Keratoconus

Epidemiology, treatment effects and economic evaluation

Daniel Godefrooij

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en economische evaluatie
(met een samenvatting in het Nederlands)

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1
Introduction to this thesis

Daniel A. Godefrooij

The field of keratoconus care underwent major changes over the last decade, with innovations such as deep anterior lamellar transplantation techniques and corneal crosslinking.[1,2] The increased availability of crosslinking treatments has a considerable impact on the amount of keratoconus patients treated. The aim of this thesis is to provide evidence for decisions concerning the treatment of keratoconus, with a special focus on crosslinking. This thesis encompasses the epidemiology of keratoconus, treatment effects, and economic evaluation of keratoconus treatment.

A CONCISE INTRODUCTION TO KERATOCONUS

Keratoconus is a disease of the cornea that usually has its onset during puberty or early adulthood.[3] The disease is almost exclusively bilateral, although the onset and manifestation are not always symmetrical.[4,5] The aetiology of keratoconus disease is presumed to be a multifactorial interplay of genetic susceptibility, environmental factors and chronic low grade inflammation.[6] The typical keratoconus patient would be a young male with an atopic constitution, who tends to rub his eyes frequently.[7] His first symptoms would be a deterioration of uncorrected visual acuity due to progressive myopisation and the development of astigmatism. Because of his typical irregular astigmatism, spectacle correction did not suffice and he was fitted with rigid gas permeable contact lenses and experienced an adequate quality of vision.[8] Advanced cases with progressive stromal and epithelial thinning are at risk for corneal hydrops and subsequent corneal scarring.[9] In these cases with corneal scarring a corneal transplantation is often warranted to restore visual function. Another indication for corneal transplant surgery is an intractable contact lens intolerance, leaving irregular astigmatism poorly controlled.[10] Receiving a corneal transplant has a substantial impact on patients' lives, since follow-up after surgery is intense and patients require to apply eye drops on a daily basis and are at a constant risk of graft rejection and graft failure.[11] Most keratoconus patients receive their first corneal transplant during their twenties, thirties or forties.[12] With the median survival time for a corneal transplant approximately 20 years, most patients will require a second or even a third transplant during the course of their lives.[13] Therefore, preventing the need for corneal transplantation is one of the priorities in keratoconus care.

EPIDEMIOLOGY

The incidence and prevalence most cited in international literature is based on a single centre longitudinal study in the United States, performed in the time period from 1936 to 1982.[14] This study estimated an annual incidence of 1 per 50.000 and a prevalence of approximately 1 per 2.000 for keratoconus. Different rates are reported in various regions in the world and among different races.[15–17] **Chapter 2** provides reliable and up-to-date estimates of the incidence and prevalence of keratoconus in the Netherlands, based on the medical records of 4.4 million people from a health insurance database.

Historically, approximately 10-20% of all keratoconus patients ultimately required a corneal transplant due to the development of severe astigmatism, scar formation and/or contact lens intolerance.[3,18] Penetrating keratoplasty (PKP) was for a long time the most applied type of corneal transplantation. In this procedure, all of the recipient's corneal layers including the recipient's healthy endothelium – are replaced with donor tissue. The currently propagated alternative to PKP is (deep) anterior lamellar keratoplasty, which has the benefit of replacing the affected stromal layers whilst retaining the host endothelium. Although lamellar techniques demonstrated several advantages compared to PKP when accessed in comparative studies, we know little about the practical implementation of new transplantation techniques outside clinical trials.[19–22] In **Chapter 3** we analyzed the real-world implementation of lamellar transplantation techniques over the time span of a decade in the Netherlands based on the accurate and complete registration of corneal transplants by the Dutch National Organ Transplant Registry.

TREATMENT EFFECTS

Crosslinking is a relatively new treatment that aims to stop the progression of keratoconus. During the original crosslinking procedure, often referred to as the Dresden protocol, the central epithelium (outer layer) of the cornea is removed (epi-off).[23,24] This enables riboflavin eye drops to penetrate and saturate the corneal stroma. Riboflavin is an exciter molecule: it reacts with ultraviolet-A irradiation and enhances its effects during the irradiation phase of the treatment. New crosslinks are now formed between the proteoglycan fibrils interspersing the stromal collagen fibers, leading to an increase in mechanical strength.[25] At the commencement of this research project the short term beneficial effects of crosslinking with respect to preventing disease progression had been demonstrated convincingly in adults,

and this has helped increase the popularity of crosslinking as the treatment of choice for progressive keratoconus in adults.[26–28] To date, no controlled trials have been performed to evaluate the efficacy or safety of crosslinking in children. The prevention of disease progression in children however is crucial, based on the inverse relationship between age and keratoconus severity.[29,30] Furthermore, younger patients tend to have more aggressive disease progression than adults.[18] Various cohort studies on crosslinking in children have been published, with a maximum follow-up of three years. In **Chapter 4** we provide a systematic overview of previous results of crosslinking in children and the results of our own cohort of children treated with crosslinking with a maximum follow-up up to five years.

There are two major directives for improvement of the current crosslinking treatment: shortening the treatment time and leaving the epithelium intact during the treatment. Shortening the treatment time has the advantage of higher patient comfort and lower healthcare costs, while leaving the epithelium intact (transepithelial) has the advantage of less post-operative pain and a lower risk for post-operative complications. Although the transepithelial technique was lauded by many for its potential beneficial effects, no head-to-head comparison with conventional crosslinking had been performed. **Chapter 5** reports on a randomized controlled trial comparing transepithelial crosslinking with epi-off crosslinking. Although the transepithelial technique proved to be less effective in halting keratoconus progression than the epi-off treatment, the transepithelial group did benefit more in terms of visual acuity.

Transepithelial crosslinking has a more superficial effect than epi-off crosslinking.[31] Therefore, we investigated the hypothesis that the greater improvement in visual acuity after transepithelial crosslinking was related to higher-order aberrations in **Chapter 6**. Higher-order aberrations are optical disturbances of the cornea that are not correctable by glasses and that are much more frequent in keratoconus than in normal eyes.[32] Those higher-order aberrations can affect the quality of vision and causes glare and halos. The relationship between keratometry, visual acuity and crosslinking treatment effects remains intricate. In **Chapter 7** we investigated the relation between visual acuity, manifest refraction and changes in higher-order aberrations after epi-off crosslinking in a large treatment cohort. We also investigated whether higher-order aberrations subtypes (coma, trefoil, and spherical aberration) contributed independently to visual acuity, using a multivariable analysis.

Questions that are frequently asked by patients with progressive keratoconus are related to the prognosis after crosslinking treatment. **Chapter 8** is dedicated to factors that influence visual acuity and stabilization of the cornea after crosslinking. We aimed to identify factors that are related to treatment success

and additionally created a model to predict individual visual outcomes after crosslinking. In **Chapter 9** we validated these findings in a new separate treatment cohort. Insight in those factors could aid ophthalmologists when counselling patients with regard to crosslinking treatment.

ECONOMIC EVALUATION

Preventing the need for corneal transplantation in keratoconus patients is one of the priorities in keratoconus care. The short term efficacy of crosslinking has been adequately addressed in several clinical trials.[26–28] However, whether the implementation of crosslinking actually results in a reduction of corneal transplantations was an unanswered question that deserved further attention. Within the Netherlands all corneal transplantations are registered in the National Organ Transplant Registry and all crosslinking treatments are performed in a small number of expert treatment centers. **Chapter 10** reports on the relationship between the introduction of crosslinking, the increasing number of crosslinking treatments, and the development of corneal transplantations rates for keratoconus.

Crosslinking is evidently associated with short term costs in terms of diagnostic screening, the crosslinking procedure itself and postoperative consultations, including possible complications. We investigated the costs that are associated with crosslinking in **Chapter 11**, based on a consecutive cohort of keratoconus patients from our own treatment center. How do the evident excess short term costs of crosslinking for progressive keratoconus relate to long-term preservation of quality of life and potential lower transplantation rates later in life? Or in other words, should society invest money in crosslinking now, to secure more quality of life and less transplantations in the future? To answer those questions we performed a cost-effectiveness analysis. This includes mathematical long term modeling based on various characteristics of keratoconus and its treatments. In **Chapter 12** we investigated the quality of life of keratoconus patients in various disease stages in the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) cohort, which contains more than 8,000 patients years of measurements. Estimation of Quality Adjusted Life Years, a common outcome measure in health economics reflecting one year in optimal health, is challenging in ophthalmology since loss of visual acuity has a variable impact on quality of vision, due to our binocular physiological state. Together with the progressive nature of keratoconus, a complex modeling approach was needed to provide sound estimates of changes in quality of life for this archetypical disease. The results of our cost-effectiveness analysis on crosslinking for progressive keratoconus are presented in **Chapter 13**.

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2

Age-specific incidence and prevalence of keratoconus: a nationwide registration study

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ABSTRACT

Purpose

To determine the age-specific incidence and prevalence of keratoconus in the modern era of diagnostics.

Design

Nationwide registration study.

Participants

4.4 million people from a mandatory health insurance database.

Methods

Data were extracted from the largest health insurance provider in the Netherlands. People aged 10-40 years were defined as the relevant age category for newly diagnosed keratoconus and the annual incidence of newly diagnosed keratoconus was determined. The prevalence of keratoconus was estimated based on the annual incidence, mean age at diagnosis, and average life expectancy.

Main Outcome Measure

The annual incidence and prevalence of keratoconus.

Results

The annual incidence of keratoconus was 1:7,500 in the relevant age category (13.3 cases per 100,000, 95% CI: 11.6 to 15.2) and the estimated prevalence of keratoconus in the general population was 1:375 (265 cases per 100,000, 95%CI: 260 to 270). These values are five-fold to ten-fold higher than previously reported values in population studies. The mean age at diagnosis was 28.3 years and 60.6% of diagnosed patients were male.

Conclusion

Both the annual incidence and the prevalence of keratoconus were five-fold to ten-fold higher than previously reported.

INTRODUCTION

Keratoconus is a progressive disease of the cornea that leads to a decrease in visual acuity due to corneal thinning and irregular astigmatism. Although visual acuity can often be restored in most patients through the use of glasses or rigid contact lenses, complex corneal grafting procedures are ultimately indicated in approximately 10-20% of keratoconus patients.[1,2]

The most frequently cited occurrence of keratoconus is 1:2,000. This value is based on a registration study in the United States which was conducted from 1935 until 1982. This study reported a prevalence of 54.5 cases per 100,000 individuals.[3] Estimates of the annual incidence of keratoconus based on epidemiological studies range from 1:3,000 to 1:80,000 per year.[4,5] This wide range may be attributed to the increased sensitivity of modern diagnostic devices, regional differences with respect to accessibility to healthcare, and/or differences in study design. Furthermore, ethnic differences with respect to the incidence of keratoconus have also been reported.[4,6,7]

Incidence is defined as the number of new cases diagnosed within a specific period of time (usually one year), whereas prevalence is the number of existing cases at a given point in time. The onset of keratoconus typically occurs in the second to fourth decade of life (i.e., from age 10 through age 40) and affects patients for the remainder of their lives.[1] Therefore, the prevalence of keratoconus is by definition always higher than the annual incidence.

As computer-based technologies and imaging techniques have improved, the ability to diagnose keratoconus has also increased. New treatment options for keratoconus are currently being implemented. Therefore, determining an incidence and prevalence of keratoconus in the modern era will provide a more accurate estimate of the impact of such new treatment options on healthcare costs. We performed a nationwide registration study in order to determine the annual incidence of keratoconus and calculate the prevalence of keratoconus in the population. To perform this analysis we used data from the largest health insurance provider in the Netherlands.

The Dutch health insurance system

All residents of the Netherlands are required to have coverage for the majority of their standard healthcare needs, including primary care and hospital care. Achmea is the largest health insurance provider in the Netherlands, covering 31% of all residents.[8] In the Netherlands, health insurance providers are required to provide basic health insurance coverage for all applicants who request it. The coverage provided by this basic health insurance plan is determined by the Dutch

government and is equal among all health insurance providers.[9] Therefore, populations among different healthcare providers are similar and Achmea provides a representative sample for the population. Healthcare consumption is registered carefully using automated systems, because of the financial consequences for both healthcare providers and health insurance providers. Most expenses related to ophthalmic care for keratoconus (such as outpatient visits, diagnostic procedures, contact lenses and corneal transplants) are reimbursed, regardless of the setting in which it was provided (i.e., at a private practice or at a hospital).

METHODS

Database and keratoconus selection

We used data obtained from the Achmea Health Database (AHD) for this study. Data were extracted from the AHD for patients whose information was entered from 2011 until 2014. Diagnoses and treatments are assigned a Diagnosis and Treatment Combination (DTC, in Dutch: '*Diagnose Behandel Combinatie*'). Each DTC includes the diagnosis, the associated medical specialism and type of care delivered (including whether or not it is a new DTC). Keratoconus is coded as ophthalmological care under DTC code 457: keratoconus / cornea dystrophy.

The data also included gender, date of birth, date of death (if applicable) and the date the DTC code was assigned (i.e., the date of diagnosis). To extract keratoconus cases within DTC code 457, people aged 10-40 years were defined as the relevant age category based on the pathological properties of keratoconus; this is the age category in which the majority of new keratoconus cases are diagnosed.[1] Other clinical entities that fall under the DTC code 457 were generally excluded by specifying this age category. These other diagnoses either are predominantly found in older people (Fuchs endothelial dystrophy) or in younger patients (congenital corneal pathology). Other corneal dystrophies are extremely rare, particularly in this age category.[10] To extract new cases of keratoconus in 2014, people linked to DTC 457 in a previous year were excluded.

The data provided were anonymized and this study was performed with the permission of the scientific board of Achmea and in accordance with Dutch privacy laws and the Declaration of Helsinki.

Data analysis

The annual age-specific incidence of keratoconus was calculated by dividing the number of new keratoconus cases in 2014 by the total number of insured

people in the same age category registered in the AHD within the same year. The prevalence of keratoconus was then estimated based on the age-specific incidence, the total number of people registered in the AHD in 2014, mean patient age at the time of diagnosis and average life expectancy in the Netherlands (based on data from Statistics Netherlands).[11] Calculations were performed using Stata, version 13.1 (StataCorp, College Station, Texas). Data are represented as the annual incidence and prevalence with the corresponding 95% Poisson exact confidence interval (CI).

RESULTS

Patient characteristics

In 2014 there were 4,357,044 people registered in the AHD and a total of 1,635,517 people were within the relevant age category for newly diagnosed keratoconus (i.e., 10-40 years). Within this group of eligible individuals, 218 new diagnoses of keratoconus were identified. At the time of the keratoconus diagnosis, the mean age was 28.3 years and 60.6% of the patients were male.

Incidence of keratoconus

The age-specific annual incidence of keratoconus was calculated by dividing the number of people who were newly diagnosed with keratoconus (218) by the number of people within the relevant age category (1,635,517), yielding an annual incidence of approximately 1:7,500 or 13.3 new cases per 100,000 (95% CI: 11.6 to 15.2 per 100,000).

Prevalence of keratoconus

The prevalence of keratoconus was estimated based on the annual incidence of keratoconus in the relevant age category (i.e., 13.3 new cases per 100,000), the total number of people registered in the AHD (4,357,044), the mean age at the time of diagnosis (28.3 years) and the average life expectancy in the Netherlands (81.2 years). Based on these factors, the estimated prevalence of keratoconus in the general population is 1:375 or 265 cases per 100,000 (95% CI: 260 to 270 per 100,000).

DISCUSSION

The aim of this study was to determine the annual incidence and prevalence of keratoconus using health insurance information obtained from approximately 4.4 million people in the Netherlands. The age specific incidence of keratoconus is 1:7,500 (13.3 per 100,000) in the relevant age category and the prevalence in the general population is 1:375 (265 per 100,000).

Major strengths of this study are the large sample size and the completeness of the registration. A large sample size is essential in order to accurately determine both the incidence and prevalence of keratoconus. Moreover, as health care providers only get reimbursement of their efforts by using the DTC coding system, the database was previously found to be both accurate and complete.[11] An additional strength of our study is the high generalizability of the results. Health insurance is required for all residents of the Netherlands and virtually all expenses related to ophthalmic care for keratoconus are covered by all Dutch health insurance providers. Moreover, sophisticated diagnostic devices are widely available throughout the Netherlands and the Dutch hospital system is renowned for its excellent accessibility and high standard of care.[12] Considering these factors, we feel it is likely that our sample accurately reflects the level of care both needed and provided for patients with keratoconus.

The values for the incidence and prevalence of keratoconus obtained by our study are approximately five-fold to ten-fold higher than previous reports from population studies.[3,5] A possible explanation for this difference might be the recent increase in the availability of corneal imaging techniques, resulting in increased accuracy with respect to diagnosing keratoconus. Nevertheless, we believe that our estimates are realistic because the incidence of keratoconus in our study population corresponds with the number of corneal transplants performed annually in the Netherlands. Previous reports indicate that 10-20% of all keratoconus patients ultimately require a corneal transplant.[1,2] Approximately 6.2 million people in the Netherlands are 10-40 years of age.[13] Given that the annual incidence of keratoconus in this age category was approximately 1:7,500, an estimated 825 new keratoconus cases are diagnosed in the Netherlands each year. Since approximately 100 corneal transplants are performed for keratoconus in the Netherlands each year,[14] the lifetime chance of receiving a corneal transplant is approximately 12%, which is within the reported range of 10-20%.

Our study also included possible weaknesses. The incidence calculated in our study may be a slight overestimate, as the diagnostic code that includes keratoconus also includes other conditions. To examine whether this likely

affected our analysis, we determined how many patients who received this diagnostic code in our treatment center (a referral center for corneal pathology) were actual keratoconus cases. We found that within the relevant age category (10-40 years), more than 90% of patients with this diagnosis code were indeed keratoconus patients. On the other hand, it is also possible that some patients had late-onset keratoconus and were diagnosed after the age of 40; such patients would not have been included in our analysis.

Although previous studies found that Asians have a higher risk of developing keratoconus,[4,6,7] we were unable to validate this finding because health insurance providers in the Netherlands do not acquire racial information.

In conclusion, our results provide accurate and up-to-date information regarding the annual incidence and prevalence of keratoconus. Obtaining accurate values is essential for policy makers in order to estimate the true impact of this disease on healthcare costs. Importantly, our estimates of the annual incidence and prevalence of keratoconus are five-fold to ten-fold higher than previous reports, suggesting that keratoconus is more common than previously suggested.

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3

Trends in penetrating and anterior lamellar corneal grafting techniques for keratoconus: a national registry study

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ABSTRACT

Purpose

Keratoconus is a progressive disorder and one of the primary indications for corneal transplantation. Anterior lamellar keratoplasty offers several advantages over other techniques, including endothelial preservation and longer graft survival. Here, we examined the recent trend of using lamellar techniques for keratoconus at a national level.

Methods

Data were obtained from the Dutch national organ transplant database regarding corneal transplants for keratoconus performed in 2005 through 2014. Baseline characteristics for patients undergoing various techniques were obtained, and temporal trends were analysed.

Results

A total of 1041 operations were performed, including 736 penetrating keratoplasties (PKPs) and 297 anterior lamellar keratoplasties (ALKs). The mean age of the total surgical group was 37.4 ±13.4 years, and 68% of patients were male (p=0.0001). Preoperative patient characteristics were reported in all 1041 cases. The relative proportion of ALKs increased from 2005 (19% of cases) to 2010 (39% of cases) and remained approximately 30-40% thereafter. Descemet baring or deep anterior lamellar keratoplasty (DALK) was increasingly applied and was the predominant anterior lamellar technique performed from 2009 onwards.

Conclusions

The number of corneal transplantations performed annually for keratoconus decreased during the past ten years. Lamellar techniques were increasingly performed, accounting for approximately 35% of keratoplasties in 2010 and thereafter. Among ALK techniques, maximal depth DALK is the most prevalent keratoplasty performed for keratoconus in most recent years. Penetrating keratoplasty is still common, with a stable frequency form 2010 onwards.

INTRODUCTION

Keratoconus is a corneal condition in which the cornea protrudes due to structural changes in the stoma, resulting in astigmatism and reduced visual acuity (Mathew et al. 2015). The estimated prevalence of keratoconus is approximately 54.5 cases in 100,000 people (Kennedy et al. 1986), with the onset of keratoconus typically occurring in the second or third decade of life. In most cases, spectacles or rigid contact lenses are sufficient to restore visual acuity; however, these interventions do not affect disease progression. Due to the development of severe astigmatism, scar formation, and/or contact lens intolerance, approximately 10-20% of patients ultimately require a corneal transplant.(Rabinowitz 1998, Romero-Jimenez et al. 2010)

Historically, penetrating keratoplasty (PKP) was the surgical treatment of choice for keratoconus. In this procedure, all of the recipient's corneal layers – including the recipient's healthy endothelium – are replaced with a donor cornea. Alternative to PKP is anterior lamellar keratoplasty (ALK), which has the benefit of replacing the affected stromal layers whilst retaining the recipient's endothelium. Despite this benefit, problems that can arise at the transplant interface and reduce visual outcome, as the residual posterior stroma does not always adhere properly to the healthy donor tissue.(Soong et al. 1999) Therefore, innovations in surgical techniques led to the development of deep anterior lamellar keratoplasty (DALK), an improved version of ALK in which the complete stroma is replaced with healthy donor tissue.(Amayem & Anwar 2000, Melles et al. 1999, Knutsson et al. 2015)

Although PKP and DALK generally provide equivalent results with respect to visual outcome, DALK has several clear advantages.(Cheng et al. 2011, Funnell et al. 2006, Han et al. 2009, Kim et al. 2011) First, the prevalence of allograft rejection is lower following DALK. Indeed, Borderie et al. estimated that the graft can survive nearly three times as long following DALK. Because most keratoconus patients are relatively young, preserving the corneal transplant for as long as possible is important, particularly given that replacement transplants generally have worse clinical outcome and shorter survival.(Borderie et al. 2012, Kelly et al. 2011) Furthermore, visual rehabilitation is shorter following DALK, as the corneal stiches can be removed earlier and steroid treatment is usually shorter in duration.(Niziol et al. 2013) Despite these advantages, the DALK procedure is more difficult to master; moreover, surgical time is increased and complications like Descemet's membrane perforation, scarring at the interface, and the formation of an irregular interface surface can occur.(Cheng et al. 2011, Shimmura & Tsubota 2006, Tan & Mehta 2007)

The Dutch healthcare system is based upon obligatory health insurance and private insurance companies. Importantly, both lamellar and penetrating corneal surgeries are covered fully by insurance; thus, the patient and surgeon need not consider financial factors when choosing a treatment method. In the Netherlands, data regarding corneal transplants is registered with the Dutch Organ Transplant Registry (NOTR), which receives standardised surgical forms directly from the surgeon at the time of surgery. The compliance rate is extremely high, as surgeons must provide the NOTR with data in order to obtain donor corneas.

We previously evaluated the trend from 2005 through 2010 with respect to corneal transplantations performed for keratoconus in the Netherlands; our analysis revealed that although lamellar techniques increased in popularity, conventional PKP remained the preferred procedure in 2010.(Wisse et al. 2014) The aim of this study was to investigate whether this trend continued in more recent years (through 2014), thus providing an update and perspectives regarding the current state of corneal transplantation procedure performed at the national level.

MATERIALS AND METHODS

Data regarding the corneal grafting procedures performed over a ten-year period (2005 through 2014) were extracted from the Dutch National Organ Transplant Registry (NOTR). The database which was anonymised with respect to patient and surgeon information and permission to extract and analyse anonymised data was granted by the NOTR scientific council (the Dutch Cornea Workgroup, a subcommittee of the Dutch Ophthalmic Society). The study was designed and conducted in accordance with the tenets of the Declaration of Helsinki for medical research involving human subjects.

The following baseline data were extracted: diagnosis, age at the time of transplantation, gender, date of transplant, primary eye disease, preoperative keratometry results (K average), preoperative best corrected visual acuity (BCVA), history of corneal hydrops, and previous transplantation procedures. BCVA was measured with either spectacles or contact lenses, the highest visual acuity was noted and converted to LogMAR BCVA. Primary eye disease was noted as 'keratoconus with previous hydrops', 'keratoconus with no previous hydrops', or 'keratoconus, not specified'. Preoperative keratometry was noted as K average and was recorded using the Javal method, corneal topography, automated refraction, or an unknown method; if the method was unknown, this was noted as 'other'.

The corneal surgeon indicated the surgical procedure using a dropdown menu, which offered the following options: regular penetrating keratoplasty (PKP-r), mushroom penetrating keratoplasty (PKP-m), anterior lamellar keratoplasty (ALK), deep anterior lamellar keratoplasty with maximal depth of stromal removal (DALK-md), deep anterior lamellar keratoplasty with residual stroma (DALK-rs), non-specified deep anterior lamellar keratoplasty (DALK-ns), and 'other'. Outcomes were analysed in the following two groups: penetrating keratoplasty (PKP) and anterior lamellar keratoplasty (ALK). Cases in which the type of surgery was registered as 'other' were classified separately. Cases were excluded if the registered surgical procedure was not in accordance with procedures usually performed on patients with keratoconus (for example a posterior lamellar keratoplasty).

Summary results are reported as the median plus standard deviation (SD), mean plus SD or as a percentage, where appropriate. The predominance for gender and changes in transplantation frequencies between different years were analysed using a two-sided chi-square test. Data were analysed using SPSS, version 21.0 (IBM, Armonk, NY, USA).

RESULTS

Baseline characteristics

A total of 1041 grafting procedures for keratoconus were performed from January 2005 through December 2014. This represents a total of 909 patients, including 41 re-grafts (3.9%). None of the eyes received more than two grafts in total.

Age, gender, diagnosis, transplantation procedure, and the date of surgery were reported in 100% of cases. BCVA was reported in 94.6% and keratometry values were reported in 37.1% of the cases.

The mean age at the time of surgery was 37.3 ± 13.4 years. A statistical predominance of male patients was observed (68.0%; $p<0.001$). Mean K average was 56.0 ± 8.4 dioptres (D). Median preoperative LogMAR BCVA was 1.0 (0.1 Snellen decimal acuity),and 11.8% of patients had a preoperative LogMAR BCVA >0.3 (>0.5 Snellen decimal acuity, n=114). The presence of a previous hydrops was noted in 18.6% of cases, and the option 'keratoconus, not specified' was noted in 12.5% of cases.

Corneal hydrops and choice of treatment

In 196 cases (18.8% of all operations) a previous hydrops was recorded. Only two cases in this subgroup had a baseline LogMAR BCVA >0.3 (Snellen decimal acuity >0.5), and 11 cases underwent ALK. No information was available regarding

Table 1. Baseline characteristics of eyes that underwent keratoplasty for keratoconus in 2005 through 2014, by transplantation technique.

	PKP-r *n* = 586	PKP-m *n* = 150	ALK *n* = 62	DALK-rs *n* = 82	DALK-md *n* = 145	DALK-ns *n* = 8	Other *n* = 8
Age, years (SD)	38.49 (14.03)	36.45 (12.37)	36.90 (12.40)	35.12 (11.38)	35.61 (12.20)	32.38 (8.00)	38.75 (16.71)
Male gender, N (%)	392 (66.9%)	107 (71.3%)	38 (61.3%)	63 (76.8%)	98 (67.6%)	5 (62.5%)	5 (62.5%)
LogMAR BCVA, median (SD)	1.0 (0.70)	1.0 (0.76)	0.70 (0.70)	0.65 (0.52)	0.80 (0.55)	NA	0.70 (0.57)
K average, dioptres (SD)	55.85 (8.02)	57.65 (9.64)	54.99 (7.79)	53.92 (7.64)	56.22 (8.48)	NA	NA
Previous hydrops, N (%)	133 (22.7%)	49 (32.7%)	3 (4.8%)	2 (2.4%)	6 (4.1%)	0 (0%)	0 (0%)

n = number of keratoplasties or eyes, PKP-r = regular penetrating keratoplasty, PKP-m = mushroom penetrating keratoplasty, ALK = anterior lamellar keratoplasty, DALK-rs = deep anterior lamellar keratoplasty residual stroma, DALK-md = deep anterior lamellar keratoplasty maximal depth, DALK-ns=deep anterior lamellar keratoplasty not specified, SD = standard deviation, LogMAR BCVA = best corrected visual acuity in LogMAR, K average=average keratometry value of steepest and flattest meridian, NA = not applicable.

the number of patients who converted from ALK to PKP due to surgical adverse events. The baseline preoperative characteristics of all cases are summarised for the various transplantation techniques in Table 1.

Lamellar keratoplasty

A total of 297 lamellar procedures were performed, accounting for 29% of all keratoplasties performed for keratoconus in the 10-year study period. The relative contribution of lamellar surgeries increased steadily from 2005 (18% of all procedures) through 2010 (39% of all procedures)(P<0.001), after which this procedure reached a stable level of approximately 35% of all procedures. The relative numbers of PKP and ALK procedures are shown for each year in the study period in Figures 1 and 2.

