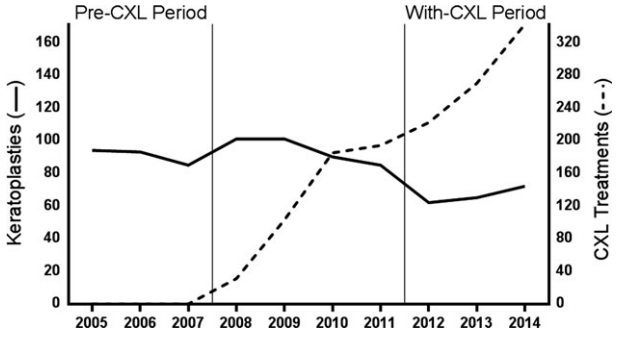

Fig. 1. Annual number of keratoplasties and number of cross-linking (CXL) treatments in the Netherlands. Annual number of keratoplasties; 2005:94, 2006:93, 2007:83, 2008:102, 2009:102, 2010:90, 2011:85, 2012:62, 2013:65, 2014:75. Annual number of corneal cross-linking (CXL) treatments; 2005:0, 2006:0, 2007:17, 2008:31, 2009:103, 2010:185, 2011:194, 2012:222, 2013:270, 2014:342.

Table 1. Preoperative characteristics of eyes of patients that underwent keratoplasty for keratoconus in the pre-CXL and with-CXL groups.

Preoperative characteristic	Pre-CXL (2005–2007)	With-CXL (2012–2014)	p-value
Number of eyes	269	201	0.005*
Mean age, years (range)[†]	33.0 (9–49)	32.3 (13–49)	0.41[‡]
Male gender, frequency (%)[†]	188 (69.9)	139 (69.2)	0.86[‡]
Mean BCVA (SD)[§]	0.20 (0.20)	0.18 (0.20)	0.27[‡]

CXL = corneal cross-linking, SD = standard deviation, BCVA = best-corrected visual acuity.
* p-value calculated using the two-proportion *Z*-test.
[†] Age and gender data were available in 100% of patients in both the pre-CXL and with-CXL period.
[‡] p-value calculated using the independent sample *t*-test.
[§] Best-corrected visual acuity data were available for 91% of patients in the pre-CXL period and 96% of patients in the with-CXL period.

keratoconus after corneal cross-linking was introduced in the Netherlands. This reduction in the prevalence of corneal transplants suggests that CXL may have a positive impact on the need for corneal transplantation in this patient population. Corneal cross-linking is a minimally invasive, relatively safe, effective procedure for slowing or even halting the progression of keratoconus (Spoerl et al. 2007; Caporossi et al. 2010; Hersh et al. 2011; O'Brart et al. 2011; Wittig-Silva et al. 2014). The ability to minimize the need for corneal transplantation is highly relevant, as this procedure is invasive and carries a significant risk of postoperative complications, including graft rejection, graft failure, secondary glaucoma, and cataract (Borderie et al. 2012). Our results at the nationwide level are consistent with a recent report by Sandvik et al. (2015), who described a similar correlation between CXL and corneal transplantation, albeit on a local scale.

In our attempt to determine whether a causal relationship exists between the nationwide introduction of CXL and the decrease in corneal transplantations, we made several assumptions. First, we assumed that the lower number of corneal transplantations performed in the with-CXL period cannot be explained simply by a decrease in the prevalence of keratoconus. No data are available regarding the current prevalence of keratoconus in the Netherlands; however, given that corneal imaging devices are more accessible to opticians and local hospitals, keratoconus is more likely to be detected in the with-CXL period. Furthermore, the advent cross-linking itself has created a renewed clinical and scientific interest in keratoconus, leading to more awareness and potentially more referrals for treatment options of this particular disease (Ali et al. 2014). Therefore, it felt conservative to assume that the prevalence of advanced keratoconus remained stable. Secondly, we assumed that the indication for performing keratoplasty did not change between the two periods examined. The baseline preoperative characteristics were similar between the two groups, suggesting that the indication for corneal transplantation likely did not change significantly. Although the preoperative keratometry values differed slightly between the two groups, these values were recorded in only 35% of patients. Our third assumption was that the preventive effect of CXL would be detectable within a timeframe of several years. In other words, we assumed that performing CXL in progressive keratoconus patients from 2007 onwards would have been able to prevent the need for corneal transplantation in the second time period. We considered this assumption to be valid based on the randomized controlled trial performed by Wittig-Silva et al. (2014), in which 10% of eyes that were not treated with CXL received a corneal transplant within 3 years, whereas no transplantation surgeries were performed in the eyes that underwent CXL. Lastly, we assumed that the preventive effect of CXL would be the most robust and relevant in patients under the age of 50 years. The age range at which CXL is usually performed for progressive keratoconus is 16–50 years (Wittig-Silva et al. 2008). Including older patients in the analysis would therefore have clouded the presumed relationship between CXL and corneal transplantations.

The implementation of CXL did increase the total number of procedures for the keratoconus considerably (see Fig. 1). Whether CXL overtreatment exists cannot be derived from these data, though national guidelines warrant the documentation of disease progression to be entitled to reimbursement (College van Zorgverzekeringen 2015). It is important to bear in mind that CXL and keratoplasty are two essentially different treatments that are not mutually exchangeable: keratoplasty procedures are reserved to restore visual acuity in the most severe cases, where CXL is indicated to prevent deterioration in progressive cases.

In conclusion, the nationwide number of corneal transplantations performed annually for keratoconus decreased significantly following the introduction of corneal cross-linking for progressive keratoconus. Although it is difficult to establish a causative relationship between these two events, it is reasonable to assume that the nationwide introduction of corneal cross-linking has played a major role in reducing the need for corneal transplantation for keratoconus in this population.

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Correspondence:
Daniel A. Godefrooij, MD
Office E03.136
University Medical Center Utrecht
PO Box 85500
3508 GA Utrecht
The Netherlands
Tel: +31 088 755 0865
Fax: +31 088 755 5417
Email: d.a.godefrooij@umcutrecht.nl

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