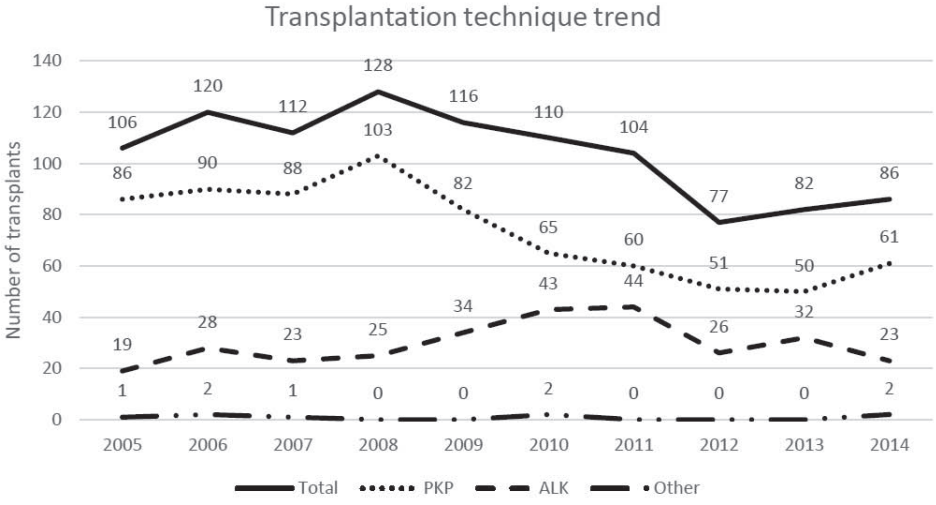

Fig. 1. Number of corneal transplantations performed for keratoconus in the Netherlands from 2005 through 2014. PKP = penetrating keratoplasty; ALK = anterior lamellar keratoplasty.

In 2005 and 2006, DALK-md was performed in 16% and 14% of all lamellar surgeries, respectively; however, by 2008 DALK-md was the most commonly used lamellar technique. In the subgroup of patients without a history of hydrops, ALK increased form 17% in 2005 to 51% of the cases in 2010 (P=0.04), thereafter varying from 30% to 40%.

Penetrating keratoplasty

A total of 736 penetrating surgeries were performed, accounting for 71% of all transplantations performed for keratoconus during the study period. Conventional PKP was the most commonly used technique throughout the

entire study period. Although the mushroom technique was used rarely in 2005 (representing 2% of all PKPs), its use gradually increased, accounting for 42% of penetrating techniques performed in 2011 (P<0.001). The mushroom technique was applied in 30-40% of the penetrating keratoplasties throughout the remaining study period (Figures 1 and 2).

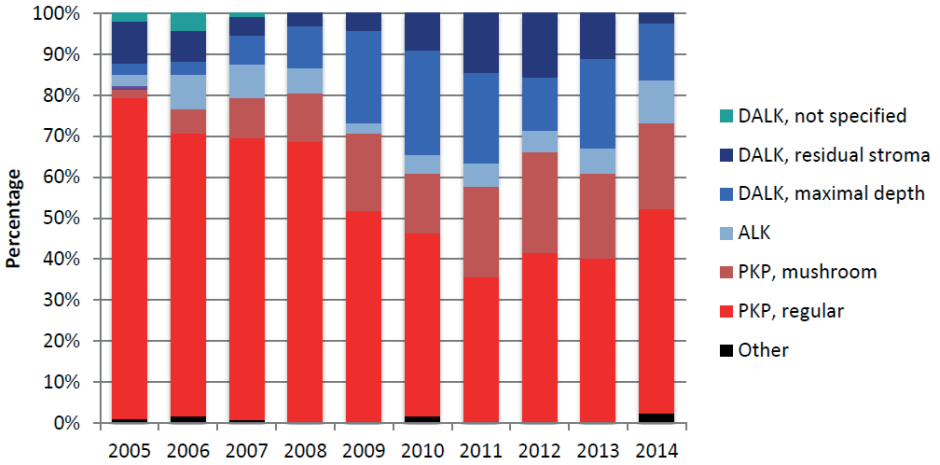

Fig. 2. Relative percentage of the indicated corneal transplantation techniques performed for keratoconus in the Netherlands from 2005 through 2014. PKP = penetrating keratoplasty; ALK = anterior lamellar keratoplasty; DALK = deep anterior lamellar keratoplasty.

DISCUSSION

In this nationwide registry-based study, more than a thousand keratometry procedures comprising a wide variety of transplantation techniques were analysed for a ten-year period spanning from 2005 through 2014. Overall, the total number of corneal transplants performed annually for keratoconus decreased and the relative contribution of lamellar techniques increased during this period. The most striking finding, however, is that penetrating keratoplasty is still common, despite the increasing body of evidence supporting the advantages of lamellar surgery over penetrating techniques. Maximal depth DALK is the most prevalent lamellar keratoplasty performed for keratoconus in most recent years.

Our finding that the number of corneal transplantations performed annually in the Netherlands has decreased in recent years differs from the United Kingdom, in which the annual number of corneal transplantations for keratoconus increased from 1999 through 2009.(Keenan et al. 2012) Interestingly, the number of corneal transplantations performed each year in Italy also decreased (by

27% from 2002 to 2008).(Frigo et al. 2015) These differences in transplantation rates might be explained by advances in contact lenses or by the introduction of corneal crosslinking, which can prevent the need for corneal transplantation. (Sandvik et al. 2015)

Our analysis revealed that lamellar keratoplasties increased in prevalence from 18% of all keratoplasties in 2005 to approximately 35% in 2010 and thereafter. This increase in the use of lamellar keratoplasties in the Netherlands likely does not reflect financial considerations, as insurance agencies are obligated to cover the costs, regardless of which technique the surgeon chooses. Interestingly, registry-based studies performed in other countries found a similar increase in the use of ALK procedures.(Coster et al. 2014, Fasolo et al. 2006, Frigo et al. 2015, Tan et al. 2014, Zare et al. 2012, Zhang et al. 2013) In Iran, ALK is now the most commonly used transplantation technique for keratoconus.(Zare et al. 2012) Differences in baseline conditions such as disease stage and/or corneal scarring likely explain some of this difference, while a DALK procedure might be more likely to succeed in a less advanced stage of keratoconus.

A strength of this study is our use of a nationwide database. To the best of our knowledge, this is only the second report of the prevalence of lamellar surgery for keratoconus based on a nationwide data registry.(Wisse et al. 2014) In the Netherlands, donor corneas can only be obtained by surgeons who register their patient data with the NOTR, thereby resulting in 100% compliance. The baseline characteristics of Dutch corneal transplantation patients are similar to populations in other countries. For example, the mean age of patients who underwent corneal transplantations in the Netherlands was 37.4 years, which is similar to the United States (40.6 years).(Fasolo et al. 2006) Median preoperative visual acuity in our population (LogMAR BCVA 1.0, Snellen decimal acuity 0.1) was the same as in an Australian registry study.(Kelly et al. 2011) In our population, preoperative LogMAR BCVA was >0.3 (>0.5 Snellen decimal acuity) in 11.8% of patients, which is also similar to the prevalence in Australia (8%).(Kelly et al. 2011)

This study has two limitations that merit discussion. First, conversions from ALK to PKP were not recorded in our database; rather, only the finally performed procedure was registered instead of the intended procedure. Therefore, it was not possible to analyse attempted lamellar transplantations. Previous studies estimated that the conversion rate from ALK to PKP ranges from 9% to 39% and is primarily due to Descemet's membrane perforation, which occurs more often in keratoconus with irregular steepening and corneal thinning.(Kasbekar et al. 2014, Leccisotti 2007) Second, reliable keratometry readings were available in only 37.1% of cases (392 eyes). As keratoconus progresses, the keratometry

steepens and can become more difficult, or even impossible to measure (Hashemi et al. 2015), which can lead to an underestimation of K average.

In conclusion, we report that in the Netherlands, the number of corneal transplantations performed annually for keratoconus decreased during the past ten years. Furthermore, the lamellar technique has increased in popularity among Dutch corneal surgeons, accounting for approximately 35% of keratoplasties performed in 2010 and thereafter. The most striking finding, however, is that the penetrating keratoplasty is still common , with a stable frequency form 2010 onwards, despite the increasing body of evidence supporting the advantages of lamellar surgery over penetrating techniques. This registry study is a representation of true practice, illustrating the surgical difficulties one encounters when opting for anterior lamellar surgery.

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4

Corneal crosslinking for pediatric keratoconus: long term results

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ABSTRACT

Purpose

To assess the efficacy and safety of crosslinking in pediatric keratoconus patients and to provide a systematic literature overview regarding this subject.

Methods

In this prospective cohort, 54 eyes of 36 pediatric keratoconus patients underwent standard epithelium-off crosslinking. Follow-up measurements taken up to five years after treatment were compared to baseline values. Logistic regression was used to identify the underlying cause in case of progression despite treatment. Finally, a systematic search was performed in PubMed and Embase, and data were extracted and summarized.

Results

At all follow-up visits up to five year, maximum keratometry values improved significantly (mean change at five years -2.06 diopters, P=0.01); moreover, average keratometry, uncorrected distance visual acuity and corrected distance visual acuity improved at all follow-up moments, though not always to the level of statistical significance. In twelve eyes (22%) keratoconus had progressed by ≥1.0 D by the last follow-up visit, despite corneal crosslinking. Cones that were more decentralized were identified as the underlying cause of disease progression. The systematic search yielded seventeen unique articles: ten articles on epithelium-off crosslinking, two articles on accelerated crosslinking, two articles on transepithelial crosslinking, one article on both epithelium-off and transepithelial crosslinking, and two articles on transepithelial crosslinking with iontophoresis.

Conclusions

Our long term follow-up reveals that epithelium-off crosslinking is both safe and effective when used to prevent keratoconus progression in pediatric patients. However, disease progression occurred in 22% of the treated eyes; this progression was attributed to a more decentralized cone location.

INTRODUCTION

Keratoconus is a progressive corneal disease with onset typically occurring in adolescence or early adulthood[1], although cases of severe keratoconus have been reported in children as young as four years of age.[2] Keratoconus causes visual impairment due to the formation of irregular astigmatism; in most advanced cases, corneal scarring can also occur.[1] The progression of keratoconus usually stabilizes in the fourth decade of life, leaving patients in a relatively fixed disease stage for the remainder of their lives.[1] Interestingly, an inverse relationship has been found between patient age and disease severity; on average, pediatric cases are more severe and are more likely to develop progressive keratoconus.[3] In children, the progression of keratoconus can be both rapid and devastating; as a result, younger patients have a higher likelihood of requiring corneal grafting surgery.[4,5] In addition to the clear burden associated with corneal transplant surgery, the rate of graft survival in young patients is considerably lower than in adults.[6]

Corneal crosslinking (CXL) can prevent the progression of keratoconus by increasing rigidity of corneal collagen due to the chemical production of non-covalent bonds between collagen fibrils.[7,28] The beneficial effect of CXL with respect to preventing disease progression has been demonstrated convincingly in adults, and this has helped increase the popularity of CXL as the treatment of choice for progressive keratoconus in adults.[8–10] To date, however, no controlled trials have been performed to evaluate the efficacy or safety of CXL in children, although several cohort studies on crosslinking in pediatric populations have been published.[11–26]

Here, we provide a systematic overview of the published literature regarding the outcome in children with progressive keratoconus who underwent CXL. In addition, we report the long-term outcome (i.e., up to five years after CXL) of our own pediatric patient population, focusing on the efficacy and safety and CXL.

PATIENTS AND METHODS

Dataset and study design

The prospective cohort study included all consecutive pediatric patients (i.e., under the age of 18 years) who underwent an epithelium-off CXL procedure for progressive keratoconus at the University Medical Center Utrecht, the Netherlands, from January 2010 through December 2013. The diagnosis of keratoconus was established in concordance with the global consensus on keratoconus and ectatic diseases report.[26] The following inclusion criteria were applied for CXL treatment:

Kmax progression defined as a change of ≥1.0 D within one year, a centrally clear cornea, and minimal corneal thickness of 400 μm prior to ultraviolet-A (UV-A) irradiation.

This study was approved by the Ethics Review Board of the University Medical Center Utrecht and was performed in accordance with local laws, the European guidelines for Good Clinical Practice, and the tenets established by the Declaration of Helsinki.

Surgical procedure

After the corneal epithelium was removed using a blunt knife, crosslinking was performed in accordance with the Dresden protocol, using a 30-minute isotonic riboflavin soaking time and 30 minutes of UV-A irradiation with a perpendicular emission plane (370 nm at 3 mW/cm^2, UV-X 1000, Peschke Meditrade GmbH, Waldshut-Tiengen, Germany) as described previously.[7,27,27] All procedures were performed under topical anesthesia (oxybuprocaine 4 mg/ml and tetracaine 5 mg/ml). Post-operative medication included moxifloxacin hydrochloride (Vigamox 5 mg/ml), artificial tears (Duratears Free, dextran 1 mg/ml, hypromellose 3 mg/ml), nepafenac (Nevanac 1 mg/ml) and steroids (after epithelial healing)(FML Liquifilm 1 mg/ml), as well as oral medication for pain (tramadol) if needed. The dosage and frequency of the oral medication was based on age and body weight.

Measurements and devices

Ophthalmic evaluations were performed prior to CXL and at all follow-up visits (1, 3, 6, 12, 24, 36, 48, and 60 months after CXL). This evaluation included UDVA, CDVA, manifest refraction, Scheimpflug corneal tomography (Pentacam HR type 70900, Oculus GmbH, Wetzlar, Germany), and a slit-lamp evaluation with particular focus on atopic/allergic eye disease and eyelid abnormalities. UDVA and CDVA were measured in Snellen lines and used as outcome measures together with Kavg and Kmax. Progression was defined as a change in Kavg and/or Kmax of ≥1.0 D. Cone eccentricity was defined as the distance between the apex of the cone and the pupil center. Contact lens wearers were instructed to remove their lenses two weeks prior to all evaluations.

Statistical analysis

Normality and homogeneity of residuals were checked visually using a Q-Q plot. A two-tailed paired samples Student's t-test was used to compare each baseline measurement with the respective follow-up measurements. A logistic regression was performed with the presence or absence of progression (as defined above) at the last follow-up visit as a dependent parameter, with pre-operative UDVA, CDVA,

Kavg, Kmax, cone eccentricity, central corneal thickness, and age as independent parameters. Differences with a *P*-value <0.05 were considered significant. Data were collected and analyzed using SPSS 21.0 (IBM, Armonk, NY).

Systematic literature search

A systematic search was performed in the PubMed and Embase databases on January 6, 2016. The search terms were "keratoconus", "keratoconic", and "corneal ectasia" in the title and/or abstract. The initial search yielded 4831 articles in PubMed and 5223 articles in Embase. The identified articles were then screened based on their title and abstract. All clinical studies based on crosslinking in pediatric and/or adolescent patients were included. Case reports and case series were excluded. All included articles were then used for cross-referencing. The data regarding the following outcomes were extracted: uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), keratometry in the flattest meridian (Kflat), keratometry in the steepest meridian (Ksteep), mean keratometry value (Kavg), maximum keratometry value (Kmax), and corneal thickness.

RESULTS

Baseline characteristics

Our study comprised 54 eyes of 36 patients. Twenty-nine patients (81%) were male, and mean age at the time of treatment was 14.8 years (range: 11-17 years). The baseline characteristics of the study population are summarized in Table 1.

Visual acuity outcomes

The baseline and follow-up measurements of UDVA and CDVA are summarized in Table 2. Relative to baseline, UDVA had improved at all follow-up times, with the difference reaching significance at the one-year (*P*<0.001), two-year (*P*=0.01), and three-year (*P*=0.02) visits. Moreover, CDVA improved significantly after crosslinking at all follow-up visits, with the exception of the five-year follow-up visit, in which the improvement was not significant (*P*=0.18).

Table 1. Baseline characteristics of 54 eyes of 36 patients with pediatric keratoconus (No missing values)

	Value	SD or %
Age (years), mean	14.8	±1.6
Male, n	29	81%
UDVA, mean	0.32	±0.31
CDVA, mean	0.59	±0.32
Kflat (D), mean	47.1	±4.4
Ksteep (D), mean	51.3	±5.4
Kavg (D), mean	49.1	±4.7
Kmax (D), mean	59.1	±9.0
Eccentricity (mm), mean	0.95	±0.69
Central thickness, mean	490	±39.7

Central thickness = corneal thickness at the pupil center; eccentricity = distance between the apex of the cone and the pupil center; Kavg = average keratometry; Kflat = keratometry in the flattest meridian; Kmax = maximum keratometry; Ksteep = keratometry in the steepest meridian; n = number of patients.

Table 2. Visual and keratometry outcomes in pediatric keratoconus patients after crosslinking.

	UDVA	*P*	CDVA	*P*	Kmax (D)	*P*	Kavg (D)	*P*	n
Baseline, yr	0.33		0.61		59.0		59.0		54
Δ1	+0.13	*<0.001**	+0.22	*<0.001**	-1.65	*0.001**	-0.27	*0.16*	54/54
Δ2	+0.07	*0.01**	+0.19	*<0.001**	-1.13	*0.02**	-0.18	*0.39*	46/54
Δ3	+0.09	*0.02**	+0.24	*<0.001**	-1.94	*0.001**	-0.60	*0.001**	25/37
Δ4	+0.06	*0.17*	+0.19	*0.01**	-2.14	*0.01**	-1.38	*0.03**	18/23
Δ5	+0.05	*0.38*	+0.08	*0.18*	-2.06	*0.01**	-0.65	*0.09*	9/9

*Indicates statistical significance (P<0.05).

Δ = change relative to the respective baseline value; CDVA = corrected distance visual acuity, decimals; Kavg = average keratometry; Kmax = maximum keratometry; n = number of eyes analyzed/number of eyes that had reached this follow-up moment at the time of analysis.

Keratometry outcomes

The baseline and follow-up measurements of Kmax and Kavg are summarized in Table 2. Compared to baseline, Kmax improved significantly one year after treatment, and this improvement remained significant throughout the entire follow-up period. Moreover, Kavg improved throughout the entire follow-up period, with improvement reaching significance at the three-year and four-year follow-up visits (*P*=0.001 and *P*=0.03, respectively).

Adverse events

No post-operative infections or cases of endothelial cell failure were encountered during the follow-up period (data regarding endothelial cell density are not shown). One eye with pre-operative CDVA of 1.2 deteriorated to 0.9 and 0.8 at the one-year and two-year follow-up visits, respectively; this decline in CDVA was

due to persistent haze. None of the other eyes lost ≥2 Snellen lines. No other adverse events occurred.

In twelve eyes (22%) of nine children (25%), keratoconus had progressed by ≥1.0 D at the last follow-up visit, despite CXL treatment (Kavg progression up to 4.2 D, and Kmax progression up to 7.2 D). Progression was noted at one year after treatment in ten eyes and two years after treatment in two eyes. If progression had not occurred within two years after treatment, it was not observed throughout the remaining study period. Interestingly, none of these patients suffered a decline of one or more Snellen lines in either UDVA or CDVA. None of the 36 patients underwent any additional CXL treatment or corneal transplantation.

Cause of progression

A multivariable logistic regression analysis revealed that cone eccentricity was the only independent factor significantly related to the progression of keratoconus (P=0.03, β=2.11). Specifically, eyes in which the cones were more decentralized cones were more likely to progress. None of the remaining factors were significantly associated with keratoconus progression, including pre-operative UDVA (P=0.29), CDVA (P=0.85), Kavg (P=0.66), Kmax (P=0.28), central corneal thickness (P=0.95), and age (P=0.81).

Systematic literature overview

The systematic search yielded sixteen unique articles on crosslinking for keratoconus in pediatric patients and/or adolescents. Cross-referencing did not yield any additional articles. Ten articles reported on epithelium-off crosslinking,[11–19] two articles reported on accelerated crosslinking,[20,21] two articles reported on transepithelial crosslinking,[22,23] one article reported on both epithelium-off crosslinking and transepithelial crosslinking,[24] and two articles reported on transepithelial crosslinking with ionthophoresis.[25,26] All sixteen articles were cohort studies in which treatment outcomes were compared with baseline values. Caporossi et al. compared two groups with different corneal thicknesses; for our analysis, we used the combined corneal thickness data.[12] The outcomes of the systematic search and a summary of the outcome parameters are presented in Table 3.

DISCUSSION

In our pediatric population, epithelium-off crosslinking can be considered both safe and effective, achieving stable long-term results up to five years. However,

Table 3. Overview of studies on pediatric keratoconus patients treated with crosslinking. Results of the last follow-up visit are shown.

Author (yr)	Type of CXL	Patients (eyes)	Age range	Follow-up time	UDVA	CDVA	Kflat	Ksteep	Kavg	Kmax	Corneal Thickness
Ozgurhan[21] (2014)	Accelerated	38 (44)	9-18	24	Better	Better	Better	Better	Better	NA	NA
Shetty[20] (2014)	Accelerated	18 (30)	11-14	24	Better	Better	Better	Better	NA	NA	NA
Arora[11] (2012)	Epi-off	15 (15)	10-15	12	Better	Better	–	–	–	Better	NA
Caporossi[12] (2011)	Epi-off	NA (77)	10-18	36	Better	Better	Better	NA	Better	Better	Better
Chatzis[13] (2012)	Epi-off	NA (11)	9-19	36	NA	Better	NA	NA	NA	–	–
Kodavoor[19] (2014)	Epi-off	24 (35)	9-16	12	NA	Better	NA	NA	NA	Better	Worse
McAnena[14] (2015)	Epi-off	14 (25)	13-18	12	–	Better	–	NA	–	–	–
Peyman[15] (2015)	Epi-off	37 (64)	NA	12	Better	Better	Better	Better	NA	Better	Worse
Sloot[29] (2014)	Epi-off	NA (31)	12-17	12	Better	Better	–	–	Better	Better	Worse
Uçakhan[16] (2015)	Epi-off	40 (40)	10-18	48	Better	Better	Better	Better	Better	Better	Worse
Vincinguerra[17] (2012)	Epi-off	40 (40)	9-18	24	Better	Better	Better	–	Better	NA	–
Viswananthan[18] (2014)	Epi-off	18 (25)	8-17	20.1	NA	–	Better	Better	NA	NA	NA
Magli[24] (2012)	Epi-off	19 (23)	12-18	12	–	–	Better	NA	Better	Better	NA
Magli[24] (2012)	Transepithelial	10 (14)	12-18	12	–	–	Better	NA	Better	Better	NA
Buzzonetti[23] (2012)	Transepithelial	13 (13)	8-18	18	NA	Better	Worse	Worse	Worse	NA	–
Salman[22] (2013)	Transepithelial	22 (22)	13-18	12	Better	–	NA	NA	–	Better	–
Buzzonetti[25] (2015)	Iontophoresis	14 (14)	10-18	15	NA	Better	–	–	–	–	–
Magli[26] (2015)	Iontophoresis	13 (13)	11-18	18	–	Better	NA	–	NA	Worse	Better

– = no significant change; Accelerated = accelerated crosslinking with epithelium removal; Better = significant improvement (P<0.05); CDVA = corrected distance visual acuity; Epi-off = standard epithelium-off crosslinking; Follow-up time = (mean) follow-up time in months; Iontophoresis = transepithelial crosslinking with iontophoresis; Kavg = average keratometry; Kflat = keratometry in the flattest meridian; Kmax = maximum keratometry; Ksteep = keratometry in the steepest meridian; NA = data were not available; Patients (eyes) = number of patients and number of eyes at the last follow-up visit; Transepithelial = transepithelial crosslinking; Worse = significant deterioration (P<0.05); yr = year in which the study was published.

22% of the eyes had disease progression in terms of increased keratometry readings, although no additional CXL treatment or corneal transplantation was applied in any patient, as none of these eyes lost a Snellen line in either UDVA or CDVA.

Given the relentless progression of keratoconus often observed in pediatric patients, Chatzis and Hafezi proposed that CXL should be performed as early as possible, before disease progression occurs.[13] One of the principal advantages of CXL is that it minimizes the need for corneal transplantation. Indeed, the link between crosslinking and the reduced need for keratoplasty was reported recently by Sandvik et al.[30] Hersh et al. performed a randomized trial and reported that only 10% of patients (5/49) had progressive keratoconic disease (i.e., Kmax progression ≥1.0 D), despite treatment.[9] Furthermore, Wittig-Silva et al. reported that only 2% of patients (1/46) had disease progression after crosslinking; it is worth noting, however, that their definition of progression was ≥2.0 D.[10] The prevalence of progression was much higher in our pediatric cohort than in the aforementioned studies in adults, suggesting that crosslinking may have different effects in different age groups. Thus, in children, crosslinking may provide somewhat less protection against the future need for corneal transplantation.

Our analysis of the cause of progression revealed that decentralized cone location was the only independent underlying cause of keratoconus progression in this subset of patients. This finding is consistent with our previous results in which cone eccentricity was identified as a major predictor of Kmax outcome.[31] Greenstein et al. previously hypothesized that this could be due to less homogenous UV light exposure and/or the distribution of irradiation over a larger area in the peripheral parts of the cornea.[32] Riboflavin uptake and depth of the stromal demarcation line were not routinely measured and were therefore not suitable for statistical analysis.[33,34]

Caporossi et al. performed the largest study on crosslinking in children to date; their study initially included 152 keratoconus patients in which 77 eyes were available for analysis three years after treatment.[12] Their results were analyzed by comparing patients with corneal thickness <450 µm and patients with corneal thickness >450 µm to their respective pre-operative measurements. In both groups, both UDCA and CDVA improved significantly within one year. Moreover, topographic results showed significant improvement in keratometry readings, and these effects lasted at least three years after treatment (the last reported follow-up visit). This is in concordance with results from Uçakhan et al., who published an improvement in both visual and keratometry outcomes four years after treatment.[16] Those findings are in contrast with the findings reported by Chatzis and Hafezi, who concluded that the effect of crosslinking may not be long-

lasting, as the initial Kmax improvement was no longer significant at two-year follow-up and revealed a trend—albeit not significant—towards deterioration at the three-year follow-up visit.[13] On the other hand, the improvement in CDVA did remain significant.[13] In our study, the effect of crosslinking on Kmax did not decline over time; in fact, significant improvement was measured throughout the entire five-year follow-up period.

In conclusion, our results support the notion that epithelium-off crosslinking is a safe and effective method for preventing keratoconus progression in pediatric patients, providing clinical benefits for at least five years following treatment. However, disease progression occurred in 22% of the treated eyes; this progression was attributed to a more decentralized cone location.

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5

Transepithelial versus epithelium-off corneal crosslinking for the treatment of progressive keratoconus: a randomized controlled trial

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ABSTRACT

Purpose

To compare the clinical effects and safety of transepithelial corneal crosslinking (CXL) to epithelium-off (epi-off) CXL in progressive keratoconus.

Design

Randomized clinical trial.

Methods

Patients received either transepithelial CXL with Ricrolin TE (n=35) or epi-off CXL with isotonic riboflavin (n=26) in 1 academic treatment center, using a simple unrestricted randomization procedure. The main outcome measure was clinical stabilisation of keratoconus after 1 year, defined as a maximal keratometry (Kmax) increase < 1 diopter (D).

Results

Average Kmax was stable at all visits in the transepithelial group, while after epi-off CXL a significant flattening of 1.2 to 1.5 D was demonstrated from the 3 months follow-up onwards. The trend over time in Kmax flattening was significantly different between the groups (*P*=0.022). Eight eyes (23%) in the transepithelial group showed a Kmax increase of > 1 D after 1 year (range 1.3 to 5.4 D) vs none in the epi-off group (*P*=0.017). There was significant different trend in corrected distance visual acuity (CDVA), with a more favorable outcome in the transepithelial group (*P*=0.023). In the transepithelial group, no complications occurred and in the epi-off group, 4 eyes (15%) developed complications due to healing problems (sterile infiltrate, herpes keratitis, central haze and stromal scar).

Conclusion

This study showed that although transepithelial CXL was a safe procedure without epithelial healing problems, 23% of cases showed a continued keratoconus progression after 1 year. Therefore, at this time, we do not recommend replacing epi-off CXL by transepithelial CXL for treatment of progressive keratoconus.

INTRODUCTION

Progressive keratoconic corneas can be stabilized and strengthened by corneal crosslinking (CXL).[1] The standard technique of CXL was first applied in 1998 and consists of an epithelial removal, after which riboflavin eye drops and ultraviolet-A (UVA) light are applied.[1,2] The rationale for the removal of the epithelium was described as allowing adequate penetration of riboflavin into the stromal tissue, where it absorbs the UVA light and produces the actual crosslinking between collagen fibrils in the corneal stroma.[3]

The downside of epithelial removal is that it causes significant pain and discomfort during the first postoperative days, in addition to the 3-8% chance of epithelial healing problems.[4–6] To circumvent these downsides of epithelium removal, a transepithelial CXL technique was developed. Transepithelial CXL avoids the need for epithelial removal. Wollensak et al. investigated the biomechanical effect in rabbit eyes and estimated that transepithelial CXL with benzalkonium chloride would create one fifth of the corneal biomechanical rigidity compared with epithelium-off (epi-off) CXL in human eyes.[7] Transepithelial CXL with the use of sodium ethylenediaminetetraacetic acid (EDTA) in riboflavin (Ricrolin TE) has been investigated in ex-vivo rabbit eyes as well, showing minimal riboflavin uptake in the group with intact epithelium receiving Ricrolin TE solution.[8]

The clinical effects of transepithelial CXL with Ricrolin have been reported in case series and non-randomized comparative trials. Filippo et al. reported clinical outcomes after 18 months in 20 eyes treated by Ricrolin assisted transepithelial CXL, compared with their untreated fellow eye.[9–11] A significant improvement in visual acuity (0.35 to 0.24 logMAR) and decreased central keratometry values (steepest keratometry (Ksteep): 51.0 to 48.1 diopter (D)) were seen in the transepithelial CXL eyes, not in the untreated group. A stromal demarcation line at 60 μm depth was measured, indicative of an effective treatment. Caporossi et al. performed Ricrolin assisted transepithelial CXL in 26 eyes, age 11 to 26 years, and reported unchanged visual acuities, but significantly increased maximal keratometry (Kmax) values (48.6 to 50.1 D) after two years of follow-up.[12] Leccisotti et al. reported the one year results on transepithelial CXL with Ricrolin TE in 51 eyes with the untreated fellow eye serving as control and found some stabilizing effect in the transepithelial CXL group (Kmax changed from 54.3 to 54.8 D, compared to 51.7 to 53.3 in the control group).[13] A prospective case series by De Bernando et al. in 36 eyes treated by Ricrolin assisted transepithelial CXL showed an increased visual acuity and stable keratometry after 6 months of follow-up.[14]

The natural course of keratoconus can be long-lasting, with years of apparent stable keratometry readings after a period of latent progression.[15] Furthermore, the clinical effects of epi-off CXL have been well described in randomized controlled trials with adequate follow-up.[16–18] To address these two considerations and adequately describe the clinical effects of transepithelial CXL, a non-inferiority randomized study design is mandatory.

In this randomized controlled study, we investigated the clinical effects and safety of transepithelial CXL with Ricrolin compared to epi-off CXL in progressive cases of keratoconus and tested the hypothesis that transepithelial CXL is equally effective.

MATERIALS AND METHODS

Study group & protocol

This non-inferiority randomized controlled trial included patients diagnosed with progressive keratoconus who were found eligible for a CXL procedure at a tertiary academic centre (University Medical Center Utrecht, The Netherlands), from May 30, 2011 through September 4, 2013 with a follow-up of 1 year. The study was prospectively approved by the University Medical Center Utrecht Ethics Review Board (REF number NL29961) and registered at ClinicalTrials.gov (identification number NCT02349165). All procedures complied with the Declaration of Helsinki and local laws regarding research on human subjects. Written informed consent was obtained from all patients prior to their participation.

Inclusion criteria were age ≥ 18 years, a clear central cornea, and a documented progression as defined by an increase in Kmax, Ksteep, mean keratometry and/or topographic cylinder value by ≥ 0.5 D over the previous 6 to 12 months. Exclusion criteria were a minimal pachymetry of less than 400 μm prior to UVA irradiation, pregnancy or breastfeeding, and a history of previous ocular infection.

Keratoconus diagnosis and study eligibility were determined by one corneal specialist (NT). Progression of keratoconus was documented by minimally 2 topography measurements in all patients. Patients were randomized using a simple unrestricted randomization procedure to either transepithelial CXL or epi-off CXL.

Measurements and Devices

Patients were examined at baseline and at 1, 3, 6 and 12 months post-CXL. Manifest refraction, visual acuity, Goldmann applanation tonometry, slit lamp examination and Scheimpflug topography (Pentacam HR, Oculus, Germany) measurements were performed at each follow-up. Endothelial cell density (Topcon, SP3000P,

Tokyo, Japan) was measured at baseline and at the 6 and 12 month follow-up. Demarcation line depth was measured at the 1, 3 and 6 month follow-up using high resolution corneal imaging (Visante Optical Coherence Tomography, Carl Zeiss, Germany). All contact lens wearers were instructed to discontinue contact lens wear at least 1 week for scleral and soft contact lenses or 2 weeks for hybrid and rigid permeable lenses prior to all evaluations.

During CXL, pachymetry measurements were performed with a handheld ultrasound (US) pachymeter (Handy Pachymeter, SP-3000, Tomey, Japan). The CXL device was used at a working distance of 5 cm with an irradiance of 3 mW/cm^2 (UV-X, Peschke Meditrade, Switzerland). Before every treatment session, a calibration was performed to confirm the correct UVA emission level. Throughout the whole study, the same devices and time points were applied.

Surgical Technique

In the transepithelial CXL group, local anaesthetic eye drops (oxybuprocaïne 0.4% and tetracaïne 1%) were applied 3 times during 5 minutes, and Ricrolin TE solution (consisting of riboflavin 0.1% eye drops with Dextran T500 15 mg and EDTA, SOOFT Italia) were instilled every 2 minutes for 15 minutes. Next, an eyelid speculum was placed and a silicone ring was positioned between the eyelids, which was filled with Ricrolin TE and used to remain a Ricrolin 'pool' on the cornea. After 15 minutes, the silicone ring was removed, the cornea was rinsed with balanced salt solution, and pachymetry was performed. UVA irradiation was performed during 30 minutes, while Ricrolin TE solution was re-applied to the cornea every 5 minutes.

The epi-off CXL technique was performed following the Dresden protocol, adjusted with the avoidance of the eyelid speculum during riboflavin instillation.[19,20] Epithelial removal (9-mm) was performed using a blunt knife. After pachymetry measurements, isotonic riboflavin 0.1% solution with 20% Dextran (Medio Cross™) was applied every 3 minutes during 30 minutes, with no eye lid speculum in place. When pachymetry was < 400 µm, hypoosmolar riboflavin was additionally applied every 20 seconds during 5 minutes and repeated up to 2 times until the required pachymetry value of ≥400 µm was achieved.[21] With an eye lid speculum in place, UVA irradiation was performed during 30 minutes, during which isotonic riboflavin drops was given every 5 minutes.

In both groups, the post-CXL medication consisted of antibiotic eyedrops (Vigamox®,5mg/ml Alcon Nederland BV) and preservative-free artificial tears (Duratears Free®,2% Alcon Nederland BV) and were used for 4 weeks, while non-steroidal anti-inflammatory drops (Nevanac® 0.1% Alcon Nederland BV) were used during the first week. Starting 1 week after CXL, topical steroids

(Fluorometholone 0.1% drops, Allergan BV) were applied twice a day for two weeks. In the epi-off group only, oral pain medication (Tramadol 50 mg 1-2 a day; diclofenac 25 mg 1-2 a day) were prescribed on the treatment day and the day after. A bandage lens (Purevision, Bausch & Lomb) was placed in the epi-off group, and was removed after 1 week if the epithelial healing was complete.

Statistical analysis and power calculation

Baseline measurements between the treatment groups were compared using an independent samples t-test. Primary outcome was pre-defined in the study protocol as clinical stabilisation of keratoconus one year after CXL, defined as a Kmax increase of no more than 1 D over the preoperative Kmax value. Fischer's exact test (two tailed) was used to determine the relation between treatment and stabilisation.

Decimal visual acuity was converted to the logarithm of the minimal angle of resolution (logMAR).

We analyzed all outcome measures at all follow-up visits using a linear mixed model with a generalized estimating equations correction.[22] The outcomes over time were corrected for baseline values. Normality and homoscedasticity of the residuals were tested visually, and in a Q-Q plot and scatterplot, respectively. A *P*-value <0.05 was considered statistically significant. Data are recorded as mean ± standard deviation. All tests were performed in SPSS version 20.0 for Windows.

Power of this study was calculated based on a non-inferiority design, which was determined by the expected average Kmax change after treatment (Raiskup et al.: -1.46 D[23]) minus the acceptable average Kmax change after treatment (Koller et al: Kmax + 1 D[5]). The standard deviation reported by Raiskup et al. was 3.76. Using alpha 0.05, beta 0.2, and a non-inferiority margin of -2.46, we calculated a sample size of 29 for each group.[24]

RESULTS

Of the 105 patients eligible for this study, 61 patients were willing to participate and provided informed consent. This study included 61 eyes from 61 patients (47 males and 14 females) with progressive keratoconus, who were randomly assigned to either epi-off (n=26) or transepithelial CXL (n=35). One eye in the epi-off group received hypoosmolar riboflavin, since the corneal thickness was <400 µm after 30-minutes of isotonic riboflavin instillation.

Four patients (6%), two in each group, did not complete the one year-follow-up; two patients were lost to follow up due to a move abroad, one patient scheduled

Table 1. Transepithelial versus epithelium-off corneal crosslinking for keratoconus, baseline characteristics (n=61).

Baseline parameter	Transepithelial CXL	Epithelium-off CXL
Median age (years, range)	24 (18-48)	24 (18-44)
Male / Female (n)	28 / 7	19 / 7
Right / left (n)	19 / 16	13 / 13
Spherical Equivalent (D)	-1.5 ± 2.5	-3.0 ± 3.0
Uncorrected distance visual acuity (logMAR)	0.8 ± 0.5	1.1 ± 0.6
Corrected distance visual acuity (logMAR)	0.3 ± 0.3	0.3 ± 0.3
Pachymetry thinnest point (µm)	457 ± 27	467 ± 29
Maximal keratometry (D)	56.4 ± 5.0	57.8 ± 7.1
Intraocular pressure (mmHg)	10 ± 2	11 ± 3
Endothelium (cells/mm^2)	2627 ± 363	2764 ± 252

CXL = corneal crosslinking; D = diopter; mean ± SD

the follow-up visits in another hospital closer by, and one patient was re-treated by epi-off CXL after 10 months (see the complication section for details).

Both groups were comparable at baseline, apart from a lower spherical equivalent and logMAR UDVA in the transepithelial CXL group. Mean keratoconus progression before treatment was not significantly different between the groups. Baseline characteristics are listed in Table 1. All variables, except for age, were normally distributed.

Table 2 shows the outcomes at all follow-up time points in the transepithelial CXL and the epi-off group.

Table 2. Transepithelial versus epithelium-off corneal crosslinking for keratoconus. Outcome after 1, 3, 6 and 12 months compared to baseline.

Parameter	Group	1 month	3 months	6 months	12 months	*P*-value[a]
ΔKmax (D)	Transepithelial	-0.1 ± 1.1	0.0 ± 1.0	-0.1 ± 1.2	0.3 ± 1.8	0.022*
	Epithelium-off	0.3 ± 1.1	-1.2 ± 2.0	-1.4 ± 2.0	-1.5 ± 2.0	
ΔCDVA (logMAR)	Transepithelial	-0.05 ± 0.24	-0.10 ± 0.21	-0.12 ± 0.22	-0.14 ± 0.21	0.023*
	Epithelium-off	0.09 ± 0.18	-0.04 ± 0.18	-0.09 ± 0.23	-0.07 ± 0.21	
ΔUDVA (logMAR)	Transepithelial	-0.06 ± 0.25	-0.08 ± 0.29	-0.02 ± 0.31	-0.06 ± 0.37	0.591
	Epithelium-off	-0.10 ± 0.36	-0.18 ± 0.31	-0.16 ± 0.35	-0.15 ± 0.43	
ΔSE (D)	Transepithelial	0.4 ± 1.1	0.3 ± 1.1	0.3 ± 1.6	0.3 ± 1.6	0.436
	Epithelium-off	0.6 ± 1.4	0.5 ± 1.6	0.9 ± 1.8	0.4 ± 3.0	
ΔCorneal thickness (µm)[b]	Transepithelial	0 ± 7	2 ± 9	-3 ± 8	0 ± 12	<0.001*
	Epithelium-off	-18 ± 10	-14 ± 15	-9 ± 11	-4 ± 8	

CDVA = corrected distance visual acuity; Δ = differences post pre-crosslinking; D = diopter; SE = spherical equivalent; UDVA = uncorrected
distance visual acuity.
[a]P value from generalized estimating equations corrected for baseline; * = statistically significant.
[b]Corneal thickness on thinnest point.

Keratometry

Transepithelial CXL showed less potent effects on keratoconus stabilization and regression compared to epi-off CXL; in the transepithelial CXL group, Kmax remained virtually stable at all follow-up visits, while in the epi-off group, Kmax demonstrated flattening from 3 months post-treatment onwards (Figure 1). The trend over time in Kmax flattening was significantly different between both groups (P=0.022).

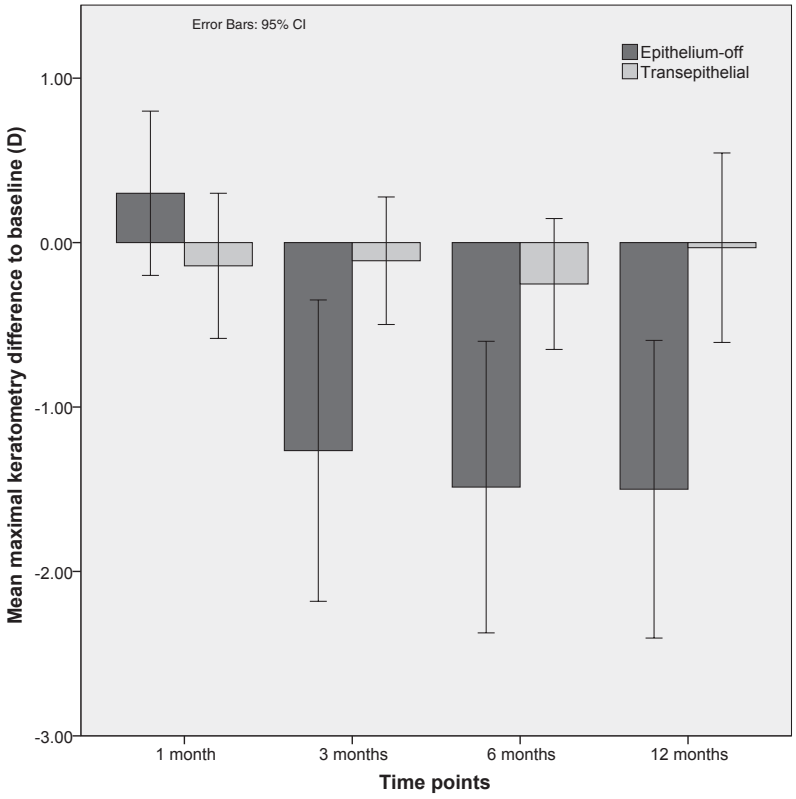

Figure 1. Difference in maximal keratometry over time compared to baseline in transepithelial versus epithelium-off corneal crosslinking for keratoconus.

The steep and flat central keratometry values (Ksteep and Kflat) increased slightly over time in the transepithelial CXL group, and decreased slightly in the epi-off group (supplementary data).

Primary outcome: treatment failure, as pre-defined in the study protocol

In the transepithelial CXL group, 8 eyes (23%) showed continued progression of the disease (range 1.3 to 5.4 D). One eye showed a 4.7 D increase in Kmax after 10 months and was retreated by epi-off CXL, seven other eyes showed a Kmax increase after 1 year, of which currently four eyes are retreated by epi-off CXL, Table 3. In the epi-off group, all eyes demonstrated clinical stabilisation after one year.This difference in clinical stabilization between the two treatments was statistically significant (P=0.016).

Table 3. Overview of patients from the transepithelial group, re-treated by epithelium-off corneal crosslinking for keratoconus.

Patient #	Maximal keratometry (Kmax) increase	Time after initial treatment	Result after retreatment
1	4.7 diopter	10 months	Kmax decreased 1.6 diopter after 1 year
2	1.8 diopter	27 months	Kmax decreased 1.1 diopter after 1 year
3	2.9 diopter	15 months	Kmax decreased 0.2 diopter after 1 year
4	5.4 diopter	13 months	Kmax decreased 0.4 diopter after 1 month
5	4.6 diopter	33 months	No data available after retreatment

The number of patients with a continued progression was considered too small for subgroup analysis to detect predictors for the transepithelial CXL outcome. The baseline characteristics of the eyes that presented with continued progression after transepithelial CXL compared to the transepithelial CXL group in general, or the total study population were shown in Table 4.

Table 4. Transepithelial versus epithelium-off corneal crosslinking for keratoconus: baseline characteristics and outcome after 1 year (stabilization, regression or progression)

Group	Kmax (D)	Range	CDVA (logMAR)	Range	CCThin (µm)	Range
Transepithelial CXL entire group	56.4	46.2 to 68.1	0.30	-0.08 to 1.00	457	410 to 516
Transepithelial CXL stable/ regression	56.4	46.2 to 68.1	0.32	-0.08 to 1.00	456	410 to 516
Transepithelial CXL progression	55.8	50.7 to 59.6	0.21	0.00 to 0.52	460	424 to 495
Epithelium-off CXL entire group	57.8	47.2 to 73.8	0.26	-0.08 to 1.00	467	412 to 546

CCThin = corneal thickness, measured at the thinnest location; CDVA = corrected distance visual acuity; CXL = corneal crosslinking; D = diopter; Kmax = maximal keratometry.

Visual acuity and refraction

There was a statistically significant different trend in corrected distance visual acuity (CDVA) between both groups, with a more favorable outcome in the

transepithelial CXL group (*P*=0.023). Figure 2 shows the largest difference in CDVA at the one month follow-up. When analyzing the data without the one month results, there is no significant difference between the two groups (*P*=0.088). No difference in the trend over time in uncorrected visual outcomes was observed between the groups (*P*=0.591).

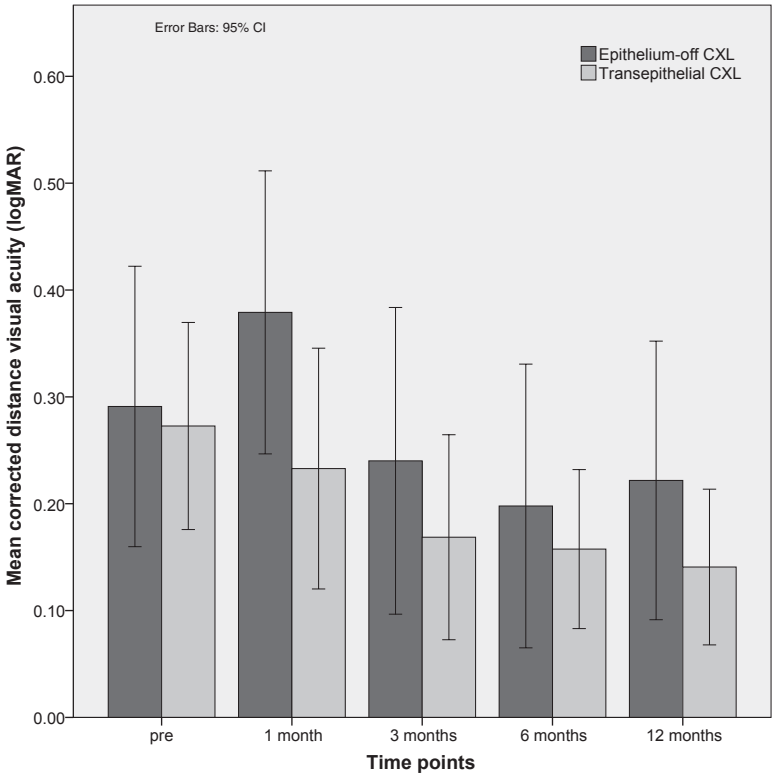

Figure 2. Corrected distance visual acuity at different time points in transepithelial versus epithelium-off corneal crosslinking for keratoconus.

Refractive cylinder values increased in both groups after treatment by ± 1.5 D, with no difference in trend over time between the groups (*P*=0.720). Spherical refraction increased in both groups by ± 1 D, with no difference in trend over time between the groups (*P*=0.281). Trend over time in spherical equivalent was also unchanged between treatment groups (*P*=0.436).

Pachymetry, intra ocular pressure and endothelium cell counts

Corneal thickness remained stable in the transepithelial CXL group. The epi-off group showed an expected lowered optical pachymetry after treatment, which normalized at the 12 month time point. No difference in IOP over time was measured between the groups, the endothelial cell counts were unremarkable (supplemental table).

Demarcation line

In none of the transepithelial CXL cases, a demarcation line was visible after 1 month (Table 5). The average demarcation line depth the epi-off group was 266 µm ± 64 after 1 month, measured in 22 of 26 eyes; data of 4 eyes was missing by equipment failure at location.

Table 5. Demarcation line depth 1 and 3 months after transepithelial versus epithelium-off corneal crosslinking for keratoconus.

Demarcation line depth[a]	1 month post-CXL	3 months post-CXL
Transepithelial CXL group	No demarcation line	218 µm in 1 of 35 eyes (3%)
Epithelium-off CXL group	266 ± 64 µm (range 155-359) in 22 of 26 eyes (85%)	231 ± 50 µm (range 173-336) in 15 of 26 eyes (58%)

CXL = corneal cross-linking.
[a]*Measured by anterior segment optical coherence tomography; data recorded as mean 6 standard deviation.*

Adverse events

In all eyes in the transepithelial CXL group, the epithelium remained intact after one week and no adverse events were recorded.

Adverse events occurred in four eyes (15%) in the epi-off group. One eye developed a herpes simplex keratitis one week post-CXL, which was adequately treated and did not result in visual acuity loss (pre- and post-CXL decimal CDVA was 0.8) or scarring. One eye developed a sterile infiltrate, though a clear cornea was seen at the 1 month follow-up. One eye had epithelial healing problems and a small central haze spot in the anterior stroma one week post-CXL, possibly associated with his peri-ocular eczema (pre-CXL decimal CDVA was 0.6, after 1 year 0.8). Finally, one eye also showed delayed epithelial healing leading to a “cloudy stroma” at the 3 month follow-up and a deep stromal haze at the 6 month follow-up (pre- and post-CXL decimal CDVA was 0.1).

DISCUSSION

This non-inferiority randomized controlled trial showed that transepithelial crosslinking with EDTA riboflavin (Ricrolin TE), although showing no adverse events, was less effective to halt keratoconus progression after 1 year compared to epithelium-off crosslinking; 8 eyes (23%) showed an increase of maximal keratometry of more than 1 diopter compared to none of the eyes in the epi-off group.

A major strength of this study was the adequately powered design and the very low percentage of cases who were lost to follow-up (approximately 4%). The interventions were standardized and did not change throughout the course of study. All diagnoses were made by a corneal specialist (NT) and all refractions were measured by a trained optometrist (NS). The unequal sample size in this (non-double blinded) study can be considered a limitation, however, some discrepancy would be expected since a simple unrestricted randomization procedure was followed instead of a block randomization.[25]

The rigidity of the cornea and the Ricrolin TE concentration in the stroma have not been investigated in this study, since our main focus was to show the clinical effects. Unfortunately, confocal microscopy to analyze changes in corneal structures after CXL was not available in our setting. We were therefore unable to assess and compare potential keratocyte apoptosis, as was reported by Fillipello et al.[10]

The general indicators for a CXL effect (with stabilization being the main purpose) are a visible demarcation line, a flattened keratometry and reduced pachymetry.[26,27] Recent developments of transepithelial CXL in another manner, for instance by iontophoresis, showed increased uptake of riboflavin into the stroma, and resulted in stable and decreased keratometry and improved UDVA or CDVA after 1 year in small groups of patients (20 to 22 eyes).[28,29] In our study, no demarcation line was found in the transepithelial CXL group and the average central keratometry, maximal keratometry, and pachymetry were unchanged after treatment. The fact that these indicators were absent in the transepithelial CXL group suggests this treatment was not sufficiently effective in halting progressive keratoconus. However, if we compare the mean Kmax value after 1 year in our transepithelial CXL group (+ 0.3 D) to the untreated control groups of three randomized controlled trials (+1.2D[16] , -0.1 D (18 months)[30] and +0.3D)[18], the effect is debatable. Another notable finding in our transepithelial CXL group was a significant CDVA increase, in addition to a significantly increased cylinder. This indicates that there might be something going on in transepithelial CXL with Ricrolin TE after all.

The average Kmax flattening after one year in the epi-off group in our study was more pronounced (-1.5 D) compared to the results of Wittig-Silva et al. (-0.7 D), which could be explained by the steeper corneas at baseline in our study (52 D versus 58 D) which are known to flatten more after CXL.[19] The statistically different trend in CDVA over time between the groups can be explained by the haze formation at the 1 month follow-up in the epi-off group which was noted after epithelium removal.[31] Another explanation for CDVA and keratometry changes at the 1 month follow-up could be the remodeling of epithelium (in keratoconus, the epithelium layer is thinnest at the cone, and the epithelium thickness profile can re-establish a smoother surface). [32]

In our transepithelial CXL group, eventually 5 eyes (14%) were retreated, which is in line with the study of Caporossi et al. who decided to retreat 19% of the Ricrolin-assisted transepithelial CXL patients after 2 years.[12] In contrast to Filippello et al. who reported flattening of Kmax 18 months after transepithelial CXL, average Kmax remained stable in our transepithelial CXL group after 1 year.[9,11] Furthermore, the authors measured a demarcation line in the transepithelial CXL group which was more superficial than generally reported in eyes undergoing epi-off CXL, while the demarcation line was absent in our transepithelial CXL group. The most apparent difference in surgical technique was the use of the silicone ring throughout the entire procedure (including UVA irradiation) by Filippo et al. We adhered to the manufacturer's instruction and removed the ring prior to UVA irradiation

Endothelial damage has been described when thin corneas were irradiated with UVA without containing sufficient riboflavin to absorb the UVA light.[20,33] In transepithelial CXL, both the Ricrolin TE solution and corneal epithelium absorb UVA.[34] ECD count remained stable in both treatment groups, suggesting sufficient UV absorption to avoid endothelium damage.

In general, keratoconus progression does not follow a linear trend over time. In contrast, periods of progression intersperse with periods of stability. Keeping this in mind, the patients who underwent transepithelial CXL and were classified as 'stable' after 1 year, could also have passed a physiologic stable period of their condition. Some patients showed stable keratometry values at the 1 year follow-up, and progression 2 years after treatment (unpublished data), suggesting either a less effective treatment or an ineffective treatment with physiologic stable period. Considering whether transepithelial CXL is unsuitable for any patient group, is difficult. Perhaps transepithelial CXL would be advisable for patients with a corneal thickness < 350 μm who are excluded for epi-off CXL, or patients whose lack of compliance increases the risk of post-operative adverse events.

In this study, we showed the clinical results of a randomized controlled trial with transepithelial CXL with Ricrolin TE versus epi-off CXL. transepithelial CXL showed a poor potential for halting keratoconus progression when compared to regular epi-off CXL: a demarcation line could not be identified and a considerable percentage of transepithelial CXL treated eyes needed retreatment due to an increased maximum keratometry.

Therefore, although epithelial removal is a painful procedure and associated with considerably more adverse events, we would recommend epi-off CXL for patients who present with a progressive keratoconus.

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Supplemental table. Mean variables at baseline and 1, 3, 6 and 12 months after transepithelial versus epithelium-off corneal crosslinking for keratoconus.

Parameter	Group	pre	1 month	3 months	6 months	12 months	P-value[a]
UDVA (logMAR)	Transepithelial	0.76 ± 0.48	0.70 ± 0.47	0.66 ± 0.49	0.70 ± 0.49	0.71 ± 0.50	0.591
	Epithelium-off	1.07 ± 0.58	0.97 ± 0.45	0.89 ± 0.46	0.99 ± 0.51	0.97 ± 0.49	
CDVA (logMAR)	Transepithelial	0.30 ± 0.27	0.25 ± 0.30	0.19 ± 0.28	0.16 ± 0.19	0.16 ± 0.21	0.023*
	Epithelium-off	0.26 ± 0.29	0.35 ± 0.29	0.22 ± 0.31	0.20 ± 0.29	0.21 ± 0.28	
Sphere (D)	Transepithelial	-0.3 ± 2.5	0.6 ± 2.7	0.6 ± 2.7	0.7 ± 3.0	0.8 ± 2.8	0.281
	Epithelium-off	-1.6 ± 3.1	-0.6 ± 3.2	-0.7 ± 2.9	-0.7 ± 2.3	-0.9 ± 3.4	
Cylinder (D)	Transepithelial	-2.4 ± 1.5	-3.3 ± 1.8	-3.4 ± 1.9	-3.3 ± 1.8	-4.0 ± 2.1	0.720
	Epithelium-off	-2.7 ± 1.8	-3.5 ± 2.0	-3.6 ± 1.9	-3.4 ± 1.8	-4.0 ± 2.0	
SE (D)	Transepithelial	-1.5 ± 2.5	-1.0 ± 2.7	-1.1 ± 2.8	-0.9 ± 2.8	-1.2 ± 3.0	0.436
	Epithelium-off	-3.0 ± 3.0	-2.4 ± 2.8	-2.5 ± 2.6	-2.4 ± 2.1	-2.8 ± 3.4	
Ksteep (D)	Transepithelial	49.3 ± 3.6	49.5 ± 3.7	49.3 ± 3.7	49.5 ± 3.7	49.5 ± 3.8	0.202
	Epithelium-off	50.6 ± 4.6	51.1 ± 5.0	50.3 ± 4.5	50.5 ± 4.5	50.5 ± 4.4	
Kflat (D)	Transepithelial	45.4 ± 3.0	45.6 ± 3.1	45.7 ± 3.3	46.0 ± 3.4	45.8 ± 3.5	0.104
	Epithelium-off	46.4 ± 4.0	46.8 ± 4.4	46.2 ± 4.2	46.4 ± 4.2	46.4 ± 4.3	
Kmax (D)	Transepithelial	56.4 ± 5.0	56.4 ± 5.2	56.3 ± 5.1	56.3 ± 5.0	56.6 ± 5.2	0.022*
	Epithelium-off	57.8 ± 7.2	58.1 ± 7.2	56.8 ± 6.3	56.9 ± 6.0	56.8 ± 6.1	
Corneal thickness (µm)[b]	Transepithelial	457 ± 27	457 ± 27	460 ± 29	456 ± 25	459 ± 28	<0.001*
	Epithelium-off	467 ± 29	449 ± 32	454 ± 33	455 ± 30	460 ± 28	
IOP (mmHg)	Transepithelial	10 ± 2	11 ± 2	11 ± 3	10 ± 2	11 ± 2	0.065
	Epithelium-off	11 ± 3	12 ± 2	11 ± 2	11 ± 3	11 ± 3	
ECD (cells/m^2)	Transepithelial	2628 ± 363	n/a	n/a	2618 ± 325	2639 ± 308	0.350
	Epithelium-off	2764 ± 252	n/a	n/a	2627 ± 287	2705 ± 308	

CDVA= corrected distance visual acuity; D = diopter; ECD = endothelial cell density; epi-off = epithelium-off crosslinking; IOP= intraocular pressure; Kflat = flattest keratometry value; Kmax = maximal keratometry value; Ksteep = steepest keratometry value; SE = spherical equivalent; TE = transepithelial cross-linking; UDVA = uncorrected distance visual acuity.

[a]*P value from generalized estimating equations corrected for baseline; * = statistically significant.*

[b]*Corneal thickness on thinnest point.*

6

Higher-order optical aberrations and visual acuity in a randomized controlled trial comparing transepithelial versus epithelium-off corneal crosslinking for progressive keratoconus

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Submitted

ABSTRACT

Purpose

To compare the effects of transepithelial crosslinking (trans-CXL) versus epithelium-off crosslinking (epi-off CXL) for progressive keratoconus with respect to the development of higher-order aberrations (HOAs) and their effects on visual acuity.

Setting

Tertiary academic referral center, Utrecht, the Netherlands.

Design

Randomized controlled trial.

Methods

Sixty-one patients were randomized and examined preoperatively and 1, 3, 6, and 12 months postoperatively. HOAs were compared between the two treatment groups using mixed linear modeling. Types of HOAs (coma, trefoil, and spherical aberration) that differed between groups were entered in a multivariable analysis to test their effect on uncorrected distance visual acuity (UDVA) and corrected distance visual acuity (CDVA).

Results

The epi-off CXL group had more flattening in maximal keratometry compared to the trans-CXL group (P=0.02). UDVA did not differ significantly between the groups (P=0.59); however, CDVA was significantly more improved in the trans-CXL group (P=0.02). Horizontal trefoil improved more in the epi-off group compared to the trans-CXL group (P=0.04), whereas the other HOAs were virtually unchanged in both groups. Differences in changes in HOAs between the two groups had no effect on either UCVA (P=0.76) or CDVA (P=0.96).

Conclusions

Although HOAs are clinically relevant determinants of vision quality in keratoconus patients, only horizontal trefoil differed significantly post-treatment between the trans-CXL and epi-off CXL groups. However, this difference did not independently affect either uncorrected or corrected distance visual acuity. We suggest that HOAs should not be considered as a factor when determining which form of CXL is appropriate for treating specific patients.

INTRODUCTION

Keratoconus is a disorder of the cornea characterized by changes in corneal collagen structure and progressive stromal thinning. The etiology of this thinning has been studied extensively and is believed to arise from a multifactorial interplay between genetic susceptibility, environmental factors, and chronic low-grade inflammation.[1] The resulting decrease in the cornea's mechanical stability leads to progressive ectasia, which in turn can lead to myopia, irregular astigmatism, higher-order aberrations (HOAs), and—eventually—corneal scarring, all of which can result in a marked decrease in vision quality.[2,3]

Corneal collagen crosslinking (CXL) can be performed in order to stabilize the progression of keratoconus and prevent the need for corneal transplantation.[5,6] The standard CXL treatment includes removal of the epithelium (i.e., epi-off CXL), followed by the application of riboflavin and UV-A irradiation.[5] However, removing the epithelium causes significant postoperative pain and discomfort that can last several days, and it increases the risk of developing postoperative complications such as bacterial keratitis.[8,9]

Unlike epi-off CXL, transepithelial CXL (trans-CXL) does not require removal of the epithelium, thereby reducing postoperative pain and decreasing the risk of post-operative infection. However, because riboflavin does not readily penetrate the intact epithelium, various techniques have been developed to promote the absorption of riboflavin by the corneal stroma. The clinical effects of trans-CXL on corneal curvature have been studied in several studies; however, the results are inconsistent—two randomized controlled trials (RCTs) concluded that trans-CXL was less effective at treating progression of corneal ectasia compared to epi-off CXL, whereas another RCT concluded that the effects were similar between treatment groups.[11–13] Interestingly, all three trials found significantly higher improvement in visual acuity in the trans-CXL group. We hypothesized that this improvement may be due to differences in the development of HOAs, as trans-CXL does not cause complications due to wound repair or long-lasting epithelial remodeling, both of which occur in epi-off CXL as a result of epithelial abrasion.

To test this hypothesis, we used data collected from a previously published RCT[13] in order to investigate the effects of trans-CXL and epi-off CXL on HOAs, and we examined their effects on visual acuity.

MATERIAL AND METHODS

Dataset and study design

Data were derived from an RCT in which trans-CXL and epi-off CXL were performed to treat progressive keratoconus; this trial was conducted at the University Medical Center Utrecht in the Netherlands.[13] Adult patients who were diagnosed with progressive keratoconus and were candidates for CXL were enrolled from 30 May 2011 through 4 September 2013. Trans-CXL was performed with Ricrolin TE solution (consisting of riboflavin 0.1% eye drops with dextran T500 15 mg and EDTA; SOOFT Italia). Epi-off CXL was performed in accordance with the Dresden protocol, using 0.1% riboflavin with 20% dextran (Medio Cross). Riboflavin soaking time (30 min) and UV irradiation (3 mW/cm^2 for 30 min) were identical between the treatment groups. Detailed information regarding the inclusion criteria and surgical procedures have been published previously.[13] The study was approved and monitored by the University Medical Center Utrecht Ethics Review Board (ref. number NL29961), and all procedures were conducted in accordance with the ethical standards established by the Declaration of Helsinki and local laws regarding privacy and research in human subjects.

Assessment of corneal optical aberrations

Patients were examined preoperatively and 1, 3, 6, and 12 months postoperatively. At each visit, measurements included manifest refraction, uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA), and Scheimpflug corneal tomography (Pentacam HR, Oculus, Wetzlar, Germany). In the event that the tomogram did not reach the minimum quality criterion of 90%, tomography was repeated up to three times and the best scan was used to assess HOAs. Patients who wore contact lenses were instructed to discontinue use at least one week (for scleral and soft contact lenses) or two weeks (for hybrid and rigid gas-permeable lenses) prior to each examination.[13] Corneal optical aberrations were measured at each visit using the Pentacam device, which measures anterior and posterior corneal elevations over the central 6.0 mm and calculates HOAs from these elevation data. The software program reports aberrations at the anterior and posterior surfaces, as well as for the total cornea. Total corneal aberrations were used as the outcome parameter in this study because this outcome is most relevant to patients; however, an ancillary analysis was also performed based on changes in anterior HOAs only. The Pentacam software subdivides this outcome into the following two composite values: total corneal lower-order aberrations, and total corneal higher-order aberrations. Normalized coefficients were expressed in microns of wavefront error (in root mean square, RMS) and labeled

with ISO-standardized double index Zernike symbols. HOAs were reported with their Zernike weight coefficient, as the polynomial coefficient is considered to be invariant. Total corneal HOAs were calculated based on the 3rd - 8th-order aberrations. The following lower-order aberration (LOA) subtypes were reported in detail: defocus (Z_2^0), vertical astigmatism (Z_2^{-2}), and horizontal astigmatism (Z_2^2). HOA subtypes were reported in detail for horizontal coma and vertical coma (Z_3^1 and Z_3^{-1}, respectively), horizontal trefoil and vertical trefoil (Z_3^3) and Z_3^{-3}, respectively), and spherical aberration (Z_4^0).

Statistical analysis

Visual acuity was converted to the logarithm of the minimal angle of resolution (logMAR). Baseline measurements were compared between the two groups using an independent-samples *t* test. Because both positive and negative HOAs can impair visual acuity, we used absolute values for all HOAs. We used a linear mixed model with generalized estimating equations correction to analyze trends over time and outcomes were corrected for baseline values. HOAs that differed significantly between the two treatment groups were entered in a multivariable analysis with treatment as an interaction term and visual acuity as the outcome, while correcting for changes in LOAs. Uncorrected visual acuity and corrected visual acuity were analyzed separately. To determine whether the choice of using either total corneal HOAs or anterior corneal HOAs affected the results, an ancillary analysis using anterior corneal HOAs was performed. Except where indicated otherwise, data are reported as the mean ± standard deviation. Differences with a *P*-value <0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY).

RESULTS

Baseline characteristics

Sixty-one eyes of 61 patients (47 men and 14 women) with progressive keratoconus were included in this randomized clinical trial. These 61 patients were randomly assigned to either the epi-off CXL group (n=26) or the trans-CXL group (n=35). Baseline characteristics were similar between the two treatment groups and are summarized in Table 1.

Table 1. Baseline characteristics of the epithelium-off and transepithelial groups

Baseline Parameter	Epithelium-off corneal crosslinking	Transepitalial corneal crosslinking	*P* value*
Number	26	35	
Right eyes/Left eyes	13/13	19/16	
Males/Females	19/7	28/7	
Age (years)	25.9 (7.6)	26.9 (8.0)	0.60
Spherical equivalent (D)	-3.0 ± 3.0	-1.5 ± 2.5	**0.04**
UDVA (logMAR)	1.1 ± 0.6	0.8 ± 0.5	**0.03**
CDVA (logMAR)	0.3 ± 0.3	0.3 ± 0.3	0.58
Pachymetry thinnest point (mm)	467 ± 29	457 ± 27	0.17
Maximal keratometry (D)	57.8 ± 7.2	56.4 ± 5.0	0.38
Endothelial cell count (cells/mm^2)	2764 ± 252	2627 ± 363	0.14
Lower-order aberrations (RMS)			
Total LOAs	11.8 ± 5.6	11.8 ± 4.4	0.56
Defocus (Z_2^0)	3.01 ± 2.95	2.95 ± 2.92	0.93
Vertical astigmatism (Z_2^{-2})	1.47 ± 1.20	1.55 ± 1.33	0.81
Horizontal astigmatism (Z_2^2)	2.10 ± 2.08	1.90 ± 1.44	0.66
Higher-order aberrations (RMS)			
Total HOAs	3.29 ± 1.42	3.09 ± 1.18	0.97
Vertical trefoil (Z_3^{-3})	0.22 ± 0.16	0.28 ± 0.21	0.22
Vertical coma (Z_3^{-1})	2.69 ± 1.45	2.56 ± 1.23	0.71
Horizontal coma (Z_3^1)	0.94 ± 0.71	0.86 ± 0.67	0.67
Horizontal trefoil (Z_3^3)	0.25 ± 0.18	0.19 ± 0.20	0.26
Spherical aberration (Z_4^0)	0.66 ± 0.63	0.56 ± 0.52	0.53

Except when indicated otherwise, values are presented as a mean ± standard deviation
D= diopter, UDVA= uncorrected distance visual acuity, logMAR= log of the minimal angle of resolution CDVA= corrected distance visual acuity, RMS= root mean square, LOAs= lower-order aberrations, HOAs= higher-order aberrations *P*-values were calculated using the independent-samples *t* test. *Significant *P*-values (<0.05) are shown in bold

Follow-up and adverse events

A total of four patients (6% of patients, two patients in each group) were lost to follow-up. Two of these patients moved abroad, one patient received follow-up care at another hospital, and one patient (in the trans-CXL group) was re-treated with epi-off CXL ten months after the first epi-off CXL treatment. No adverse events were reported in the trans-CXL group; in contrast, four patients in the epi-off CXL group (15% of patients) developed an adverse event: one patient developed herpes simplex keratitis, one patient had a sterile infiltrate, and two patients had delayed epithelial healing.[13]

Clinical outcomes

The clinical outcomes in the trans-CXL and epi-off CXL groups 1, 3, 6, and 12 months post-treatment are summarized in Table 2. The two groups differed significantly with respect to both maximal keratometry (*P*=0.02) and corneal thickness (*P*<0.001). The two groups did not differ significantly with respect to their change in UCVA (*P*=0.59). In contrast, CDVA differed significantly between the two groups *(P*=0.02), with the trans-CXL group having a larger improvement compared to the epi-off CXL group. Complete details regarding the clinical outcomes of this trial have been published.[13]

Table 2. Epithelium-off vs. transepithelial corneal crosslinking for keratoconus: Outcomes 1, 3, 6, and 12 months after crosslinking relative to baseline

Parameter	Group	1 month	3 months	6 months	12 months	*P* value*
Δ Maximal keratometry (D)	Epi-off	0.3 ± 1.1	-1.2 ± 2.0	-1.4 ± 2.0	-1.5 ± 2.0	**0.02**
	Trans	-0.1 ± 1.1	0.0 ± 1.0	-0.1 ± 1.2	0.3 ± 1.8	
Δ CDVA (logMAR)	Epi-off	0.09 ± 0.18	-0.04 ± 0.18	-0.09 ± 0.23	-0.07 ± 0.21	**0.02**
	Trans	-0.05 ± 0.24	-0.10 ± 0.21	-0.12 ± 0.22	-0.14 ± 0.21	
ΔUDVA (logMAR)	Epi-off	-0.10 ± 0.36	-0.18 ± 0.31	-0.16 ± 0.35	-0.15 ± 0.43	0.59
	Trans	-0.06 ± 0.25	-0.08 ± 0.29	-0.02 ± 0.31	-0.06 ± 0.37	
Δ Spherical equivalent (D)	Epi-off	0.6 ± 1.4	0.5 ± 1.6	0.9 ± 1.8	0.4 ± 3.0	0.44
	Trans	0.4 ± 1.1	0.3 ± 1.1	0.3 ± 1.6	0.3 ± 1.6	
Δ Corneal thickness (mm)	Epi-off	-18 ± 10	-14 ± 15	-9 ± 11	-4 ± 8	**<0.001**
	Trans	0 ± 7	2 ± 9	-3 ± 8	0 ± 12	

Except when indicated otherwise, values are presented as a mean ± standard deviation D= diopter, CDVA= corrected distance visual acuity, logMAR= log of the minimal angle of resolution UDVA= uncorrected distance visual acuity, *P*-values were calculated using trend analysis with generalized estimating equations while correcting for baseline values. *Significant *P*-values (<0.05) are shown in bold

Higher-order aberrations

Table 3 summarizes the change in optical aberrations in the two treatment groups. Only horizontal trefoil differed significantly between the two groups (*P*=0.04), with a larger improvement in the epi-off CXL group. We found no significant difference between the treatment groups with respect to total LOAs (*P*=0.41) or total HOAs (*P*=0.98). Similar results were obtained when we performed an ancillary analysis using anterior corneal HOAs rather than total corneal HOAs (data not shown).

Table 3. Trend analysis on lower-order and higher-order aberrations 1, 3, 6, and 12 months after crosslinking relative to baseline

Parameter	Group	Baseline	1 month	3 months	6 months	12 months	*P* value*
Lower-order aberrations (RMS)							
ΔTotal LOAs	Epi-off	11.8 ± 5.6	0.31 ± 1.83	-0.66 ± 1.79	-1.10 ± 2.35	-1.12 ± 1.86	0.42
	Trans	11.8 ± 4.4	0.04 ± 1.20	-0.06 ± 1.33	-0.34 ± 1.86	-0.13 ± 2.21	
ΔDefocus (Z_2^0)	Epi-off	3.01 ± 2.95	0.71 ± 1.70	-0.47 ± 1.61	-0.46 ± 1.39	-0.36 ± 1.48	0.90
	Trans	2.95 ± 2.92	0.12 ± 0.82	0.14 ± 1.17	-0.05 ± 1.11	0.06 ± 1.43	
ΔVertical astigmatism (Z_2^{-2})	Epi-off	1.47 ± 1.20	0.07 ± 0.69	0.14 ± 0.75	0.00 ± 0.63	-0.10 ± 0.74	0.59
	Trans	1.55 ± 1.33	0.03 ± 0.51	0.01 ± 0.42	0.00 ± 0.46	0.23 ± 0.63	
ΔHorizontal astigmatism (Z_2^2)	Epi-off	2.10 ± 2.08	0.21 ± 0.55	0.11 ± 0.40	-0.10 ± 0.50	0.08 ± 0.78	0.18
	Trans	1.90 ± 1.44	-0.08 ± 0.48	-0.03 ± 0.55	-0.02 ± 0.53	-0.06 ± 0.70	
Higher-order aberrations (RMS)							
ΔTotal HOAs	Epi-off	3.29 ± 1.42	0.16 ± 0.44	-0.06 ± 0.37	-0.16 ± 0.43	-0.18 ± 0.36	0.98
	Trans	3.09 ± 1.18	0.02 ± 0.27	0.01 ± 0.33	-0.03 ± 0.37	0.03 ± 0.54	
ΔVertical trefoil (Z_3^{-3})	Epi-off	0.22 ± 0.16	-0.02 ± 0.20	0.07 ± 0.24	0.05 ± 0.17	0.01 ± 0.28	0.29
	Trans	0.28 ± 0.21	0.02 ± 0.29	-0.01 ± 0.31	-0.01 ± 0.26	0.02 ± 0.33	
ΔVertical coma (Z_3^{-1})	Epi-off	2.69 ± 1.45	0.05 ± 0.43	-0.07 ± 0.29	-0.19 ± 0.38	-0.17 ± 0.40	0.44
	Trans	2.56 ± 1.23	-0.01 ± 0.27	0.02 ± 0.29	-0.02 ± 0.35	-0.05 ± 0.58	
ΔHorizontal coma (Z_3^1)	Epi-off	0.94 ± 0.71	0.20 ± 0.30	0.08 ± 0.28	0.09 ± 0.22	0.06 ± 0.26	0.45
	Trans	0.86 ± 0.67	0.10 ± 0.19	0.00 ± 0.23	0.02 ± 0.18	0.03 ± 0.23	
ΔHorizontal trefoil (Z_3^3)	Epi-off	0.25 ± 0.18	-0.08 ± 0.17	-0.07 ± 0.22	-0.05 ± 0.22	0.05 ± 0.19	**0.04**
	Trans	0.19 ± 0.20	0.09 ± 0.28	0.04 ± 0.22	0.02 ± 0.18	0.11 ± 0.31	
ΔSpherical aberration (Z_4^0)	Epi-off	0.66 ± 0.63	0.16 ± 0.23	-0.09 ± 0.29	-0.07 ± 0.28	-0.05 ± 0.25	0.42
	Trans	0.56 ± 0.52	0.03 ± 0.12	0.01 ± 0.19	0.01 ± 0.21	0.05 ± 0.23	

Except when indicated otherwise, values are presented as a mean ± standard deviation. RMS= root mean square, LOAs= lower-order aberrations, HOAs= higher-order aberrations;*P*-values were calculated using the independent-samples *t* test. *Significant *P*-values (<0.05) are shown in bold.

Relationship between visual acuity and horizontal trefoil

Our analysis revealed that the difference in horizontal trefoil between the two treatment groups did not independently affect either UDVA (P=0.76) or CDVA (P=0.96). Similar results were obtained when we corrected for the change in LOAs (P=0.75 and P=0.84 for UDVA and CDVA, respectively).

DISCUSSION

Changes in higher-order aberrations do not differ between patients who undergo transepithelial CXL and patients who undergo epithelial-off CXL; only horizontal trefoil differed significantly between groups. Moreover, we found no independent relationship between the change in horizontal trefoil and visual acuity outcome. Therefore, we conclude that no clinically relevant differences exist between treatment groups with respect to the effect of treatment on HOAs.

A major strength of this study is our use of data obtained from a randomized clinical trial, which provided the best setting to compare treatment effects without confounding factors. In addition, all measurements and refractions were performed by one senior optometrist with extensive experience in keratoconus care. Moreover, the follow-up rate was high, with 57 out of 61 patients completing the follow-up course. In this study, we focused on the HOA subtypes that are most relevant to clinical practice (i.e., coma, trefoil, and spherical aberrations). We also performed our analyses using total corneal HOAs as well as anterior HOAs only, with nearly identical results. Finally, the clinical results of our RCT are consistent with other results comparing trans-CXL and epi-off CXL.[2,19,20]

One limitation of this study is the use of a Scheimpflug-based device—which calculates Zernike coefficients and HOAs based on anterior and posterior elevation maps—rather than using a wavefront device, which directly measures optical aberrations. Furthermore, in some cases optical aberrations within the eye (i.e., internal aberrations) can compensate for corneal aberrations, particularly in young patients.[14–16] Whole-eye optical aberrations were not measured during this RCT; however, repeated tomography measurements are considered suitable for identifying changes in corneal optical aberrations.[25] Another limitation of this study is that the RCT only tested high-contrast visual acuity. Previous studies found that low-contrast visual acuity testing can be more sensitive when measuring the effect of HOAs on visual acuity.[17,18] To the best of our knowledge, however, the effect of HOAs on low-contrast visual acuity following CXL has never been studied.

Vinciguerra et al.[21] and Caporossi et al.[22] reported that total HOAs and/or HOA subtypes improved following trans-CXL or epi-off CXL; however, neither group studied the relationship between HOAs and visual acuity. Studies by Greenstein et al.[23] and Ghanem et al.[24] found significant reductions in coma, spherical, and trefoil aberrations that were not correlated with an improvement in visual acuity. On the other hand, we previously reported that changes in horizontal coma have an effect on UCVA following epi-off CXL.[25]

Three RCTs studying trans-CXL versus epi-off CXL found significant improvement in visual acuity in the trans-CXL group.[11-13] This improvement in visual acuity could be related to the development of HOAs following trans-CXL; alternatively, it could be due to the reduced need for wound repair with trans-CXL compared to epi-off CXL. However, neither of these possibilities is supported by the results of our study. Therefore, the mechanism by which visual acuity improves following transepithelial CXL remains unclear. One possible explanation is that measured visual acuity may improve over time through a learning effect, with patients performing better simply because they have undergone these measurements previously. Alternatively, the refraction that is used to measure CDVA may become optimized over time, as the previous refraction is used as the starting point for the next refraction.

In conclusion, our randomized clinical trial detected no clinically relevant difference between patients who received trans-CXL and patients who received epi-off CXL for keratoconus with respect to the development of HOAs or the independent effect of HOAs on visual acuity. Specifically, only horizontal trefoil differed significantly between treatment groups, but did not affect visual acuity outcome in either group of patients. Based on these results, we suggest that HOAs need not be taken into consideration when determining whether transepithelial or epithelial-off CXL is more appropriate for treating progressive keratoconus.

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7

Higher-order aberrations one year after corneal crosslinking for keratoconus and their independent effect on visual acuity

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ABSTRACT

Purpose

To evaluate the effect of corneal crosslinking (CXL) in progressive keratoconus patients on higher-order aberrations (HOAs) and the effect of change in HOAs on visual acuity between baseline and one year after CXL.

Setting

Tertiary academic referral center, Utrecht, the Netherlands.

Design

Prospective cohort study.

Methods

This study included consecutive keratoconus patients who were treated with epithelium-off CXL and followed for a minimum of one year. The following corneal HOAs were reported as measured with Scheimpflug tomography (Pentacam HR type 70900): coma, trefoil, spherical aberration and total corneal HOAs. A two-tailed paired-samples *t* test was used to compare baseline and postoperative aberrations. A multivariable linear regression was applied to assess the independent effects of HOA subtypes on changes in uncorrected (UDVA) and corrected (CDVA) distance visual acuity.

Results

Overall, the degree of corneal HOAs in the patient cohort (N = 187) was relatively unchanged after CXL, with an average change of -1.34% (P=0.272). Horizontal coma contributed most to the total amount of HOAs, but was virtually unchanged on average. The HOA subtype spherical aberrations decrease significantly (-15,68%)(P<0.001). There was no effect of the change in HOAs on the change in CDVA, but there was a significant effect of the change in horizontal coma on the change in UDVA (P= 0.003; B -0.475).

Conclusions

Corneal HOAs in general were relatively unchanged from baseline one year after crosslinking for progressive keratoconus. A change in horizontal coma had a strong and independent effect on UDVA.

INTRODUCTION

Keratoconus is a progressive corneal disease in which an ongoing loss of stromal tissue leads to irregular astigmatism and reduced quality of vision.[1] In recent years, corneal crosslinking (CXL) has become an established treatment modality designed to increase the mechanical and biochemical strength of the stromal tissue.[2] The effectiveness of CXL stems from its potency to stabilize keratoconus and its effects on corneal curvature.[3] Specifically, crosslinking flattens the cone, which in turn increases both uncorrected (UDVA) and corrected (CDVA) distance visual acuity.[4–6] This flattening can persist for several years or longer.[7] Factors that can potentially predict treatment outcomes following CXL have been studied extensively.[5]

Corneal CXL is considered to be a safe, effective, and predictable treatment for the prevention of keratoconus progression. With respect to safety, adverse events occur in a minority of cases, with only a small risk of severe keratitis.[8] A transient demarcation line or subepithelial haze has been reported after CXL, although these are rarely observed one year after treatment. High visual acuity (CDVA >20/25) is not usually regarded as an exclusion criterion for performing corneal CXL.[2] This fact, combined with the favorable safety profile and increased availability of CXL, has led to an increase in the number of patients with high visual acuity who receive this treatment. The archetypal corneal curvature in keratoconus contributes to an increase in higher-order aberrations (HOAs) and subsequent decreased CDVA. Overall, visual acuity is reported to increase after crosslinking.[5] However, from a clinical perspective, it is important to assess whether acceptable levels of HOAs can be retained after CXL.

We examined the relationship between visual acuity, manifest refraction, and changes in HOAs one year after CXL performed to treat keratoconus. We also assessed whether HOA subtypes contribute independently to visual acuity outcomes or manifest refraction using multivariable modeling.

PATIENTS AND METHODS

Dataset and study design

Data were derived from an ongoing prospective treatment cohort of patients at our institution who had CXL for the treatment of progressive keratoconus. All consecutive patients who were treated at the University Medical Center Utrecht, Utrecht, from January 2010 through April 2013, with one year of follow-up were included. The study of HOAs in this treatment cohort was approved by the institution's Ethics Review Board, and the requirement for informed consent was waived.

The following inclusion criteria were applied: a progression of maximum keratometry (K) of more than 1.00 diopter (D) within 6 to 12 months and corneal thickness (at the thinnest point) of greater than 400 µm. The exclusion criteria included corneal scarring, the presence of a concurrent infection, and pregnancy, and lactation. Treatment effects were assessed at the one year follow-up visit. The detailed data collection and surgical procedure have been reported[7] and were adapted for this study.

Surgical procedure

An epithelium-off procedure was performed following the Dresden protocol.[9] The epithelium was removed with a blunt spatula. After instillation of isotonic riboflavin was instilled for 30 minutes, the cornea was exposed to a 3 mW/cm^2 ultraviolet (UV) light source (UV-X, Peschke Meditrade GmbH, Germany) equipped with a perpendicular emission plane and with a wavelength of 365 ± 10 nm (SD); the total exposure time was 30 minutes.

Data collection

Measurements included UDVA, CDVA, corneal tomography measured with Scheimflug tomography (Pentacam HR type 70900, Oculus GmbH), endothelial cell count with noncontact specular microscopy (SP-3000P, Topcon Europe Medical B.V.), and automated tonometry (CT-80, Topcon Europe Medical B.V.). If the tomogram failed to reach the 90% quality criterion it was repeated up to three times and the best scan was used for calculation of HOAs. The CDVA was measured using manifest refraction taken by the same optometrist (N.S.). The measurements were repeated one, three, six, and twelve months after CXL. All patients were requested to stop using their contact lenses two weeks before each evaluation.

Assessment of corneal optical aberrations

Corneal optical aberrations were calculated using the Pentacam Scheimpflug imaging software program based on the central 6.0 mm as determined by the corneal apex, of anterior and posterior elevation maps obtained using Scheimpflug imaging. The software program reports corneal optical aberrations for the anterior and posterior surfaces as well as for the total cornea. Total cornea optical aberrations were chosen as the outcome parameter. The Pentacam software then subdivides this outcome into the following two composite values: total corneal lower-order aberrations (LOAs), and total corneal HOAs. Normalized coefficients were used, expressed in microns of wavefront error (root mean square [RMS]), and labeled with International Organisation for Standardization (ISO) standardized

double-index Zernike symbols.[10] The HOAs were reported with their Zernike weight coefficient because the polynomial coefficient is considered invariant. Total corneal HOAs were calculated based on the 3rd- to 8th-order aberrations. The following HOA subtypes were reported in detail: horizontal coma Z(3,1), vertical coma Z(3,-3), horizontal trefoil Z(3,3) and vertical trefoil Z(3,3), and spherical aberration Z(4,0).

Statistical analysis

Visual acuity was converted to logMAR notation. The UDVA and CDVA were both used as outcome parameters. A two tailed paired-sample Student *t* test was used to determine significance between HOAs at baseline and one year after CXL. In cases with missing data at the one year follow-up, the six month follow-up data were entered, if available (i.e., the last measurement was carried forward). The baseline characteristics of the cases lost to follow-up were compared with all other cases in the cohort. Linearity of the baseline data and outcome measurements was determined visually in a scatter plot, normality was tested based on skewness, and kurtosis was based on a cut-off value of 3.29 (P<0.001). Mutual correlations between the different HOA subsets were calculated.

Univariate analyses with changes in UDVA and CDVA as dependent variables were performed for all baseline parameters to aid in identifying potential confounders for the relationship between changes in HOAs and changes in UDVA and CDVA. The following factors were determined to be potential confounders: visual acuity at baseline and the LOAs defocus Z(0,2)), horizontal astigmatism Z(2,2) and vertical astigmatism Z(2,-2). These factors were entered into the multivariable analysis. This analysis was performed using generalized estimating equations to correct for patients in whom both eyes were included in the dataset. Data collection and analyses were performed using SPSS softwear (version 21.0, International Business Machines Corp.). Patients who developed post-operative scarring, haze, or both were excluded from the HOA analysis because this this might reflect a pathophysiological mechanism other than a change in corneal curvature that affected visual acuity.

RESULTS

One hundred eighty-seven eyes of 162 patients were treated consecutively. Five of 187 eyes (2.6%; 3.1% of patients) were excluded from analysis they were lost to follow-up, and eight eyes (4.3%; 4.9% of patients) had the last follow-up measurement carried forward. The baseline characteristics of these thirteen

patients did not differ significantly from the main group; however, only patients with an affected right eye were lost to follow-up. Table 1 shows the patients' baseline characteristics.

Table 1. Patient characteristics at baseline and at one year.

	Mean ± SD				
	Baseline	1 year postop	*P* value*	Corr.	LTFU (%)
logMAR UDVA	0.81 ± 0.51	0.71 ± 0.52	0.002	.692	9
logMAR CDVA	0.33 ± 0.35	0.20 ± 0.29	<0.001	.562	3
Manifest refraction (D)					
Sphere	-0.75 ± 3.28	-0.11 ± 3.58	0.002	.689	3
Cylinder	-3.15 ± 2.20	-3.77 ± 2.41	<0.001	.516	3
Maximum keratometry (D)	58.6 ± 8.2	57.4 ± 8.1	<0.001	.950	3
Thinnest pachymetry (µm)	456 ± 42	448 ± 47	<0.001	.895	3
Astigmatism† (D)	4.12 ± 2.65	4.06 ± 2.59	0.493	.903	3

CDVA = corrected distance visual acuity; Corr. = correlation coefficient UDVA; CXL = collagen crosslinking; LTFU: lost to follow-up; UDVA = uncorrected distance visual acuity
**Paired-samples *t* test with missings excluded pairwise*
†Corneal astigmatism power reported by Scheimpflug tomography

Clinical outcomes

By the one year follow-up visit, maximum K value had decreased or was unchanged in 164 of 187 eyes. In 16 eyes, the keratoconus progressed by more than 1.00 D, with a mean increase in K_{max} of 2.6 ± 2.0D (range: 1.0 to 9.40 D). The improvement in UDVA and CDVA from baseline to the one year follow-up was statistically significant (*P*=0.002 and *P*<0.001, respectively). At one year, the logMAR UDVA was better (mean improvement 0.25 ±0.29) in 92 (49%) of 187 eyes, remained stable (within ±0.03) in 41 eyes (22%), and was worse (mean decrease 0.32 ±0.24) in 54 eyes (29%). The logMAR CDVA was better in 120 (64%) of 187 eyes, remained stable (within ± 0.03) in 32 eyes (17%), and was worse (mean decrease 0.20 ±0.22) in 35 eyes (19%).

The cylinder value obtained using manifest refraction increased significantly (mean increase 0.62 D)(*P* < 0.001), whereas the corneal astigmatism obtained using tomography remained virtually stable (mean -0.06D)(*P*=0.493). The endothelial cell density (ECD) was unchanged from baseline; the mean ECD at the one year follow-up was 2526 SD±366 cells/mm^2, with no apparent clinical signs of endothelial dysfunction. At the one year follow-up, 16 eyes had a slight, albeit persistent, haze. The baseline characteristics of this subgroup did not differ significantly from those in the main group, with the exception of CDVA, which was worse in the eyes with haze (0.52 logMAR versus 0.31 logMAR)(*P*=0.026); in 14 of these 16 eyes with persistent haze, preexisting striae were noted. The mean

CDVA at follow-up was also significantly worse in this subgroup (0.37 logMAR versus 0.17 logMAR)(*P*=0.011). These 16 eyes were excluded from further HOA analysis. None of the patients in the cohort developed infectious keratitis.

Change in higher-order aberrations

Table 2 shows the absolute values for optical aberrations at baseline and one year after CXL as well as the percentage of change. Total LOAs significantly decreased after CXL (*P*<0.001). However, total HOAs did not (*P*=0.272), although the HOA subtype of spherical aberration did decrease significantly (P<0.001). The effect size of this decrease was relatively small. Vertical coma HOAs contributed the most to the total corneal HOAs; however, this subtype did not change significantly after treatment. Univariate confounder analysis of CDVA identified baseline spherical refraction (*P*=0.037, B=0.12), maximum K (*P*=0.004, B=-0.009), baseline logMAR UDVA (*P*=0.034; B -0.102), and baseline logMAR CDVA (*P*<0.001, B=0.748) significantly associated with the dependent variable. Based on the effect size, only pre-treatment CDVA was considered a relevant confounder. Next for UDVA, baseline logMAR UDVA was the only parameter significantly associated (*P*=0.003, B=0.257) and considered relevant. An analysis of mutual correlations for each HOA subtype revealed a significant correlation for horizontal coma Z(1,3) and vertical coma Z(3,-1)(*P*=0.009, ρ=-0.204), horizontal trefoil Z(3,3) and vertical trefoil Z(3,-3) (*P*= 0.006, ρ=0.213), and vertical coma and vertical trefoil (*P*=0.001, ρ=0.264).

Table 2. Changes in corneal optical aberrations one year after crosslinking (n = 166*).

	Mean ± SD				
	Baseline	1 year postop	Change (%)	*P* value†	Corr.
Compound variables (RMS)					
Total corneal aberrations	5.751 ± 2.994	5.378 ± 2.886	-6.49	<0.001	0.934
Corneal LOAs	5.601 ± 2.939	5.221 ± 2.824	-6.78	<0.001	0.932
Corneal HOAs	1.268 ± 0.647	1.251 ± 0.665	-1.34	0.272	0.955
HOA subtypes					
Horizontal coma	-0.888 ± 0.562	-0.888 ± 0.621	0.00	0.995	0.950
Vertical coma	-0.082 ± 0.488	0.001 ± 0.483	-101.22	0.465	0.950
Horizontal trefoil	0.048 ± 0.176	0.061 ± 0.166	27.08	0.374	0.444
Vertical trefoil	0.017 ± 0.148	-0.007 ± 0.159	-141.18	0.101	0.291
Spherical aberration	-0.370 ± 0.416	-0.312 ± 0.418	-15.68	<0.001	0.911

CXL = collagen crosslinking; HOAs = higher-order aberrations; LOA = lower order aberrations . RMS = Root Mean Square
*Eyes with postoperative haze excluded from analysis
†Paired samples *t* test

Multivariable analysis

Table 3 shows the results of the multivariable analysis of CDVA and UDVA. The calculated effects of the potential confounders (visual acuity and LOAs at baseline) and the HOA subtypes are given for both determinants. No independent relationship between any HOA variable and change in CDVA was observed. The putative confounder CDVA at baseline was indeed strongly related to the change in CDVA. An independent effect of the change in horizontal coma was observed on the change of UDVA (*P*= 0.003, B=-0.475), and again UDVA at baseline was strongly related to this changes.

Table 3. Multivariable analysis of the effect of a change in optical aberrations on CDVA and UDVA one year after crosslinking (n=166).

	B coefficient	95% CI	*P* value
CDVA			
Confounding factors at baseline			
CDVA	-0.575	-0.724 to -0.426	<0.001*
Defocus	0.000	-0.050 to 0.049	0.993
Horizontal Astigmatism	-0.091	-0.223 to 0.042	0.180
Vertical Astigmatism	0.051	-0.068 to 0.171	0.398
HOA subtypes			
Δ Horizontal coma	0.032	-0.195 to 0.130	0.698
Δ Vertical coma	-0.095	-0.378 to 0.188	0.511
Δ Horizontal trefoil	0.068	-0.215 to 0.351	0.638
Δ Vertical trefoil	-0.093	-0.318 to 0.132	0.416
Δ Spherical aberration	-0.084	-0.442 to 0.275	0.647
UDVA			
Confounding factors at baseline			
UDVA	-0.315	-0.432 to -0.198	<0.001*
Defocus	0.062	0.010 to 0.115	0.020
Horizontal Astigmatism	-0.081	-0.217 to 0.056	0.247
Vertical Astigmatism	-0.011	-0.278 to 0.257	0.937
HOA subtypes			
Δ Horizontal coma	-0.475	-0.787 to -0.163	0.003*
Δ Vertical coma	0.205	-0.273 to 0.684	0.400
Δ Horizontal trefoil	0.044	-0.230 to 0.318	0.753
Δ Vertical trefoil	-0.060	-0.423 to 0.303	0.746
Δ Spherical aberration	-0.346	-0.909 to 0.217	0.228

Δ = changes in variable after crosslinking; CDVA = corrected distance visual acuity; CI = confidence interval; HOA = higher-order aberrations; RMS = Root Mean Square; UDVA = uncorrected distance visual acuity
*Statistically significant

DISCUSSION

The principal aim of this study was to report on HOAs one year after corneal CXL to treat keratoconus and to determine whether variations in HOAs are independently associated with a change in CDVA. On average, with the exception of spherical aberration HOAs, the HOAs were largely unchanged after treatment. Multivariable analysis found no independent effect of any HOA subtype on change in CDVA after CXL. However, changes in horizontal coma were significantly and strongly associated with the postoperative change in UDVA. Strikingly, the measured corneal astigmatism did not change (mean 4.12 D versus 4.06 D); however, the manifest refraction increased and became more in agreement with the topographical cylinder (mean -3.15 D versus -3.77 D)($P < 0.001$).

A major strength of this prospective study is the inclusion of a relatively large treatment cohort (187 eyes from 162 patients), with few cases lost to follow-up (approximately 3% of patients). The intervention was standardized in accordance with current protocols and did not change throughout the course of study. All patients had epithelium-off crosslinking with non-accelerated UVA irradiation, and all refractions were measured by an optometrist experienced in keratoconus care. Moreover, the treatment outcomes (i.e., improvement in keratometry, UDVA, and CDVA) are consistent with recent published literature.[7,11,12] Furthermore, we focused on the HOA subtypes that are most relevant to clinical practice (i.e., coma, trefoil, and spherical aberration), and the effect of more complex forms of optical aberrations were assessed via the compound HOA variable. The Pentacam Scheimpflug tomography software program calculates the total corneal HOA based on anterior and posterior elevation maps. We therefore chose to measure these composite HOAs because individual anterior and posterior outcomes are less relevant from a patient-oriented perspective.

On the other hand, several features of our study and analysis may have affected the results. First, we used the Pentacam Scheimpflug tomography software program, which calculates/expands optical aberrations, rather than using an aberrometer, which measures optical aberrations. A wavefront device was not used in this study and we are unable to determine whole eye HOAs. Furthermore, internal optical aberrations can potentially compensate for aberrations that are attributable to the anterior segment; however, a previous study reported that these internal optical aberrations are relatively unchanged after corneal treatment.[13] Our study design could be considered suitable to detect changes in corneal HOAs after treatment, rather than measuring whole-eye HOAs. The Pentacam Scheimpflug tomography is considered a reliable instrument to assess corneal shape with good repeatability and reproducibility[14–17], although

recent studies debate its reproducibility with regards to the HOA assessment. A second consideration is that we excluded from our analyses cases with an apparent corneal haze. Corneal haze can, at least in principle, affect optical aberrations without changing the corneal curvature (or the resulting elevation maps). Although the Pentacam can perform densitometry measurements, these measurements are not used to calculate corneal HOAs.[18] A corneal haze might have influenced the edge-detection software; however, this likely had little effect because all of the Scheimpflug images used in this study were of sufficient quality.

Previous reports of post-CXL HOAs point towards a general decrease in ocular HOAs. For example, Greenstein et al. reported a significant decrease in corneal coma HOAs based on anterior and posterior elevation maps.[19] The authors also found no significant correlation between HOAs and the change in visual acuity, although their analysis was based on only 31 keratoconus eyes. In 2009, Vinciguerra et al. reported a significant decrease in total ocular HOAs, coma HOAs, and spherical aberrations in 28 eyes.[20] In a more recent study using a larger cohort (n=92), the same group reported a decrease in total HOAs and coma HOAs, but not in spherical aberrations.[6] They did not, however, examine the correlation between HOAs and treatment outcome. The authors used absolute values to calculate the change in HOAs, thus accounting for shifts from negative to positive HOAs. Here, we chose to report the outcomes as they were supplied by the Pentacam tomographer. Analyses were performed based on absolute values and did not materially alter our findings (data not shown). Ghanem et al. reported both 12-month and 24-month follow-up measurements in 42 eyes. Both coma and trefoil showed a solid decline, possibly resembling continued corneal flattening, although spherical aberration did not change materially from baseline. No correlations were found in changes of individual corneal aberrations and visual acuity after CXL.[21] Baumeister et al. reported no significant change in HOAs at the 6-month follow-up visit (n=20).[22] This finding is more consistent with our finding that, with the exception of spherical aberration, no relevant change in corneal HOAs was observed. We used ISO standard double-indexed Zernike polynomials in an effort to present our findings unambiguously.

Previous experimental research showed that the individual Zernike polynomials have a different impact on visual function; spherical aberration RMS error contributes more than coma, which in turn contributes more than trefoil.[23,24] Our results do not repeat those findings because horizontal coma had the strongest relationship with changes in UDVA in our multivariable analysis. Naturally, keratoconus eyes have a different distribution of HOAs than healthy eyes, and decentered cones in particular might induce high amounts of coma.

The inconsistency in our data of changes in astigmatism obtained using manifest refraction and corneal tomography deserves attention. On average, manifest cylinder measurements increased whereas topographic derived corneal astigmatism did not. This effect could partly be attributable to the inability to correct for HOAs using spectacles. A wrong amount of astigmatic correction can be measured when the cylinder axis is placed on top of the coma because the patients perceives a slight improvement. We hypothesize that an increased visual acuity leads to an improved quality of manifest refraction, whereas the better perception of coma partly translates to a higher manifest refraction. The discrepancy of the independent effect of horizontal coma in UDVA versus CDVA might reflect this. Without spectacle correction, horizontal coma is a strong independent factor for visual acuity; however, after a manifest refraction, this effect diminishes (on average). We hypothesize that horizontal coma is coincidentally corrected by increasing the cylinder power, meaning that it lost its independent effect on visual acuity. On the other hand, one can debate whether the Pentacam Scheimpflug tdevice is the best tool to detect these subtleties in corneal tomography.

Determining the true effects of CXL requires seperating many interrelated variables.[5] The continuous flattening of the cone is a structural parameter that can affect HOAs, and the possible migration of the cone apex can result in reduced cone eccentricity.[7,25] Changes in corneal collagen fibril composition and/or the development of corneal haze can exert effects on both contrast sensitivity and HOAs.[18] We therefore used a structured approach to identify potential confounders regarding the role of measured HOAs on changes in visual acuity, and we assessed the independent contribution of each HOA subtype on the treatment outcomes. Future studies should perform wavefront analyses in addition to Scheimpflug tomograper-calculated aberrations to better discernthe effect of CXL on whole-eye HOAs.

In conclusion, on average, HOAs are essentially unchanged one year after corneal CXL to treat progressive keratoconus when assessed using Scheimpflug imaging. Only changes in horizontal coma had a strong and independent effect on uncorrected visual acuity.

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8

A multivariate analysis and statistical model for predicting visual acuity and keratometry one year after crosslinking for keratoconus

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ABSTRACT

Purpose

To investigate putative prognostic factors for predicting visual acuity and keratometry 1 year following corneal crosslinking (CXL) for treating keratoconus.

Design

Prospective cohort study.

Methods

This study included all consecutively treated keratoconus patients (102 eyes) in 1 academic treatment centre, with minimal 1-year follow-up following CXL. Primary treatment outcomes were corrected distance visual acuity (logMAR CDVA) and maximum keratometry (Kmax). Univariable analyses were performed to determine correlations between baseline parameters and follow-up measurements. Correlating factors (P<0.20) were then entered into a multivariable linear regression analysis, and a model for predicting CDVA and Kmax was created.

Results

Atopic constitution, positive family history, and smoking were not independent factors affecting CXL outcomes. Multivariable analysis identified cone eccentricity as a major factor for predicting Kmax outcome (ß-coefficient = 0.709, P= 0.02), whereas age, gender and baseline keratometry were not independent contributors. Post-treatment visual acuity could be predicted based on pre-treatment visual acuity (ß-coefficient= -0.621, P <0.01, R2 =0.45). Specifically, a low visual acuity predicts visual improvement. A prediction model for Kmax did not accurately estimate treatment outcomes (R2 =0.15).

Conclusions

Our results confirm the role of cone eccentricity with respect to the improvement of corneal curvature following CXL. Visual acuity outcome can be predicted accurately based on pre-treatment visual acuity. Age, gender and Kmax are debated as independent factors for predicting the outcome of treating keratoconus with CXL.

INTRODUCTION

Keratoconus is a progressive non inflammatory disease, in which the cornea becomes thinner, inducing irregular astigmatism and reducing quality of vision.[1] Corneal crosslinking (CXL) is a relatively new treatment designed to increase the mechanical and biochemical strength of the stromal tissue, by exposing the ectatic cornea to riboflavin and ultraviolet-A light.[2,3] When successful, CXL prevents the progression of keratoconus and can even cause the ectatic cornea to regress.[4] This stabilization of the keratoconus can prevent the future need for a corneal graft.[5] The clinical outcome following CXL with respect to visual acuity is generally positive, although loss of visual acuity can occur as a complication of the procedure.[6] In addition, CXL can affect the healthy endothelium, and treatment safety guidelines have been proposed to prevent this.[7,8] Importantly, the clinical benefits of CXL can vary among patients; indeed, nearly every clinician has encountered patients whose keratoconus proceeds seemingly unhampered despite CXL treatment. Therefore, the ability to reliably predict of the outcome of performing CXL prior to the procedure will help clinicians manage their patients' expectations and minimize the exposure to potential side-effects.

The etiology of keratoconus has been studied extensively, and factors associated with keratoconus include a positive family history,[9] an atopic constitution,[10] eye rubbing,[1,11] contact lens use[12] and a myriad of syndromes such as Down,[13] chromosome 7,11 translocation[14] and chromosome 13 ring abnormality.[15] However, whether these factors also play a role in the effectiveness and consequences of CXL treatment has not been established yet. Our understanding of the factors that are related with CXL treatment success is beginning to emerge. Achieving treatment success is based on a combination of clinical features, including post-operative visual acuity, improved keratometry, and the absence of adverse events. A systematic literature search to identify putative prognostic factors revealed that pre-operative visual acuity, eccentricity of the cone, pre-treatment maximum keratometry (Kmax), age above 35 years and gender are all predictors of CXL efficacy and safety.[16,17]

For example, Greenstein et al. reported that males and patients with a central cone location seem to benefit more from CXL treatment in terms of Kmax regression. However, whether a high Kmax prior to treatment affects Kmax regression is controversial.[18] Lamy et al. addressed post-CXL visual acuity outcomes and found that central cone location, visual acuity ≤20/25 and age ≤35 years predicted higher corrected distance visual acuity (CDVA) one year after treatment.[19] In addition, Spoerl et al. reported a negative association between smoking and keratoconus,[20] and Hafezi et al. suggested that this might be

explained by biomechanical changes that can occur in the cornea as a result of smoking.[21] Moreover, Altinors et al. reported that smoking can cause deterioration of the lipid layer in the pre-corneal tear film.[22] Therefore, smoking can affect the treatment outcome, particularly when CXL is performed in the presence of a corneal abrasion.

Here, we investigated the value of the aforementioned factors in predicting CXL treatment effectiveness in keratoconus patients. In addition we assessed additional putative prognostic factors such as family history, atopic constitution and smoking. By combining these factors, we attempted to create a prediction model, that can assist clinicians in therapeutic decision making.

MATERIALS AND METHODS

Data set and study design

The data were obtained from a cohort of patients with progressive keratoconus who received CXL treatment in our institution. We recruited all patients who were treated consecutively at the University Medical Center Utrecht, from January 2010 through December 2010, followed by follow-up visit after one year. The inclusion criteria included a progression of Kmax≥1.0 D within 6-12 months, and corneal thickness ≥400μm (at the thinnest point). The exclusion criteria included corneal scarring, the concurrent presence of an infection, pregnancy, and/or lactation. The treatment effects were assessed at the one year follow-up visit. This study for predictor research was approved by the University Medical Center Utrecht Ethics Review Board, and the requirement for informed consent was waived. The treatment of the patient cohort was in accordance with the Declaration of Helsinki and local laws regarding research using human subjects.

Surgical procedure

The surgical procedure was performed as described previously4,23 A 9mm corneal abrasion was made using a blunt knife, after which a 0.1% solution of riboflavin (Peschke Meditrade GmbH) was applied every 3 minutes for 30 minutes. When corneal pachymetry was less than 400 μm, hypo-osmotic riboflavin was applied every 20 seconds for 5 minutes and repeated up to two times until adequate thickness (ie, ≥400 μm) was achieved. The cornea was exposed to a UV light source (UV-X, Peschke Meditrade GmbH, using a perpendicular emission plane) with a wavelength of 365 ± 10 nm for a total cumulative exposure time of 30 minutes. Riboflavin drops were instilled every 5 minutes during the UV irradiation. Following the treatment, a bandage lens (PureVision®, Bausch + Lomb Nederland BV) was placed. Post-

operative medication included nepafenac 0.1% drops (Nevanac®, Alcon Nederland BV) TID for one week, moxifloxacine 0.5% drops (Vigamox®, Alcon Nederland BV) TID for one month, and dextran/hypromellose drops (Duratears®, Alcon Nederland BV) TID for one month. When the epithelium was healed the bandage contact lens was removed and fluormetholon 0.1% drops (FML Liquifilm®, Allergan BV) BID were applied.

Data collection

Standardized pre-operative assessment yielded a series of potential predictive factors. These measurements included uncorrected distance visual acuity (UDVA), corrected distance visual acuity (CDVA, obtained using manifest refraction), corneal tomography (Pentacam HR type 70900, Oculus), endothelial cell count (SP-3000P, Topcon), and automated tonometry (CT-80, Topcon). These measurements were repeated post-operatively at one, three, six, and twelve months. All patients were instructed to stop wearing their contact lenses 2 weeks before each evaluation.

Patients histories were obtained using standardized forms and included their family history, atopic constitution, and smoking status. Family history for keratoconus was obtained to fourth-degree relatives (i.e. nephews/nieces), and was defined as positive in the case of a first- or second-degree relative with keratoconus. An atopic constitution was defined as having asthma, hay fever, eczema, food allergies, and/or anti-allergy medication usage. Smoking status included current smoking status or smoking in the personal history, and the number of pack-years was noted. Any missing data in the medical files were obtained by consulting with the patients by phone or mail.

Statistical analysis

Visual acuity was converted to the logMAR of visual acuity. The following two primary outcomes were defined: 1) differences in visual acuity (logMAR CDVA) between baseline and at one-year follow-up visit, and 2) differences in Kmax between baseline and at the one-year follow-up visit. The paired-samples student's t-tests was used to analyze the differences between Kmax and logMAR CDVA at baseline and one year after treatment. Missing measurements were excluded pair wise from the analysis.

Linearity of the baseline data and outcome measurements was determined visually in a histogram. Normality was tested based on skewness and kurtosis with a cut-off value of 3.29 ($P<0.001$) and showed no deviations. The pre-treatment measurements and potential prognostic factors (atopic constitution, family history, smoking habits, factors derived from a literature review, and pre-operative measurements) were included in a univariate analysis. Pearson's correlation

coefficients were determined between the potential prognostic variables and the primary outcomes. The ß-coefficient represents how a dependent variable will change, per unit increase in the predictor variable and has both a magnitude and a positive or negative direction; for example, a ß-coefficient of +2 for age indicates that for every year a subject ages, the dependent variable will increase by 2 units.

To determine the independent relationship between potential prognostic factors and the outcome, a multivariable linear regression model was built. This model initially included all variables with $P \leq 0.20$ in the univariate analysis. This analysis was performed with generalized estimating equations, correcting for patients who included both eyes in the data-set. A prediction model was created by performing stepwise backward selection of the least-contributing variables. These variables were removed until the quasi-likelihood ratio began to deteriorate. Internal model validity was tested by plotting the predicted value of the linear predictor against the measured differences after one year and then calculating the linear coefficient between the predicted and measured outcome values (R2). A likelihood ratio test was performed after a squared term was included in the regression model. The data were collected and analyzed using SPSS 20.0 (IBM SPSS statistics).

RESULTS

Dataset characteristics

One-hundred-and-two eyes of 79 patients were treated consecutively. Six eyes (of four patients) were excluded from the analysis because the patients were lost to follow-up (=5%); the baseline characteristics of these patients did not differ significantly from the remaining patient group. The baseline characteristics are presented in Table 1. At the one-year follow-up visit, Kmax decreased or stabilized in 85 of 96 eyes (88.5%). In the remaining 11 eyes, the keratoconus progressed by >1.0D, with a mean increase in Kmax of 2.6D (range 1.3-5.2).

Clinical outcomes

Both primary outcomes improved significantly at the one-year follow-up compared to baseline. Mean Kmax decreased by 1.3 D from 60.1 to 58.7 ($P<0.01$) and mean logMAR CDVA decreased by 0.13 from 0.33 to 0.19 ($P<0.01$). These values are based on the 96 included eyes. Endothelial cell density was unchanged with a mean cell density at follow-up of 2831±309 cells/mm^2, with one case showing a decline of more than 10% (to 2584 cells/mm^2). One month after treatment, a mild post-operative haze occurred and then largely resolved in 22 eyes; at one year three of these eyes still had a slight yet persistent haze. The epithelium was healed within

one week, within two weeks, and after two weeks in 80.5%, in 16.1%, and in 3.4% of eyes, respectively. None of the patients developed nfectious keratitis.

Table 1. Baseline table. Characteristics of 102 eyes of 79 keratoconus patients

	mean / n	range / %	missing
Age (years)	23	12 to 50	0
Male	56	71%	0
Right eye	43	42%	0
Kmax (D)	59.5	44.8 to 82.2	0
Snellen CDVA	20/32	20/400 to 20/16	0
logMAR CDVA	0.31	-0.08 to 1.30	0
ECD (cells/mm^2)	2744	1900 to 3347	32*
Positive family history	8	10%	2
First degree	3	4%	2
Second degree	7	9%	2
Third degree	0	0%	2
Fourth degree	2	3%	2
Atopic constitution	34	43%	2
Asthma	14	18%	2
Eczema	20	20%	2
Hay fever	28	35%	2
Food allergy	10	13%	2
Anti-allergic medication	25	32%	2
Smokers	11	14%	3
Average pack-years	0.5	0.25 to 7	3

CDVA = corrected distance visual acuity; ECD = endothelial cell density; Kmax = maximum keratometry; logMAR = logarithm of minimal angle of resolution. Lost to follow-up: 6 eyes (6%) in 4 patients (5%).
**In severe keratoconus endothelial densitieswere not attainable.*

Univariate analysis

All putative predictors were univariate correlated with both primary outcomes. Table 2 provides an overview of the predictors that were assessed. Notable predictors include higher improvement in Kmax in males then in females (ß-coefficient: 1.222, $CI_{95\%}$0.272;2.172, P=0.01) and a slight yet significant decrease in improvement in visual acuity in atopic patients (ß-coefficient: 0.121, $CI_{95\%}$ 0.010;0.232, P=0.03). Neither a family history of keratoconus nor smoking influenced the treatment outcomes. The significant univariate associations were entered in the multivariable analysis.

Table 2. Univariate factor analysis of baseline characteristics for corneal crosslinking effects at one year follow-up in keratoconus eyes.

	Changes in CDVA (logMAR)			Changes in maximum keratometry		
	ß-coefficient[a]	95% CI	P-value	ß-coefficient[a]	95% CI	P-value
Age (years)	0.001	-0.006 to 0.008	0.77	0.044	-0.130 to 0.102	0.13
Male gender	0.041	-0.079 to 0.162	0.50	1.222	0.272 to 2.172	0.01*
Positive family history	0.003	-0.168 to 0.173	0.97	0.693	-0.689 to 2.075	0.32
Atopic constitution	0.121	0.010 to 0.232	0.03*	0.246	-0.679 to 1.171	0.60
Smoking	-0.047	-0.203 to 0.109	0.54	-0.417	-1.688 to 0.854	0.52
Spherical equivalent (D)	-0.002	-0.018 to 0.013	0.99	0.104	-0.022 to 0.230	0.12
LogMAR UDVA pre-treatment	-0.180	-0.290 to -0.070	<0.01*	-0.871	-1.791 to 0.049	0.06
LogMAR CDVA pre-treatment	-0.523	-0.641 to -0.405	<0.01*	-0.771	-2.062 to 0.520	0.24
Kmax pre-treatment (D)	-0.009	-0.016 to -0.003	<0.01*	-0.039	-0.091 to 0.014	0.14
Eccentricity (mm)	0.098	0.029 to 0.168	<0.01*	0.957	0.400 to 1.151	<0.01[b]
Central corneal thickness (µm)	0.001	0.000 to 0.003	0.04*	0.011	0.001 to 0.023	0.04[b]

CDVA = corrected distance visual acuity; CI = confidence interval; D = diopter; Kmax = maximum keratometry; LogMAR = logarithm of minimal angle of resolution; UDVA = uncorrected distance visual acuity. Statistical analysis using univariate linear regression.

[a]*ß coefficient is a value referring to how a dependent variable will change, per unit increase in the predictor variable.*

[b]*Significant P values; significance set at <0.05. P values <0.20 were included in multivariate analysis.*

Multivariable regression analysis and prognostic models

Next, we performed a multivariable linear regression analysis for both primary outcomes. The results of this analysis are shown in Table 3. With respect to visual acuity outcome, only the pre-treatment logMAR CDVA was an independent factor (ß- coefficient: -0.621, CI95%-0.995;-0.247, P<0.01);specifically, a higher pre-treatment logMAR was associated with a lower logMAR at the one-year follow-up visit. Similar results were obtained for cone eccentricity with respect to Kmax outcome (ß- coefficient: 0.709, CI95% 0.117;1.301, P=0.02); having a more eccentric cone pre-treatment was associated with less flattening of Kmax at the one-year follow-up visit. All other parameters that were assessed in this multivariable analysis, including atopic constitution, did not appear to have an individual effect on treatment outcome.

Table 3. Multivariable predictor analysis of selected baseline characteristics for corneal crosslinking effects at one year follow-up in keratoconus eyes.

Changes in CDVA (logMAR)			
	ß-coefficient[a]	95% CI	P-value
Atopic constitution	-0.052	-0.122 to 0.018	0.14
logMAR UDVA	0.067	-0.083 to 0.217	0.38
logMAR CDVA	-0.621	-0.995 to -0.247	<0.01[b]
Kmax (D)	0.005	-0.002 to 0.011	0.14
Eccentricty (mm)	0.018	-0.045 to 0.080	0.58
Central corneal thickness (µm)	0.000	-0.001 to 0.001	0.61
Changes in maximum keratometry			
	ß-coefficient[a]	95% CI	P-value
Male gender	0.823	-0.277 to 1.932	0.14
Spherical equivalent (D)	0.103	-0.045 to 0.251	0.17
logMAR UDVA	-0.017	-1.105 to 1.071	0.98
Kmax (D)	-0.009	-0.068 to 0.050	0.77
Eccentricty (mm)	0.709	0.117 to 1.301	0.02[b]
Central corneal thickness (µm)	0.001	-0.010 to 0.012	0.84

CDVA = corrected distance visual acuity; CI = confidence interval; D = diopter; Kmax = maximum keratometry; LogMAR = logarithm of minimal angle of resolution; UDVA = uncorrected distance visual acuity.
Statistical analysis using multivariable linear regression.
[a]*ß coefficient is a value referring to how a dependent variable will change, per unit increase in the predictor variable.*
[b]*Significant P values; significance set at <0.05.*

Next, we created prediction models for both primary outcome parameters. Preoperative logMAR CDVA was the strongest individual predictor of visual acuity at the one-year follow-up. The correlation between predicted and measured outcomes was high with an R2 for the model fit of 0.45, indicating robust predictive value. Adding a squared term did not increase model fit. The statistical prediction model for visual acuity yielded the following equation:

LogMAR CDVA after CXL = (-0.518 x Baseline logMAR CDVA) + 0.043.

Figure 1 shows a scatter plot with the observed values plotted against the predicted values. Low pre-treatment logMAR CDVA is a predictor of visual improvement following treatment, whereas high pre-treatment logMAR CDVA generally decreases following treatment. The details of this relationship are presented in Table 4.

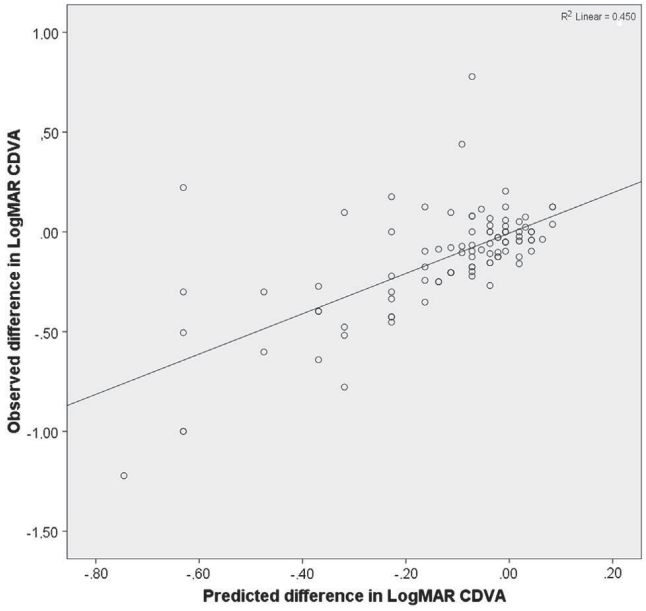

Figure 1: The observed logMAR Corrected Distance Visual Acuity values are plotted against the predicted outcomes after corneal crosslinking for keratoconus. The solid line is a linear fit of the data.

A model consisting of cone-eccentricity, pre-operative spherical equivalent and gender best predicted keratometry at one-year follow-up. However, the correlation between predicted and measured outcomes was poor with an R^2 for model fit of 0.15, indicating low predictive value.

Table 4. Predicted visual acuity after crosslinking treatment at one year follow-up in keratoconus eyes, based on baseline visual acuity.

Baseline Snellen CDVA	Baseline logMAR CDVA	Calculated change in logMAR CDVA[a]	Predicted logMAR CDVA	Predicted Snellen CDVA
20/16	-0.097	0.084	0.005	20/20
20/20	0.000	0.043	0.043	20/22
20/25	0.097	-0.007	0.090	20/25
20/32	0.222	-0.072	0.150	20/28
20/40	0.301	-0.113	0.188	20/31
20/50	0.398	-0.163	0.235	20/34
20/100	0.699	-0.319	0.380	20/48
20/125	0.796	-0.369	0.427	20/53
20/400	1.301	-0.631	0.670	20/94

CDVA = corrected distance visual acuity; LogMAR = logarithm of minimal angle of resolution.
[a]The statistical prediction model for visual acuity led to the following equation: change in logMAR CDVA = - 0.518 x baseline logMAR CDVA + 0.043.

DISCUSSION

The principal aim of this study was to investigate whether atopic constitution, family history and/or smoking are predictive factors of visual acuity and keratometry one year after CXL treatment in patients with keratoconus. Patients with an atopic constitution had less improvement with respect to visual acuity after CXL (P=0.03). On the other hand, smoking and a positive family history did not seem to affect the treatment outcomes. These novel results provide new insights into the pathogenesis of keratoconus following corneal crosslinking. However, because these outcomes were assessed primarily using a univariate analysis, the results should be interpreted with caution, as many potential predictors are interrelated due to crosstalk between atopic constitution and visual acuity.

This study provides a multivariable analysis of factors that predict the effect of treating keratoconus patients with CXL. Due to the high interrelationship between many prognostic factors, only a limited number of distinct predictive factors remain. The factors that we assessed (such as atopic constitution, family history and smoking) were not significantly correlated with treatment outcomes in our multivariable analysis. The results with respect to smoking was an unexpected outcome, particularly since Hafezi et al. reported that smoking causes the cornea to stiffen, which would likely affect the outcome of CXL treatment.[21] However, the patients in our study were considerably younger (23 vs. 44 years, respectively), and did not smoke as many pack years (0.5 vs. 10 pack years).

With respect to visual acuity at the one-year follow-up, the only independent predictor identified was the pre-treatment logMAR visual acuity with a ß-coefficient of -0.621 ($CI_{95\%}$-0.995;-0.247, P P<0.01); thus, having a lower visual acuity at baseline leads to improved visual acuity after treatment. In our univariate analysis, cone eccentricity was also associated with visual acuity at follow-up; however this effect was not significant in the multivariable analysis. This results could be explained by the fact that eyes with an eccentric cone had a better visual acuity at baseline (data not shown), indicating an interrelationship between cone location and visual acuity.

Cone eccentricity was the sole predictor of keratometry outcomes at the one-year follow-up, with a ß-coefficient of 0.709 ($CI_{95\%}$ 0.117;1.301 P=0.03). Thus, a more eccentric cone is associated with higher keratometry one-year after CXL treatment. No other factors remained significantly associated with either visual acuity or keratometry in our multivariable analysis. A role for cone eccentricity has been suggested previously,[18] and may be explained by the fact that we used a flat, perpendicular emission plane for delivering the UV light. Because of the oblique incident angle of UV light rays, the peripheral cornea is exposed to less

intense UV light compared to the central part.[24] Alternatively, the biomechanical effect of CXL tends to make the cornea more symmetrical, causing a peripheral cone to migrate to a more central location. Both of these possibilities were addressed previously by Greenstein et al.[18]

Higher age is considered to be a prognostic factor for the development of keratoconus.[25] Although, the likelihood of progression is lower among older individuals, the progression of ectatic disorders at higher age has been reported.[26] The role of age as a predictor for the effectiveness of crosslinking is not supported by our study results, as our multivariable analyses did not suggest that age is an independent factor. All of our patients had a topographic progression of >1D prior to treatment, irrespective of age. Moreover, a subgroup analysis of our patients over 35 years of age showed the same crosslinking effectiveness as the full cohort (data not shown).

The final goal of this study was to create prediction models to assist the ophthalmologist in clinical decision-making. In this respect, we succeeded for visual acuity, with an R^2 of 0.45. Our model shows that pre-treatment CDVA can be used to reliably predict CDVA one year after treatment. Specifically, patients with a low pre-treatment CDVA are likely to have an improvement in corrected distance visual acuity following treatment. On the other hand, in patients with a Snellen CDVA of 20/25 and better, this effect diminishes and may even reverse. The proposed prediction model for keratometry did not yield accurate estimates based on pre-treatment parameters.

The primary strength of our study is in the completion of data gathered by standardized examinations nearly exclusively by one trained optometrist (NS). Another strength of our study is the low percentage of patients who were lost to follow-up, meaning that our results are unlikely affected by for attrition bias. Moreover, our treatment outcomes following CXL are in line with other studies,[2–4] supporting the generalizability of our analyses. Finally, we experienced only minor CXL-related safety concerns in our treatment cohort, including the absence of infectious complications, stable endothelial cell densities, and a persisting haze in rare cases only.

A consideration of our study is that model-derived outcomes are statistical by nature and may not necessarily reflect the true pathophysiological process. With respect to the improved vision following CXL, one hypothesis is that -on average- the crosslinked cornea has a more regular shape, with subsequently a better visual acuity. Alternatively, some baseline characteristics, such as cone eccentricity, could be interrelated with visual acuity at baseline. Thus, the independent predictive effect might not be caused by merely by improved visual acuity, but also reflect an improvement of the interrelated components.

The reversal of this effect at in patients with a high pre-treatment visual acuity might be due to regression to the mean. Thus, by random chance, a very good pre-treatment visual acuity is likely to have a more average visual acuity at follow-up. This idea is supported by our clinical finding that these patients do not report a loss in visual acuity. Another consideration is the fact that our choice of predictors remains arbitrary. Although we attempted to ensure all currently regarded predictive factors and pre-treatment measurements were included in our univariate analysis. A, presently unknown -yet possibly important and interrelated- factor could have been overlooked.

In conclusion, our multivariable analysis of CXL to treat keratoconus revealed a large interrelation between previously identified predictors. Both pre-treatment cone eccentricity and pre-treatment corrected distance visual acuity were identified as individual predictors of treatment outcome one year after CXL in patients with keratoconus. Specifically, cone eccentricity was negatively associated with corneal flattening, and post-treatment visual acuity can be predicted reliably using baseline visual acuity. The true test of these prediction models will be to apply these methods to a new crosslinking data-set and compare the predicted with the measured outcomes.

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9

Predictors for treatment outcomes after corneal crosslinking for keratoconus: a validation study

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ABSTRACT

Purpose

Previous research suggested that baseline corrected distance visual acuity (CDVA) and maximum keratometry (Kmax) are predictors for effectiveness of corneal crosslinking (CLX) for keratoconus. The aim of this study was to validate the previously determined predictors in a new treatment cohort.

Methods

A prospective cohort of 112 eyes in 90 consecutive patients was used to validate the results of 102 eyes in 79 patients from our previous prospective cohort. All patients were treated using epithelium-off corneal CXL in a tertiary hospital setting. Primary outcomes were changes in CDVA (LogMAR) and Kmax between baseline and one-year post-treatment. Predictive factors for both outcomes were determined using univariable and multivariable analyses.

Results

Lower pretreatment CDVA was found to be the sole independent factor predicting an improvement in CDVA one year after CXL (β coefficient: -0.476, $P < 0.01$). Kmax flattening is more likely to take place in eyes with preoperative central cones (β coefficient: 0.655, $P < 0.01$). These results are consistent with our initial research and indicate high reproducibility in the new cohort. The previously postulated prediction model for postoperative CDVA showed limited predictive value in the validation cohort ($R^2 = 0.15$).

Conclusions

The clinical implication of these results is that patients with lower pretreatment visual acuity are more likely to benefit from CXL (with respect to visual acuity), and patients with more central cones will benefit more in terms of cone flattening. Furthermore, those results can be used to guide customization of the crosslinking treatment.

INTRODUCTION

Keratoconus is a progressive disease in which protrusion of the cornea causes visual impairment through the formation of irregular astigmatism.[1,2] The typical age of onset for keratoconus is early adulthood, and the disease is likely multifactorial in origin.[3] Genetic factors, environmental factors, positive family history, atopic constitution, contact lens use, and eye-rubbing have all been associated with keratoconus.[4-9] To halt disease progression, corneal crosslinking (CXL) has shown promising results in patients with keratoconus.[10-12] However, continued disease progression and a further decrease in visual acuity have been reported following CXL.[13]

Many factors that might be related to the efficacy of CXL have been studied previously. For example, age is associated with changes in visual acuity, as pediatric patients show better improvement than older patients in terms of corrected distance visual acuity (CDVA) following CXL.[14,15] A Snellen CDVA value worse than 20/40 is also correlated with an improvement in visual acuity following CXL.[16,17] With respect to flattening of maximum keratometry (Kmax) following CXL, higher pretreatment Kmax (≥54 diopters), a more central cone, and central cornea thickness ≥450 μm have all been reported as predictive factors.[16-21] The majority of these associations were established using univariable analyses, although CDVA is known to be influenced by many interrelated factors.[22]

Predictors of CXL efficacy have previously been studied by our group in a consecutive treatment cohort; specifically, differences in CDVA and Kmax one year after CXL were assessed using a multivariable model.[23] Interestingly, baseline CDVA was the only independent factor for predicting change in CDVA one year after CXL, and cone eccentricity was the only independent factor associated with change in Kmax following CXL. Moreover, a reliable model for predicting post-CXL changes in CDVA was constructed (R^2 = 0.45). In order to determine the reliability and generalizability of this model, external validation of these findings is essential.

Predictors are often not generalizable to patients outside the study population. Our primary purpose was to validate the reproducibility of previously determined predictors in a new treatment cohort. Only after validation such results should be implemented in clinical practice. Our secondary purpose was to validate the previously published model for the prediction visual outcomes for individual patients following CXL.[23]

METHODS

Dataset and study design

Our current cohort included patients who were treated with epithelium-off corneal crosslinking (CXL) for progressive keratoconus in our institution from January 1, 2012 through October 31, 2013. Here, we refer to this cohort as the validation cohort. The study design, inclusion and exclusion criteria, data collection, and surgical procedure were adapted from the initial treatment cohort, which included patients who were treated from January 1, 2010 through December 31, 2011.[23] The inclusion criteria included a prior Kmax progression of ≥1.0 diopter (D) within 6-12 months and thinnest corneal pachymetry ≥400 μm. Patients with corneal scarring or infection, pregnant patients, and lactating patients were excluded. The following primary outcomes were examined: 1) change in corrected distance visual acuity (logMAR CDVA) between baseline and one-year post-CXL, and 2) change in Kmax between baseline and the one-year post-CXL. This study was approved by the Ethics Review Board of the University Medical Center Utrecht and was performed in accordance with local laws, the European guidelines of Good Clinical Practice, and the tenets of the Declaration of Helsinki.

Surgical procedure

After the corneal epithelium was removed, crosslinking was performed in accordance with the Dresden protocol, using UV radiation with a perpendicular emission plane (370 nm at 3 mW/cm2, UV-X, Peschke Meditrade GmbH, Waldshut-Tiengen, Germany) as described previously.[22-24]

Data collection

Standard measurements were obtained at all follow-up visits and included uncorrected distance visual acuity (UDVA), CDVA, manifest refraction, Scheimpflug corneal tomography (Pentacam HR type 70900, Oculus GmbH, Wetzlar, Germany), and slit lamp evaluation. Parameters were measured prior to treatment and at regular follow-up visits (1, 3, 6, 12, and 18 months post-treatment). Patient-related factors, including family history, atopic constitution, and smoking history, were collected from the patient charts and supplemented using standardized forms completed by phone or e-mail in case they were not noted in the patient charts. Family history was considered positive if a first-degree or second-degree relative had been diagnosed with keratoconus. Patients with asthma, eczema, hay fever, or anti-allergy medication were marked as positive for atopic constitution. Patients

who were current smokers or previous smokers were marked as smokers, and the number of pack-years was noted.

Statistical analysis

Progression of keratoconus one year after CXL treatment was defined as an increase in Kmax ≥1 D. The paired Student's *t*-test was used to analyze the differences in logMAR CDVA and Kmax between baseline and the 12-month follow-up visit. Five patients missed the 12-month follow-up visit, but they did attend the 6-month and 18-month visits; for these patients, simple longitudinal imputation was used to estimate their CDVA and Kmax values at 12 months.[26]

In this validation cohort, univariable analysis was performed in order to identify factors associated with the primary outcome parameters (i.e., change in CDVA and Kmax). All factors with $P \leq 0.20$ from the univariable analysis were entered into a multivariable linear regression analysis to identify independent predictive factors. This method is consistent with the statistical method used to analyze the initial treatment cohort. The analysis was performed using generalized estimating equations, with correction for patients in which both eyes were included in the study.

The prediction model, which was postulated based on the initial treatment cohort, was sequentially validated; pretreatment logMAR-transformed visual acuity measurements of the validation cohort were entered in the model. The predicted and observed differences in logMAR CDVA values were compared using linear regression and presented in a calibration plot. Discrimination was summarized using R^2 to quantify the model's performance. A new prediction model based on the validation cohort was produced by stepwise, backward removal of the least significant factors derived from the multivariable analysis. To validate the performance of the refined prediction model, both calibration and discrimination were tested. A calibration plot and additional R^2 of the observed and predicted values were obtained. Data were collected and analyzed using SPSS 21.0 (IBM, Armonk, NY).

RESULTS

Dataset characteristics

The validation cohort consisted of 112 eyes from 90 patients who were treated using CXL within the study period. Ten eyes were lost to follow-up due to the patients moving abroad (n=2) or unknown reasons (n=8). These patients did not differ from the remaining study sample with respect to their baseline

characteristics. Patient-related factors were unknown in five patients. The baseline characteristics of the initial and validation cohorts were similar and are summarized in table 1.

Table 1. Baseline Characteristics of the Initial cohort of 102 eyes of 79 and Validation Cohort of 112 eyes of 90 Keratoconus Patients

	Initial cohort (102 eyes in 79 patients)			Validation cohort (112 eyes in 90 patients)		
	N	SD/%	Missing	N	SD/%	Missing
Age (years), mean	23	± 8	0	23	± 8	0
Male, N	56	71%	0	59	66%	0
Right eye, N	43	42%	0	60	54%	0
Snellen CDVA, mean	20/32	± 20/64	0	20/33	± 20/68	1
logMAR CDVA, mean	0.3	± 0.4	0	0.3	± 0.3	1
Kmax (D), mean	59.5	± 8.8	0	57.4	± 7.7	0
Positive family history, N	8	10%	2	7	8%	8
Atopic constitution, N	34	43%	2	55	61%	6
Smokers, N	11	14%	3	19	21%	9

N = number of patients; SD = standard deviation; CDVA = corrected distance visual acuity; D = diopters; logMAR = logarithm of the minimal angle of resolution; Kmax = maximum keratometry.

At the one-year post-CXL follow-up, progression had halted in 94 of the 102 eyes that were still in the study (92%). The remaining eight eyes had progressed, with a mean increase in Kmax of 3.9 D (range: 1.40-9.40 D). Both visual acuity and Kmax had improved significantly one year after CXL treatment. On average, LogMAR CDVA improved from 0.30 to 0.21 ($P < 0.01$), and Kmax decreased from 57.2 to 56.2 D ($P < 0.01$).

Univariable analysis

The outcomes of our univariable analysis of the initial treatment cohort and the current validation cohort are summarized in Table 2. Both age (β coefficient: 0.006, $P = 0.04$) and pretreatment CDVA (β coefficient: -0.385, $P < 0.01$) were associated with a change in visual acuity. Of those two factors, only pretreatment CDVA had been identified in the initial cohort.

None of the baseline factors was significantly associated with Kmax outcome in the validation cohort. Because pretreatment Kmax and cone eccentricity demonstrated a trend towards association (β coefficient: -0.046, $P = 0.15$ and β coefficient: 0.356, $P = 0.17$, respectively), they were entered in the multivariable analysis. In the initial cohort, gender, cone eccentricity, and corneal thickness were associated with Kmax outcome.

Table 2. Univariable analysis of baseline characteristics related to treatment effect in keratoconus patients in the initial and validation cohorts one year after corneal crosslinking treatment

	Difference in CDVA (logMAR)					
	Initial cohort			Validation cohort		
	β coefficient[§]	95% CI	*P*-value	β coefficient[§]	95% CI	*P*-value
Age (years)	0.001	-0.006 to 0.008	0.77	0.006	0.000 to 0.013	0.04‡
Male gender	0.041	-0.079 to 0.162	0.50	0.066	-0.040 to 0.172	0.22
Positive family history	0.003	-0.168 to 0.173	0.97	-0.061	-0.288 to 0.166	0.60
Atopic constitution	0.121	0.010 to 0.232	0.03‡	-0.008	-0.124 to 0.109	0.90
Smoking	-0.047	-0.203 to 0.109	0.54	0.070	-0.065 to 0.205	0.31
Spherical equivalent (D)	-0.002	-0.018 to 0.013	0.99	-0.003	-0.023 to 0.018	0.80
LogMAR UDVA pretreatment	-0.180	-0.290 to -0.070	<0.01‡	-0.011	-0.119 to 0.096	0.83
LogMAR CDVA pretreatment	-0.523	-0.641 to -0.405	<0.01‡	-0.385	-0.545 to -0.224	<0.01‡
Kmax pretreatment (D)	-0.009	-0.016 to -0.003	<0.01‡	0.001	-0.006 to 0.008	0.68
Cone eccentricity (mm)	0.098	0.029 to 0.168	<0.01‡	0.026	-0.030 to 0.081	0.36
Central corneal thickness (μm)	0.001	0.000 to 0.003	0.04‡	0.000	-0.001 to 0.002	0.80
	Difference in Maximum Keratometry (Kmax)					
	Initial cohort			Validation cohort		
	β coefficient[§]	95% CI	*P*-value	β coefficient[§]	95% CI	*P*-value
Age (years)	0.044	-0.130 to 0.102	0.13†	-0.029	-0.087 to 0.029	0.33
Male gender	1.222	0.272 to 2.172	0.01‡	0.404	-0.572 to 1.381	0.41
Positive family history	0.693	-0.689 to 2.075	0.32	0.663	-1.441 to 2.766	0.53
Atopic constitution	0.246	-0.679 to 1.171	0.60	0.142	-0.928 to 1.213	0.79
Smoking	-0.417	-1.688 to 0.854	0.52	0.674	-0.578 to 1.925	0.29
Spherical equivalent (D)	0.104	-0.022 to 0.230	0.12†	-0.072	-0.259 to 0.115	0.45
LogMAR UDVA pretreatment	-0.871	-1.791 to 0.049	0.06†	0.162	-0.832 to 1.156	0.75
LogMAR CDVA pretreatment	-0.771	-2.062 to 0.520	0.24	0.541	-1.117 to 2.198	0.52
Kmax pretreatment (D)	-0.039	-0.091 to 0.014	0.14†	-0.046	-0.109 to 0.017	0.15†
Cone eccentricity (mm)	0.957	0.400 to 1.515	<0.01‡	0.356	-0.151 to 0.863	0.17†
Central corneal thickness (μm)	0.011	0.001 to 0.023	0.04‡	0.003	-0.012 to 0.018	0.70

CDVA = corrected distance visual acuity; logMAR = logarithm of minimal angle of resolution; CI = confidence interval; D = diopters; Kmax = maximum keratometry; UDVA = uncorrected distance visual acuity. [§] ß coefficient is the value referring to how a dependent variable will change, per unit increase in the predictor variable. ‡ P < 0.05 indicates significance and this factor is included in multivariable analysis. † P values ≤ 0.20 were also included in the multivariable analysis.

Multivariable analysis

Table 3 summarizes the results of the multivariable analyses in both cohorts. In the validation cohort, age (β coefficient: 0.007, $P = 0.03$) and pretreatment CDVA (β coefficient: -0.476, $P < 0.01$) were related independently to a change in visual acuity at the one-year follow-up visit. Age was not identified as an independent predictor in the initial cohort. With respect to change in Kmax, cone eccentricity was confirmed as an independent predictor of CXL outcome one year after treatment (β coefficient: 0.655, $P < 0.01$).

Table 3. Multivariable analysis of predictors of treatment effect in keratoconus patients in the initial and validation cohort one year after corneal crosslinking treatment

	Difference in CDVA (logMAR)					
	Initial cohort			Validation cohort		
	β coefficient[§]	95% CI	*P*-value	β coefficient[§]	95% CI	*P*-value
Age (y)	-0.002	-0.008 to 0.004	0.50	0.007	0.001 to 0.013	0.03‡
Atopic constitution	-0.048	-0.129 to 0.023	0.18			
logMAR UDVA	0.069	-0.083 to 0.221	0.37			
logMAR CDVA	-0.628	-0.997 to -0.258	<0.01‡	-0.476	-0.680 to -0.271	<0.01‡
Kmax (D)	0.005	-0.001 to 0.011	0.13			
Cone eccentricity (mm)	0.026	-0.044 to 0.096	0.46			
Central corneal thickness (µm)	0.000	-0.001 to 0.001	0.53			
	Difference in Maximum Keratometry (Kmax)					
	Initial cohort			Validation cohort		
	β coefficient[§]	95% CI	*P*-value	β coefficient[§]	95% CI	*P*-value
Male gender	-0.823	-1.923 to 0.277	0.14			
Spherical equivalent (D)	0.103	-0.045 to 0.251	0.17			
logMAR UDVA	-0.017	-1.105 to 1.071	0.98			
Kmax (D)	-0.009	-0.068 to 0.050	0.77	0.012	-0.059 to 0.083	0.74
Cone eccentricity (mm)	0.709	0.117 to 1.301	0.02‡	0.655	0.210 to 1.101	<0.01‡
Central corneal thickness (µm)	0.001	-0.010 to 0.012	0.84			

CDVA = corrected distance visual acuity; logMAR = logarithm of minimal angle of resolution; CI = Confidence interval; D = Diopter; Kmax = maximum keratometry; UDVA = uncorrected distance visual acuity. [§] ß coefficient is a value referring to how a dependent variable will change, per unit increase in the predictor variable. ‡ P < .05 indicates significant values.

Visual acuity and cone eccentricity were found to be the sole repeatable and independent factors influencing outcomes of keratoconus patients undergoing CXL, demonstrating that patients with lower pretreatment visual acuity are more likely to benefit from CXL (in terms of visual acuity), and patients with more central cones will benefit more in terms of cone flattening.

Validation of prediction model

The following equation was used in the initial model to predict the change in logMAR CDVA one year after CXL[23]:

Difference in logMAR CDVA one year after CXL =
(-0.518 x baseline logMAR CDVA) + 0.043

This model showed robust predictive value in the initial treatment cohort (R^2 = 0.45), explaining 45% of the variation in CDVA. Validation of the model, in which the validation cohort data are entered into the existing prediction model, showed a mediocre fit (R^2 = 0.18), only explaining 18% of the variation. It was not possible to create a better prediction model based on the validation dataset (R^2 = 0.19). With respect to change in Kmax one year after CXL, the model showed limited predictive value in our initial cohort (R^2 = 0.15).[23] Fitting a new model to the validation data showed even worst predictive value (R^2 = 0.02).

Although postoperative CDVA was accurately predicted based on pre-treatment patient characteristics in the original study, both visual acuity and maximum keratometry were not predictable for individual patients in this validation study.

DISCUSSION

The aim of this study was to validate and test the reproducibility of previously determined predictors of CXL effectiveness in a new treatment cohort. This validation cohort confirmed that pretreatment visual acuity and cone eccentricity are the only two independent factors for predicting change in postoperative CDVA and Kmax, respectively. Repeatability of those results is essential to apply these findings in practice and to guide clinicians in their decision-making process.

With respect to cone flattening and visual acuity development, the clinical outcomes following CXL in our cohorts are consistent with previous studies.[11,27,28] This again underscores the ability to compare our results to other populations that were treated using the Dresden protocol. Our initial and validation cohorts are relatively large, and only a limited number of cases were lost to follow-up.

Interestingly, the univariable analysis revealed major differences between the initial and validation datasets, demonstrating the variability among outcomes when inter-factor correlation is not taken into account. Some baseline measurements are interrelated and therefore could potentially be (incorrectly) identified as predictors when correlated to a true predictor. The predictive factors derived from our multivariable analysis were consistent between the study cohorts, which reflects good reproducibility and stresses the importance of performing a multivariable analysis. The clinical implication of these results is that patients with lower pretreatment visual acuity are more likely to benefit from CXL (with respect to visual acuity), and patients with more central cones will benefit more in terms of cone flattening. This is consistent with other studies in which patients with a pretreatment CDVA of 20/40 or worse had significant visual improvement.[16,17] Therefore it might be advisable to explain to patients with low pre-treatment CDCVA that improvement might be expected, while on the other hand, this is not likely for patients with preexistent high CDVA.

Our finding that Kmax is more likely to flatten in eyes with a more central cone, is in concordance with results from Greenstein et al.[20] This latter finding might be due to exposure to UV light perpendicular to the center of the cornea during CXL. The peripheral cornea receives light rays that are less potent due to their oblique incidence. The UV light source used in this study is in accordance with this principle. Furthermore, it is know that CXL and aberrations interact and it could be that aberrations in the vicinity of a peripheral cone alter the angle of incidence of the light rays on the corneal surface even further, causing deflection and thereby resulting in less UV light penetration in the cornea and lesser treatment results.[29] Therefore, a more central cone is likely to be treated more effectively, resulting in more flattening of the cone. Focusing the UV light on the cone instead of the center of the cornea could be considered for treatment customization in patients with more peripheral cones.

Our initial study cohort did not identify age as a predictive factor for either treatment outcomes. However, in the validation dataset, younger patients benefitted significantly more with respect to visual acuity. Soeters et al. also identified age as a prognostic factor; interestingly, they also found that their younger patients had more centrally located cones.[14] Léoni-Mesplié et al. reported that disease progression in pediatric patients is more aggressive than in adults, suggesting that CXL treatment is more effective at preventing deterioration in pediatric patients.[30]

Consistent with our initial study, a variety of factors associated with keratoconus were not identified as independent contributors to the effectiveness of CXL treatment. These factors include gender, family history, atopic constitution,

smoking history, spherical equivalent, logMAR UDVA, Kmax, and central corneal thickness; none of these factors were predictive in terms of changes in visual acuity or Kmax one year after CXL. However, using univariable analyses, other studies found that pretreatment corneal thickness ≤450 µm and Kmax ≥54 D were predictors of a decrease in Kmax.[16,17,19] Although we also found a relationship between corneal thickness and Kmax flattening in our initial univariable analysis, this relationship did not hold when examined in a multivariable analysis. This finding was not replicated in the univariable analysis of our validation cohort. Previously, Greenstein et al. used a multivariable approach and found that patients with higher keratometry readings showed more improvement in response to CXL.[16] However, this finding is not supported by our data. Additional analysis using a dichotomous cut-off for of 54 D was not associated with either outcome parameter (data not shown). One explanation for this difference in findings could be the difference in sample size and the fact that Greenstein et al. examined a heterogeneous study cohort that included both patients with keratoconus and patients with post-LASIK ectasia.

Creating a model for the prediction of individual Kmax after CXL was ultimately cumbersome and yielded little additional clinical value. Moreover, our initial reliable model for the prediction of CDVA could not be confirmed in this validation study, which is an additional argument why validation studies are extremely important. The inability to validate this prediction model can be due to either over fitting of the original model or to large individual variation in the reaction to CXL treatment. Both options leading to the conclusion that the formerly proposed prediction model for individual visual outcomes after CXL treatment should not be applied for patient counseling.

In conclusion, the clinical implication of these results is that patients with lower pretreatment visual acuity are more likely to benefit from CXL (with respect to visual acuity), and patients with more central cones will benefit more in terms of cone flattening. Repeatability of those predictors supports applicability for the decision-making process of clinicians. Furthermore, those results can be used to guide customization of the crosslinking treatment.

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Nationwide reduction in the number of corneal transplantations for keratoconus following the implementation of crosslinking

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ABSTRACT

Purpose

Keratoconus is characterised 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 crosslinking (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 crosslinking can significantly reduce the need for corneal transplantation.

INTRODUCTION

Keratoconus is a corneal disease characterised by a gradual thinning of the central and peripheral corneal stroma, resulting in corneal protrusion and reduced visual acuity.(Prakash 2016, Rabinowitz 1998) 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 and colleagues introduced corneal crosslinking (CXL) as a potential treatment for keratoconus.(Wollensak et al. 2003) CXL 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 crosslinking to slow – and in some cases, halt – the progression of keratoconus has been demonstrated in randomised controlled trials, suggesting that CXL may help prevent the need for corneal transplantation in patients with keratoconus.(Caporossi et al. 2010, Hersh et al. 2011, O'Brart et al. 2011, Spoerl et al. 2007, Wittig-Silva et al. 2014).

In the Netherlands, corneal crosslinking 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. CXL is now a well-established treatment for keratoconus in the Netherlands.

In a recent study performed on a local scale, Sandvik et al. suggested that the introduction of CXL was the principal underlying factor responsible for the recent reduction in keratoplasties for treating keratoconus.(Sandvik et al. 2015) 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 pre-

treatment 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 anonymised with respect to the patients and surgeons and then provided to the researchers. Permission to extract the anonymised 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. 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 pre-treatment 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 crosslinking 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 ß-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 crosslinking treatments was performed in the Netherlands in the period September 2007 through December 2014. The distribution of crosslinking treatments per year is displayed in figure 1.

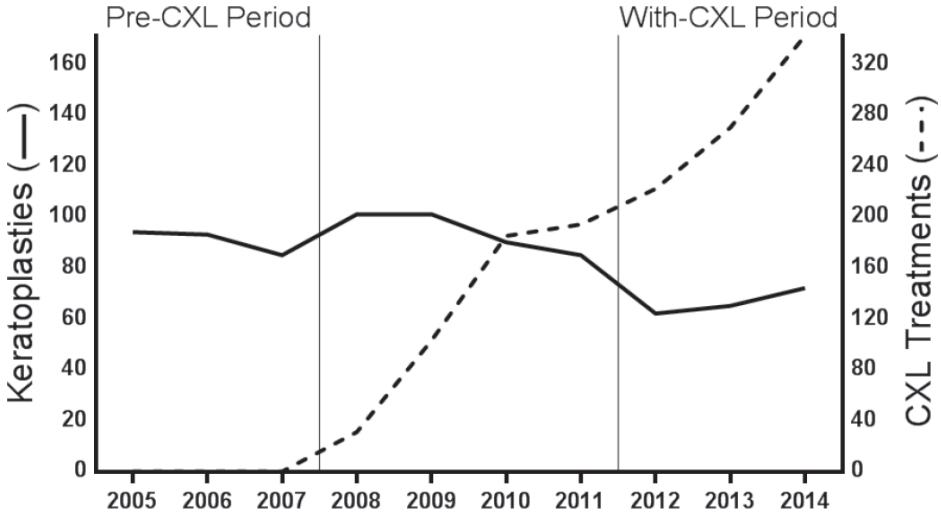

Fig. 1. Annual number of keratoplasties and number of crosslinking (CXL) treatments in the Netherlands. Annual number of keratoplasties; 2005:94, 2006:93, 2007:83, 2008:102, 2009:102, 2010:90, 2011:85, 2012:62, 2013:65, 2014:75. Annual number of corneal crosslinking (CXL) treatments; 2005:0, 2006:0,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

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, ß=-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 (±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.

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 crosslinking, 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.

DISCUSSION

Our analyses reveal that significantly fewer corneal transplantation surgeries were performed in the Netherlands for keratoconus after corneal crosslinking 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. CXL is a minimally invasive, relatively safe, effective procedure for slowing – or even halting – the progression of keratoconus.(Caporossi et al. 2010, Hersh et al. 2011, O'Brart et al. 2011, Spoerl et al. 2007, Wittig-Silva et al. 2014) The ability to minimise 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., who described a similar correlation between CXL and corneal transplantation, albeit on a local scale.(Sandvik et al. 2015)

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 crosslinking 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 randomised controlled trial performed by Wittig-Silva et al., in which 10% of eyes that were not treated with CXL received a corneal transplant within three years, whereas no transplantation surgeries were performed in the eyes that underwent CXL.(Wittig-Silva et al. 2014) 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 to 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 figure 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 crosslinking 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 crosslinking has played a major role in reducing the need for corneal transplantation for keratoconus in this population.

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11

What are the costs of corneal crosslinking for the treatment of progressive keratoconus?

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ABSTRACT

Aim

To assess the costs of corneal crosslinking (CXL) treatment for keratoconus, including pre-operative consultation and one year follow-up in a tertiary referral center.

Methods

All costs of pre-operative consultation, surgical CXL procedure and post-operative costs during one year follow-up were assessed from the healthcare perspective. A microcosting approach was followed.

Results

A total of 43 patients (86 eyes) were included in this study. In this consecutive cohort, 28 crosslinking procedures were performed in 20 patients. The mean total costs for one eye treated with CXL for progressive keratoconus was €1754.06 (±177.23) or $1929.47 (±194.95), including the costs for keratoconus patients not proceeding to CXL. The mean costs of the surgical CXL procedure were €719.50 (±18.82) or $791.45 (±20.70). Personnel costs were the main expense in the crosslinking treatment, accountable for 88.1% of the total costs.

Conclusion

The total costs of crosslinking treatment in our center, including screening keratoconus patients, pre-operative consultation and one-year follow-up, were €1754.06 ($1929.47). The average costs of the surgical procedure were 719.50€ (791.45$). These results provide insight in the financial side of crosslinking treatment and can be used in health economic evaluations and reimbursement negotiations.

INTRODUCTION

Corneal crosslinking (CXL) was introduced for the treatment of keratoconus in 2003 by Wollensak et al.[1] After removal of the central epithelium, riboflavin is instilled onto the cornea for thirty minutes and the cornea is subsequently exposed to UVA light for a certain amount of time, depending on the intensity of the UV source.

Three randomized controlled trials demonstrated the efficacy of crosslinking treatment in the prevention of keratoconus progression and contributed to the implementation of CXL in healthcare programs around the world.[2,3,4]In the UK, the National Institute for Health and Care Excellence judged CXL a safe and effective treatment by September 2013.[5] In the Netherlands, CXL is completely reimbursed by healthcare insurance companies since January 2015. FDA approval for the United States was denied in the beginning of 2015.[6]

There is limited evidence on the costs of CXL. One cost-effectiveness study was published recently, estimating the costs of the total CXL treatment for one simulated patient on £928.[7] We report on the costs of CXL for keratoconus, from a healthcare perspective, including the screening costs, the costs of the treatment itself, and all costs during one year follow-up, based on application in clinical practice. The setting of this study was a tertiary referral center with a long track record in CXL treatments; over 500 treatments were performed from 2010 onwards. A standardized keratoconus screening and treatment protocol is adhered to.

METHODS

Study population

All patients treated with CXL for keratoconus in our center are prospectively included in an ongoing cohort, approved by the Ethics Review Board of the University Medical Center Utrecht and set up in accordance with local laws, the European guidelines of Good Clinical Practice, and the tenets of the Declaration of Helsinki. For this study, all consecutive patients referred for keratoconus between September 2012 and July 2013 were included. The inclusion criteria for a CXL treatment included a prior maximum keratometry (Kmax) progression of ≥1.0 diopter (D) within 6-12 months, and a corneal pachymetry ≥400 µm. Patients with corneal scarring or infection, pregnant patients, and lactating patients were excluded. Data were recorded from the first visit until one year after the CXL procedure. Or, in case a CXL treatment was not performed, until one year after

the first visit. Baseline values of patients indicated and not indicated for CXL were compared using an independent samples t-test, with *P*-value set at 0.05. Data were collected and analyzed using SPSS 21.0 (IBM, Armonk, NY).

Cost analysis

The healthcare perspective was used to assess the costs of crosslinking. All relevant healthcare costs were assessed according to the Dutch guidelines for cost calculations in health economic research.[8] For all relevant healthcare resources without Dutch reference costs, cost prices per resource unit were estimated using a micro costing approach, implying a detailed study of time and resources used. Units of hospital resources, including (emergency) outpatient visits, consultations by phone, diagnostic procedures, per- and postoperative drugs and patients not attending scheduled visits were incorporated in the calculations. All data were extracted from the electronic patient charts. Personnel costs were based on reference prices from the Dutch guidelines for cost calculations and include overhead costs.[7] Costs of per- and postoperative drugs were obtained from the Dutch Healthcare Institution.[9]

A standardized keratoconus screening and treatment protocol was adhered to. The first outpatient consultation consisted of two 20 minute appointments with both a corneal surgeon and a specialized optometrist. These consultations consisted of a manifest refraction, Scheimpflug corneal tomography (Pentacam HR type 70900, Oculus GmbH, Wetzlar, Germany), endothelial cell density specular microscopy (SP3000P; Topcon, Tokyo, Japan), slit lamp examination, and dilated fundoscopy. Consultations to asses potential keratoconus progression took 15 minutes on average and included manifest refraction, Scheimpflug corneal tomography and slit lamp examination. For consultations by telephone an average duration of 10 minutes was assumed, excluding overhead costs. When patients did not attend a scheduled visit, 50% of personnel costs were imposed. Costs of Scheimpflug corneal tomography and endothelial cell density measurement were determined using an 10 year depreciation period for medical equipment as stated in the Dutch guidelines for cost calculations and based on average usage.

The Scheimpflug corneal tomography was used in 1224 bilateral procedures annually and the endothelial cell density measurement was used in 700 bilateral procedures annually, not restricting usage to keratoconus patiens.[6] Costs were calculated by multiplying the mean number of units of resource use with the costs per unit. The mean costs per crosslinking treatment were calculated by dividing the total costs of healthcare resources by the number of eyes treated with crosslinking. All costs were converted to 2015 euro's in accordance with

the guideline from the Dutch Healthcare Authority.[10] To convert euro's to dollars a conversion rate of 1.10 was used, based on exchange rates in the first nine months of 2015.

Surgical procedure and postoperative management

The surgical procedure was performed as described previously.[1,11] A 9-mm corneal abrasion was made by a corneal specialist or a resident using a blunt knife. A specialized optometrist performed the remainder of the procedure, starting with 0.1% riboflavin solution application (Peschke Meditrade GmbH, Waldshut-Tiengen, Germany) every 3 minutes for 30 minutes. Corneal thickness was measured with a hand held pachymeter (Handy Pachymeter, SP-3000, Tomey Corp, Phoenix). When corneal pachymetry was less than 400 μm, hypo-osmotic riboflavin (Peschke Meditrade GmbH, Waldshut-Tiengen, Germany) was applied every 20 seconds for 5 minutes and repeated up to 2 times until adequate thickness (ie, >400 μm) was achieved. The cornea was exposed to an ultraviolet (UV) light source (UV-X; Peschke Meditrade GmbH, Waldshut-Tiengen, Germany) with a wavelength of 365±10nm for a total cumulative exposure time of 30 minutes. Riboflavin drops were instilled every 5 minutes during the UV irradiation. Following the treatment, a bandage lens (PureVision; Bausch and Lomb Nederland BV, Schiphol-Rijk, The Netherlands) was placed. The total planned and observed time for the crosslinking procedure was 105 minutes. Crosslinking was applied in one eye per patient per session.

Postoperative medication included nepafenac 0.1% drops (Nevanac; Alcon Nederland BV, Gorinchem, The Netherlands) 3 times a day for 1 week, moxifloxacin 0.5% drops (Vigamox; Alcon Nederland BV, Gorinchem, The Netherlands) 3 times a day for 1 month, and dextran/hypromellose drops (Duratears; Alcon Nederland BV, Gorinchem, The Netherlands) 3 times a day for 1 month. When the epithelium was healed, the bandage contact lens was removed and fluorometholone 0.1% drops (FML Liquifilm; Allergan BV, Eindhoven, The Netherlands) were applied twice a day. Postoperative outpatient visits to verify epithelium healing (10 minutes) were usually scheduled 2-5 days after treatment. At one, three, six and twelve months after treatment a 20 minute outpatient visit was scheduled, including visual acuity with and without manifest refraction, slit lamp evaluation, Scheimpflug corneal tomography (all visits), and endothelial cell density specular microscopy (twelve months only).

RESULTS

Study population

A total of 43 patients (86 eyes) with keratoconus were included in this study. All patients were examined for eligibility for crosslinking treatment. In this cohort, 28 crosslinking procedures were performed in 20 patients (47%). The other 23 patients were not indicated for crosslinking within 1 year follow up. Characteristics of patients treated with crosslinking and patients not indicated for crosslinking are displayed in table 1. Baseline characteristics of patients in both groups were comparable except for age, that was significantly higher in patients not indicated for crosslinking (P<0.001).

Table 1. Baseline characteristics of 86 eyes of 43 patients considered for corneal crosslinking.

	Indicated for crosslinking		Not indicated for crosslinking		
	Mean / percentage	Range	Mean / percentage	Range	*P*-value
Age (years)	20.2	13-33	27.8	16-45	<0.001
Male (%)	61%	-	50%	-	0.18
UDVA	20/100	20/640-20/16	20/59	2/200-20/16	0.15
CDVA	20/29	20/32-20/16	20/25	20/400-20/12.5	0.10
Kmean (D)	47.7	41.0-54.3	47.5	41.0-76.6	0.39
Kmax (D)	57.5	46.8-69.1	54.9	42.1-112.8	0.19
Corneal thickness (µm)	470	422-543	464	219-578	0.92

UDVA = uncorrected distance visual acuity; CDVA = corrected distance visual acuity; Kmean = mean keratometry; Kmax = maximum keratometry; D = diopters; Corneal thickness = central corneal thickness. *P*-value was determined using an independent samples t-test, with P<0.05.

Costs analysis

Costs of the crosslinking treatment for keratoconus including screening costs, pre-operative consultation and follow-up during one year are displayed in table 2. The mean total costs for one eye treated with CXL for progressive keratoconus was €1754.06 (±177.23) or $1929.47 (±194.95). The mean costs of the surgical CXL procedure were €719.50 (±18.82) or $791.45 (±20.70).

Personnel costs was the main cost driver in the crosslinking treatment, accountable for 88.1% of the total costs. Further cost categories, such as medication, diagnostic tests and treatment materials were accountable for 4.6%, 4.3% and 3.0% respectively (figure 1).

Table 2. Costs of crosslinking treatment for keratoconus including pre-operative assessment and follow-up during one year.

	Costs per unit (€)	Units of resource use (mean)	Mean costs (€)
Pre-operative costs			
First outpatient visit (20+20 minutes)			
Corneal specialist	145.55/visit	1.00	145.55
Optometrist	112.87/visit	1.00	112.87
Diagnostic procedures			
Keratometry	5.72/eye	2.00	11.44
Endothelial Cell Count	3.68/eye	1.05	3.85
Progression control consultation (15 minutes)			
Corneal specialist	109.16/visit	0.05	5.08
Optometrist	84.66/visit	0.42	35.44
Resident	89.12/visit	0.02	2.07
Nurse practitioner	85.31/visit	0.05	3.97
Diagnostic procedures			
Keratometry	5.72/eye	1.07	6.12
Endothelial Cell Count	3.68/eye	0.09	0.34
Consultation by telephone (10 minutes)			
Corneal specialist	19.53/call	0.12	2.27
Optometrist	3.12/call	0.12	0.36
Non patient-related consultation	11.32/patient	0.33	3.69
No shows	12.50/visit	0.05	0.58
Costs per evaluated patient (n=43)			**333.63 ±123.30**
Costs per treated eye (n=28)			**512.36 ±52.45**
Crosslinking treatment			
Procedural costs			
Optometrist (105 minutes)	592.57/visit	1.00	592.57
Abrasion	5.79/abrasion	1.00	5.79
Materials			
UVA lamp	37.01/eye	1.00	37.01
Pachymeter	10.36/eye	1.00	10.36
Bandage contact lens	4.42/eye	1.00	4.42
Medication			
Riboflavin	59.61/eye	1.00	59.61
Hypotone riboflavin	59.61/eye	0.11	6.39
Per-operative eye drops	2.77/eye	1.00	2.77
No shows	16.39/visit	0.04	0.59
Costs surgical crosslinking procedure (n=28)			**719.50 ±18.82**

Table 2. Costs of crosslinking treatment for keratoconus including pre-operative assessment and follow-up during one year. (continued)

	Costs per unit (€)	Units of resource use (mean)	Mean costs (€)
Post-operative costs			
Medication			
Post-operative eye drops	11.78/eye	1.00	11.78
Oral medication	0.40/eye	1.00	0.40
Outpatient visit (≤1 week, 10 minutes)			
Corneal specialist	72.78/visit	0.25	18.20
Optometrist	56.44/visit	0.64	36.28
Resident	59.42/visit	0.36	21.22
Nurse practitioner	56.87/visit	0.07	4.06
Outpatient visit (>1 week, 20 minutes)			
Corneal specialist	145.55/visit	0.11	15.59
Optometrist	112.87/visit	2.64	298.30
Resident	118.83/visit	0.18	21.22
Nurse practitioner	113.74/visit	0.29	32.50
Diagnostic procedures			
Keratometry	5.72/eye	6.43	36.77
Endothelial Cell Count	3.68/eye	1.43	5.25
Emergency outpatient visit (20 minutes)			
Corneal specialist	145.55/visit	0.07	10.40
Optometrist	112.87/visit	0.04	4.03
Resident	118.83/visit	0.04	4.24
Consultation by telephone (10 minutes)			
Corneal specialist	19.53/call	0.07	1.40
Optometrist	3.12/call	0.04	0.11
No shows	3.12/visit	0.14	0.45
Post-operative costs			**522.20 ±164.71**
Total Costs per crosslinking treatment (€)	Total ± SD		**1754.06±177.23**

Costs per evaluated patient = Average pre-operative costs per patient; Costs per treated eye = Average pre-operative costs per treated eye; Abrasion = Performed by either corneal specialist or resident (weighted average); Per-operative eye drops = Oxybuprocaïne, tetracaïne, iodine and isotonic saline solution 0.9%; Post-operative eye drops = Chloramphenicol, polyvidon and fluormetholone; Oral medication = Paracetamol and diclofenac; Outpatient visit (≤1 week) = Short visit without diagnostic procedures; No shows = Patients not attending scheduled appointments

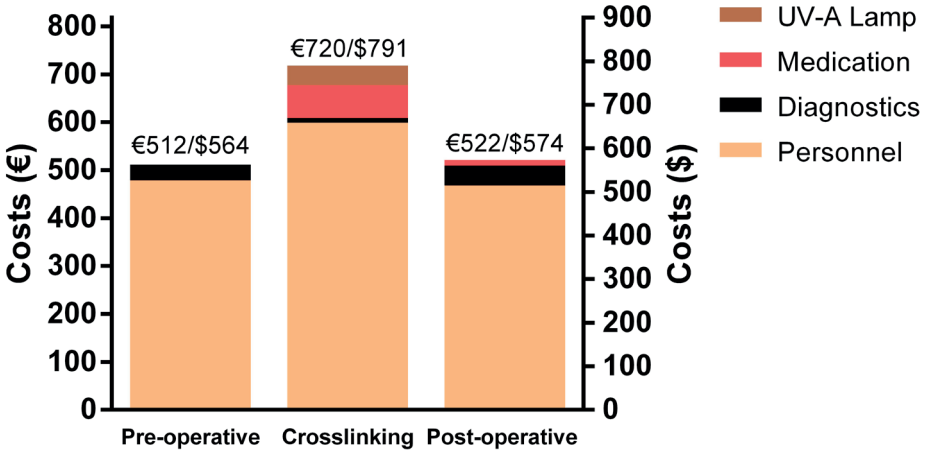

Figure 1. Costs of one eye treated with corneal crosslinking for progressive keratoconus during preoperative consultation, surgical crosslinking procedure, and 1-year postoperative follow-up. The total costs for one eye treated with crosslinking were €1,754.06 or $1,929.47. UVA = ultraviolet-A

DISCUSSION

In this paper, the costs for corneal crosslinking for the treatment of progressive keratoconus are described from a healthcare perspective. All costs made in a cohort of patients referred to our tertiary center were recorded with one year of follow-up. The total costs therefore includes costs of screening and follow-up of non-treated patients.

A crosslinking treatment is a very standardized treatment, with a low rate of adverse events necessitating additional visits or treatments. Therefore, the estimation of the costs is unlikely to be influenced by outliers. The used equipment, the treatment protocol, the frequency of additional investigations, and the costs of diagnostics are all shown in Table 2. This enables the calculation of crosslinking costs in a variety of other settings. For instance, accelerated crosslinking has shown to produce similar results with shorter UVA radiation times and thus shorter surgical procedure times. [12,13,14]A decreased radiation time from thirty to five minutes would save €141.09 (8.0% of total costs and 19.6% of treatment costs). This relatively small decrease is explained by the fact that the majority of costs incur during the pre-operative consultation and post-operative follow-up period.

While personnel costs were the main expense in the crosslinking treatment, it should be taken into account that wages can diverge among organizations and countries. In our institution, care is delivered by lower-qualified personnel (i.e.

optometrists, nurses) whenever possible. The investment of (costly) medical specialist time is therefore reduced. If all care would be delivered by an ophthalmologist the costs of the treatment itself would increase by 23.5%, and the overall cost by 20.3% (calculations not shown). Other costs may be influenced by the geographic location and economic situation as well, though again those values can be adjusted using the summary in table 2.

This study was performed from the healthcare perspective, limiting the scope to costs within the hospital, leaving healthcare costs outside hospital (e.g. general practitioner visits), costs for society (e.g. productivity losses) and costs for the individual patient (e.g. travel costs and time costs) uninvestigated. In our center the crosslinking procedure is performed in a specially equipped treatment room at the outpatient clinic, while in other clinics an operating theater might be used, probably resulting in higher costs for the crosslinking procedure.[15] Some centers may prefer additional diagnostic procedures like optical coherence tomography, while in our center only corneal topography and endothelial cell density are applied routinely. Lastly, the ophthalmologist is substituted by cheaper personnel when appropriate, as mentioned previously. These factors were carefully balanced treatment decisions, made to optimize keratoconus treatment efficiency, and could also be considered as opportunities in other centers. However, costs per treatment in general tend to be higher in tertiary centers, mainly because of patient selection and the highly trained and specialized personnel. When taken this into account, costs per treatment might be lower in smaller hospitals, but no data is currently available to support this hypothesis.

CONCLUSION

The total costs of crosslinking treatment in our center, including screening keratoconus patients, pre-operative consultation and one-year follow-up, were €1754.06 ($1929.47). The average costs of the surgical procedure were 719.50€ (791.45$). These results provide insight in the financial side of crosslinking treatment and can be used in health economic evaluations and reimbursement negotiations.

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Comment on ‘Cost effectiveness of collagen crosslinking for progressive keratoconus in the UK NHS’

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Marie-Josee J. Mangen and Robert P.L. Wisse

Eye (Lond). 2016 Aug;30(8):1150-2.

Sir,

It is difficult to overestimate the importance of the UK National Health Service (NHS) policy to structurally assess the cost effectiveness of novel treatments. This policy serves as an example for policy makers in many developed countries, and the outcomes of the analyses are made available to fellow researchers in the field. The recent publication by Salmon et al1 regarding the cost effectiveness of crosslinking for progressive keratoconus is an excellent example of this. The authors concluded that crosslinking is likely to be cost effective, with an incremental cost of £3174 per quality-adjusted life year (QALY), supporting the NHS' decision to reimburse this treatment.

We would like to address the methods used in this study, specifically the authors' calculation of QALYs in keratoconus. QALYs represent the value of the impact of disease on quality of life measured over a lifetime. The concept is based on the measurement of utilities. A utility is represented on a scale anchored at 0 (representing death) and 1 (representing full health) and can be assessed using specific questionnaires (eg, the Euroqol EQ-5D (Euroqol group http://www.euroqol.org/about-eq-5d.html)) or calculated from patient-reported health surveys (eg, SF-6D[2] derived from Short From 36 Health (SF-36) survey questionnaires[3]). QALYs and utilities are the preferred outcome measures used when performing a cost effectiveness analysis. The authors state that direct measures of utilities in keratoconus are not available and therefore estimated utilities based on expected visual acuity (VA) in various stages of keratoconus, leading to decreased utilities in advanced keratoconus.

However, the Collaborative Longitudinal Evaluation of Keratoconus (CLEK) study measured SF-36 in more than 1200 keratoconus patients, including appropriate descriptions of the patients' VA, keratometry, and subsequent staging using the Amsler–Krumeich classification.[4] Using the CLEK database, we classified all of the included subjects according to their keratometry readings, and we linked these results to SF-6D-derived utilities, following the method developed by Brazier et al.[2] To our surprise, we found virtually no difference in utilities among the various disease stages in keratoconus; strikingly, the utilities in patients with bilateral stage I keratoconus were identical to the utilities in patients with bilateral stage IV keratoconus (Table 1). Similar results were obtained when the results were stratified based on age and gender. Thus, if perceived quality of life does not deteriorate as the disease progresses, hardly any therapy will be cost effective.

We hypothesize that either SF-36-derived utilities lack the sensitivity to detect the apparent differences per disease stage that subjects adjust to their disease stage over time, or that a keratometry-based classification is not appropriate. Keratometry is not a clinical endpoint, and its relationship with VA is multifactorial and complex. Both VA and the patient's dependence upon visual aids are arguably more relevant for determining quality of life in keratoconus patients. Although vision-related quality of life is related to VA in the better eye,[5] we investigated the correlation between (LogMAR) VA in the better eye and utilities, and found a significant relation (P<0.001, Pearson's r =– 0.113). The utilities obtained for various VA groups are summarized in Table 2. The largest decrease in utilities occurs when LogMAR VA in the better eye is 0.6 or larger (Snellen equivalent <0.25), particularly in patients who underwent either unilateral or bilateral corneal transplantation.

Table 1. Utilities of keratoconus patients in various disease stages from the CLEK cohort

Better eye (Stage)	Worse eye (Stage)	Utilities (SF-6D)	SD	N
I	I	0.85	0.122	2629
I	II	0.83	0.123	1799
I	III	0.85	0.127	209
I	IV	0.84	0.119	446
II	II	0.85	0.124	1071
II	III	0.82	0.136	368
II	IV	0.83	0.125	555
III	III	0.82	0.139	64
III	IV	0.84	0.127	181
IV	IV	0.85	0.124	372
After corneal transplantation				
I	Tx	0.82	0.135	458
II	Tx	0.83	0.130	337
III	Tx	0.83	0.130	124
IV	Tx	0.83	0.129	250
Tx	Tx	0.80	0.137	204

Abbreviations: N, number of measurements; stage, disease severity based on the keratometry value using the Amsler–Krumeich classification; SF-6D, mean utility derived from SF-36; Tx, corneal transplantation.

Table 2. Utilities measured in keratoconus patients depend on visual acuity in the better eye

LogMAR VA better eye	Snellen VA better eye	Utilities (SF-6D)	SD	N
No previous corneal transplantation				
≤0.3	≥0.5	0.85	0.119	5168
0.3-0.6	0.25-0.5	0.83	0.131	2417
>0.6	<0.25	0.81	0.140	241
After unilateral corneal transplantation				
≤0.3	≥0.5	0.84	0.119	725
0.3-0.6	0.25-0.5	0.82	0.158	414
>0.6	<0.25	0.69	0.132	79
After bilateral corneal transplantation				
≤0.3	≥0.5	0.81	0.132	125
0.3-0.6	0.25-0.5	0.83	0.137	55
>0.6	<0.25	0.68	0.186	13

Abbreviations: LogMAR VA best eye, LogMAR visual acuity in the best eye, measured with the patient's usual correction (unaided or lenses and/or spectacles); N, number of measurements; snellen VA best eye, Snellen visual acuity in the best eye; utilities, mean SF-6D utility.

In conclusion, quality of life as measured by SF-6D in keratoconus patients is related to VA in the better eye, whereas no correlation could be identified between quality of life and keratometry values or disease stage. We postulate that VA may be a better intermediate outcome to base QALYs on than either keratometry or disease stage.

ACKNOWLEDGEMENTS

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Cost-effectiveness of corneal crosslinking for progressive keratoconus

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Submitted

ABSTRACT

Purpose

To evaluate the cost-effectiveness of corneal crosslinking (CXL) for progressive keratoconus from the healthcare payer's perspective.

Design

A probabilistic Markov-type model utilizing data from published clinical trials and cohort studies.

Methods

Two identical cohorts, each comprised of 1,000 virtual patients with progressive bilateral keratoconus, were modeled and evaluated annually over a lifetime; one cohort received CXL and the other cohort received no intervention. Quality-adjusted life years (QALYs), total cost, disease progression, and the probability of corneal transplantation and/or graft failure were calculated based on data from published trials and cohort studies, and these outcomes were compared between the two cohorts. In our base scenario, the stabilizing effect of CXL was assumed to be ten years; however, longer durations were also analyzed. One-way sensitivity analyses were performed to test the robustness of the outcomes.

Main Outcome Measure

Incremental cost-effectiveness ratio (ICER), defined as euros/QALY.

Results

Assuming a 10-year effect of CLX, the ICER was €54,384/QALY ($59,822/QALY). When we adjusted the effect of CXL to a lifelong stabilizing effect, the ICER decreased to €10,149/QALY ($11,163/QALY). Other sensitivity and scenario analyses that had a relevant impact on ICER included the discount rate, pre-CXL visual acuity, and healthcare costs.

Conclusions

CXL for progressive keratoconus is cost-effective at a willingness-to-pay threshold of €115,518 ($127,070), which is three times the current gross domestic product (GDP) per capita. Moreover, a longer stabilizing effect of CXL increases cost-effectiveness; If CXL would have a lifetime stabilizing effect on keratoconus the ICER would be under the one time GDP per capita threshold and thus very cost effective.

INTRODUCTION

Keratoconus is a corneal disease with onset typically occurring in adolescence or early adulthood. The estimated prevalence of keratoconus is one in 2000 individuals.[1] Although the precise pathophysiology is currently unknown, progressive, localized corneal thinning leads to conical ectasia with resulting irregular astigmatism and associated visual impairment. Nearly all patients present with bilateral keratoconus, although some cases may initially seem unilateral.[2,3] Disease progression usually ceases with increasing age.[4] In most cases, visual acuity can be restored non-surgically through the use of glasses; in advanced stages, specialized contact lenses may be indicated. However, more than 20% of patients ultimately require corneal transplantation in order to restore visual acuity.[5] Both decreased visual performance and the need for corneal transplantation are associated with a significant decrease in the patient's quality of life (QoL).[6]

Corneal crosslinking (CXL) is a relatively new treatment option for patients with keratoconus. CXL can prevent the progression of keratoconus by increasing the cornea's biomechanical stability using ultraviolet irradiation and riboflavin to form crosslinks between the macromolecules within the corneal stroma.[7,8] In both clinical trials and cohort studies, CXL has been shown to halt disease progression in the vast majority of treated individuals, often improving corneal shape and visual performance.[9,10,11] In addition, two recent studies found a link between the introduction of CXL and a reduced need for future corneal transplantation.[12,13]

Currently, CXL is not covered by most health insurance providers in many countries, and information regarding the cost-effectiveness of CXL is scarce. In a standard cost-effectiveness analysis, the benefits associated with an intervention can be expressed in several ways; however, quality-adjusted life years (QALYs) are often the preferred denominator, as it enables the policy maker to compare efficiency of all measures that affect human health, irrespective of the medical condition targeted by the intervention.[14] QALYs are a composite value comprised of both mortality and morbidity and express the number of healthy years gained from treatment. The number of life years is typically adjusted for quality of life by applying a "weight" factor—ranging from 0 (death) to 1 (perfect health)—to the number of life-years lived in a certain health state.[14]

Calculating QALYs in ophthalmology can be challenging, as decreased visual acuity in one or both eyes can have a varied impact on quality of vision.[34] Moreover, given the progressive nature of keratoconus, a complex modeling approach is needed to obtain a realistic estimate of the disease's impact on QoL. A recent analysis by Salmon et al. using data obtained from the UK's National

Health Service provided the first estimates of the cost-effectiveness of CXL based on keratometry outcome.[15] The authors concluded that CXL is cost-effective, and that the level of cost-effectiveness depended on assumptions regarding the duration of CXL effectiveness. However, from the patient's perspective, vision is generally a more relevant intermediate outcome than keratometry or disease stage for determining QALYs.

The aim of our study was to evaluate the cost-effectiveness of CXL for keratoconus from the healthcare payer's perspective. Our analysis was based on data from published, peer-reviewed clinical trials and cohort studies.

METHODS

Model and population

Two identical cohorts were created, each containing 1,000 virtual patients (2,000 eyes) with progressive bilateral keratoconus. One cohort received CXL, and the other cohort received no initial intervention. The clinical characteristics of these cohorts were based on the individual patient data obtained for 146 eyes of patients who had enrolled in two randomized controlled trials on CXL for progressive keratoconus.[9,10] All of the patients in these two trials were diagnosed with progressive keratoconus based on visual acuity, refractive astigmatism, and keratometry. For modeling purposes, the following three distinct best spectacle–corrected distance visual acuity categories were created and were used to represent disease severity: "Good" (defined as LogMAR visual acuity ≤0.3), "Medium" (LogMAR visual acuity 0.3-0.6), and "Bad" (LogMAR visual acuity >0.6). The virtual patients in the two cohorts were distributed throughout the three visual acuity categories using the actual distributions in the two trials (see Table 1).

A stochastic Markov-type model was built with a one-year cycle length. The model was generated in Microsoft Excel (2010, Redmond, WA) using the @ RISK (Palisade, 2010, Ithaka, NY) add-in program. The analysis began with the patients at 22 years of age, and the patients were followed until the time of death or 100 years of age, whichever came first. In our model, each patient could have different disease stages in each eye, and each of the two eyes had an individual probability of disease progression (see below). Since life expectancy of keratoconus patients was reported not to differ from the general population, mortality rates were based on data from the general population, obtained from Statistics Netherlands.[17]

Modeling disease progression and treatment effect

Each year, the patients in the two cohorts either transitioned to a different health stage or remained in their current health state. In the non-intervention cohort, the annual probability of transitioning to a different visual acuity category was based on the clinical data for the untreated eyes in the two RCTs and was modeled as a gamma (γ) distribution (see Table 1). We applied the intention-to-treat principle; therefore, if an eye in the non-intervention group of the two RCTs was transplanted or treated with CXL within one year of the baseline measurement, we assumed one stage of deterioration. When an eye was in the "Bad" category at baseline, we assumed that this eye would remain in this category. This occurred in six eyes in the non-intervention group in the two RCTs and in no eyes in the CXL group.

In the CXL cohort, the probability of transitioning to a different category was calculated similarly (Table 1). Visual acuity was assumed to be stable for up to ten years following CXL, as this is the longest published stabilizing effect.[11] In this base-case scenario, after ten years, we assumed that the disease would progress as if untreated.

Based on published data, we assumed that the progression of keratoconus would stabilize at 50 years of age (Table 1).[4] The sample sizes for transitions between the visual acuity categories were increased by a factor of ten in order to improve model stability and to correct for small sample sizes in the lower visual acuity categories.

Modeling corneal transplantation

The probability of receiving a corneal transplantation was based on data obtained from the Collaborative Longitudinal Evaluation in Keratoconus (CLEK) cohort, which includes more than 1,200 patients with a follow-up period of up to eight years.[19] The probability of receiving a corneal transplantation was dependent solely on visual acuity, and we assumed that corneal transplantation would be performed in the eye with worse visual acuity. The annual probability of transplantation was modeled for each of the three visual acuity categories using a gamma distribution (see Table 1). Based on a total follow-up of 5,231 person-years, the average annual probability of transplantation for an eye in the "Good" visual acuity category was 0.80%, and the average annual probability of eyes in the "Medium" and "Bad" visual acuity categories was 1.88% and 5.74%, respectively, based on 2,451 and 244 person-years, respectively. We assumed that the first graft based on a diagnosis of keratoconus would occur at 55 years of age or younger (Table 1).[20]

In both cohorts, the annual probability of failure for the first and subsequent grafts was based on data obtained from the Australian Graft Registry (see Table 1).[21] We modeled the probability of graft failure separately for the first and subsequent transplantations. In cases of graft failure, we assumed that a subsequent transplantation would be performed. The maximum number of transplantations per eye was three; in cases in which the third graft failed, we assumed that the eye would remain in the "Bad" visual acuity category.

Differences in graft failure rate and visual outcome between lamellar surgery and penetrating surgery were not taken into consideration in our analysis, as visual acuity outcome is generally similar between these two techniques[22] and because data regarding graft survival is unequivocal.[23,24]

Calculation of QALYs and healthcare costs

QALYs were derived for each visual acuity category based on data from the CLEK cohort (Table 1).[6] Because QoL for keratoconus patients is related to visual acuity in the better eye, QALYs were determined in both cohorts on a per-case basis according to the better-seeing eye.[25] Neither adverse events nor complications following corneal transplantation were modeled separately, as their effect on QALYs were already incorporated in the QALYs reported in the CLEK cohort.

The healthcare costs associated with CXL and corneal transplantation were based on microcosting studies performed in hospitals in the Netherlands and included both preoperative consultations and postoperative consultations for up to one year following the procedure.[26,27] Costs were expressed in 2015 euros, using the consumer price index. An exchange rate of 1 euro to 1.10 US dollars was applied.

Cost-effectiveness analyses

Our model estimated the number of first-time transplanted eyes, the total number of transplantations, healthcare costs, and QALYs for both cohorts. The number of avoided transplantations, the net costs, and QALYs gained were calculated by summing and comparing all transplantations, costs, and QALYs over the entire lifetime of the patients in both cohorts. Although the model outcome was stable after 1,000 iterations, we performed 5,000 iterations for each scenario using Monte Carlo simulation sampling, with the initial seed for each simulation fixed at 1.

The incremental cost-effectiveness ratio (ICER) was calculated by dividing the net aggregated cost differences by the net aggregated difference in effects (i.e., QALYs, the number of crosslinking treatments, and the number of first-time and subsequent transplantations) between the two simulated cohorts. We performed

this cost-effectiveness analysis from the healthcare payer's perspective; thus, only costs incurred within the healthcare system (e.g., costs associated with personnel, medication, crosslinking treatment, corneal transplantation, etc.) were included in this analysis. The discounted value (i.e., the present value of a future cost) was applied to both costs and QALYs at 3% per year in accordance with World Health Organization (WHO) criteria.[28] A strategy was considered to be highly cost-effective if ICER was under the 1x gross domestic product (GDP)/capita threshold and cost-effective if ICER was under the 3xGDP/capita threshold.[28] We used the most recent GDP per capita in the Netherlands, which is €38,506 ($42,356).[29] The results were then plotted on the cost-effectiveness plane and as a cost-effectiveness acceptability curve. This curve shows the percentage of the 5,000 iterations that indicate cost-effectiveness at a certain threshold value for the willingness to pay for one QALY.

Scenario and sensitivity analyses

The parameters that were used in this model inherently contain a degree of uncertainty. Therefore, to assess the impact of this uncertainty on our results, we performed in-depth scenario and sensitivity analyses for plausible variations. These analyses provide an indication of the model's robustness and its likelihood of revealing changes in results when assumptions are altered. Scenario and sensitivity analyses were performed by varying key input parameters from the base-case scenario. The results were plotted in a tornado graph to visually represent the relative changes in the determinants of baseline cost-effectiveness and the relative change in the baseline ICER. Scenario and sensitivity analyses were performed by drawing 5,000 times from the distribution of parameter values (see Table 1).

Table 1. Summary of model input parameters in the base-case model.

Variable	Value			Distribution/Source/Assumption Calculation
Population modeled				
Theoretical cohort of 1000 patients (2000 eyes)	Starting age: 22 years			Wittig-Silva et al. 2014 and O'Brart et al. 2011[9,10]
Distribution of population based on visual acuity[a]	Better eye	Worse eye	%	Wittig-Silva et al. 2014 and O'Brart et al. 2011[9,10]
	Good	Good	36.6%	
	Good	Medium	23.6%	
	Good	Bad	19.7%	
	Medium	Medium	10.6%	
	Medium	Bad	6.7%	
	Bad	Bad	2.8%	
Annual probability of dying	Age-dependent			Statistics Netherlands[29]
Changes in visual acuity (VA) with or without crosslinking[b]				
» Untreated eye				
Annual probability that the current VA category would change to…	Current VA	Changes to…	Transition chance/year	Wittig-Silva et al. 2014 and O'Brart et al. 2011[9,10]
	Good	Good	Calculated	$1-\beta^{G}_{1}-\beta^{G}_{2}$
	Good	Medium	60/530	β
	Good	Bad	20/530	β
	Medium	Good	Calculated	$1-\beta^{M}_{1}-\beta^{M}_{2}$
	Medium	Medium	60/160	β
	Medium	Bad	10/160	β
	Bad	Good	10/40	β
	Bad	Medium	0/40	β
	Bad	Bad	Calculated	$1-\beta^{B}_{1}-\beta^{B}_{2}$
Stabilization of keratoconus at age:	50 years			Rabinowitz 1998[2]

Table 1. Summary of model input parameters in the base-case model. (continued).

Variable	Value			Distribution/Source/Assumption Calculation
» CXL-treated eye				
Probability that due to the CXL treatment the current VA category would change in the first year to…	Current VA	Changes to…	Transition chance/year	Wittig-Silva et al. 2014 and O'Brart et al. 2011[9,10]
	Good	Good	Calculated	$1-\beta^{G}_{1}-\beta^{G}_{2}$
	Good	Medium	40/490	β
	Good	Bad	0/490	β
	Medium	Good	Calculated	$1-\beta^{M}_{1}-\beta^{M}_{2}$
	Medium	Medium	20/140	β
	Medium	Bad	20/140	β
	Bad	Good	10/50	β
	Bad	Medium	Calculated	$1-\beta^{B}_{1}-\beta^{B}_{2}$
	Bad	Bad	10/50	β
CXL effect duration	10 years same as for an untreated eye (see above)			Rasikup et al. 2015[11]
Change in VA after CXL effect has passed				We assume that the effect of CXL after CXL effect duration is equal to zero.
First and subsequent corneal transplantations (TX)[c]				
Annual probability of 1st TX in one of the two eyes	VA category with worst outcome		Transition chance/year	CLEK cohort[18] Assuming that corneal transplantation will always occur on the eye with the worst visual acuity
	Good		42/5231	β
	Medium		46/2451	β
	Bad		14/244	β
Annual probability of 1st TX of 2nd eye	0.5 times the annual probability of 1st TX (see above)			Assumption based on CLEK cohort[18]
Maximum age of 1st-time TX	55 years			Godefrooij et al 2016[20]

Table 1. Summary of model input parameters in the base-case model. (continued).

Variable	Value		Distribution/Source/Assumption Calculation
First graft: annual chance of failure	Years since transplantation	Chance of failure yearly	Australian corneal graft registry report[21]
	1	0.0300	
	2–5	0.0051	
	6–10	0.0130	
	11–15	0.0286	
	≥16	0.1019	
Second graft: annual chance of failure	Years since transplantation	Chance of failure yearly	Australian corneal graft registry report[21]
	1	0.0900	
	≥2	0.0730	
Third graft: annual chance of failure	Years since transplantation	Chance of failure yearly	Australian corneal graft registry report[21]
	1	0.230	
	≥2	0.0696	
Utilities			
QALY	Stage	QALY	Godefrooij et al. 2016[6]
	Good VA (better eye)	0.84	
	Moderate VA (better eye)	0.83	
	Bad VA (better eye)	0.81	
	TX & good VA	0.84	
	TX & moderate VA	0.82	
	TX & bad VA	0.69	
	TX & TX	0.81	
	Max TX & max TX	0.68	

Table 1. Summary of model input parameters in the base-case model. (continued).

Variable	Value	Distribution/Source/Assumption Calculation	
Costs			
Cost for corneal transplantation	Mean: €7334.67; SD: €143	γ	Biggelaar et al. 2011[27]
Cost for CXL treatment	Mean: €1754.06; SD: €177	γ	Godefrooij et al. 2016[26]

a) Three visual acuity categories were used to represent disease severity: "Good", "Medium", and "Bad" visual acuity corresponds to LogMAR visual acuity values of ≤0.3, 0.3-0.6, >0.6, respectively.
b) The change in the visual acuity of one eye was assumed to be independent of the change in visual acuity in the other eye.
c) We assumed the same probabilities for patients with crosslinking and patients without crosslinking. Moreover, we assumed that no corneal transplantation would occur in the first year and that the maximum number of transplantations in a patient's lifetime is three.

RESULTS

Prevention of visual acuity loss

In both the CXL and non-intervention cohorts, 79.9% of the patients started with "Good" VA in the better eye. After 10 and 50 years, 74.4% and 37.5% of the patients in the non-intervention cohort, respectively were still in the "Good" VA category. Assuming a 10-year stabilizing effect of CXL, after 10 and 50 years 81.1% and 40.7% of the patients in the CXL cohort, respectively, were still in the "Good" VA category.

Prevention of a first transplantation

In the non-intervention cohort, a total of 567 out of 2,000 eyes (95% CI: 422-760) in our model would require a first-time corneal transplantation at an average age of 37.7 years. In contrast, in the CXL cohort, a total of 512 out of 2,000 eyes (95% CI: 400-650) would undergo a first-time corneal transplantation at an average age of 38.9 years (assuming a 10-year stabilizing effect of CXL). This difference translates to approximately 55 fewer first-time transplantations (95% CI: 13-105), with these transplantations occurring on average a year later.

If the stabilizing effect of CXL is adjusted to a lifelong value, our model indicates that only 393 (95% CI: 331-454) first-time corneal transplantations would be needed in the CXL cohort, resulting in 174 first-time transplantations prevented (95% CI: 52-351).

Subsequent transplantations prevented

In the non-intervention cohort, a total of 915 (95% CI: 678-1,232) second and third corneal transplantations were performed at an average age of 60.1 years. In the CXL cohort, a total of 812 eyes (95% CI: 636-1,026) underwent a second and third corneal transplantation at an average age of 61.2 years (assuming a 10-year stabilizing effect of CXL). This difference translates to approximately 103 fewer subsequent transplantations (a reduction of 11.3%) with these transplantations occurring on average a year later.

If we assumed the stabilizing effect of CXL to extend over the patient's lifespan (i.e., a lifelong effect), the number of subsequent prevented transplantations would increase to 278 (95% CI: 82-564), thus reducing subsequent transplantations by 30.4% compared to the non-intervention cohort.

QALYs and healthcare costs

Assuming a 10-year effect of CXL, the mean value for estimated QALYs during the patients' lifetime was 23,457 (95% CI: 23,277-23,569) in the non-intervention

cohort and 23,508 (95% CI: 23,393-23,585) in the CXL cohort, translating to a net increase in QALY gain of 51(95% CI: 13-119). In this scenario, the total lifetime healthcare costs were €5.05/$5.56 million (95% CI: €3.70-6.87/$4.07-7.56 million) in the non-intervention cohort and €7.87/$8.66 million (95% CI: €6.68-9.21/$7.35-10.13 million) in the CXL cohort, translating to an increase in costs of €2.82/$3.10 million (95% CI: €1.84-3.76/$2.02-4.14 million) in the CXL cohort.

Cost-effectiveness

Assuming a 10-year stabilizing effect of CXL, the incremental cost-effectiveness ratio (ICER) of CXL for progressive keratoconus is €54,384/QALY (95% CI: €16,350-257,589)($59,822/QALY; 95% CI: $17,985-283,347). Thus, each QALY increase is realized at a net increase in healthcare costs of €54,384 ($59,822). The WHO applies a willingness-to-pay (WTP) threshold for interventions that is three times the GDP per capita; the most recent per-capita GDP in the Netherlands was €38,506 ($42,356).[29] The cost-effectiveness plane shows that the vast majority of simulations (82.9%) resulted in an ICER value below this WTP threshold (Figure 1). Thus, the probability that CXL at this threshold is cost-effective is 82.9%. If the WTP threshold is set to 1xGDP per capita, a treatment would be regarded very cost-effective. Assuming a 10-year stabilizing effect of CXL, the average ICER value would not fall below this WTP threshold for 1xGDP per capita.

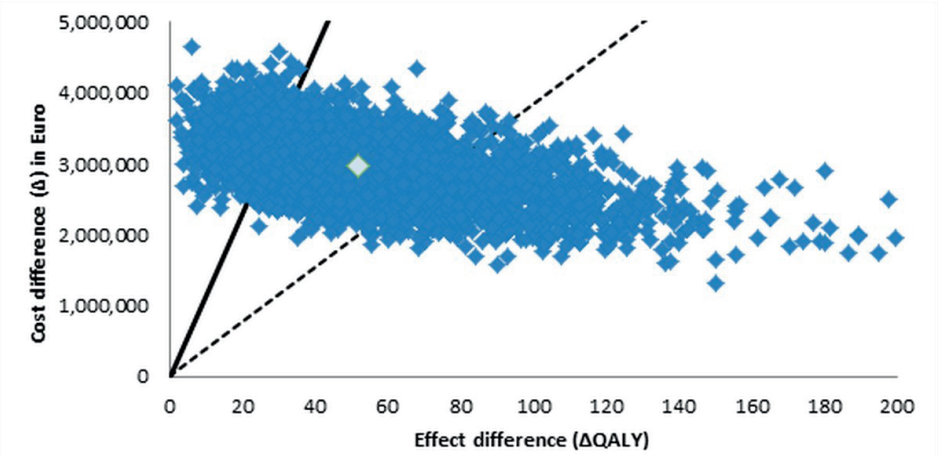

Figure 1. Cost-effectiveness plane for CXL for progressive keratoconus, assuming a 10-year stabilizing effect of CXL. The squares represent the outcomes of the 5,000 iterations of the model. The solid line indicates the willingness-to-pay (WTP) threshold of 3x the gross domestic product (GDP) (€115,518/$127,070); the dashed line indicates a WTP threshold of 1xGDP, which is €38,506 ($42,356). QALY=quality-adjusted life years.

If we increase the stabilizing effect of CXL from 10 years to 15 years, the ICER value decreases from €54,384/QALY ($59,822/QALY) to €33,899/QALY ($37,288/QALY), thereby increasing cost-effectiveness. Increasing the stabilizing effect of CXL to the patient's lifespan decreases the ICER even further, to €10,149/QALY ($11,163/QALY). The relationship between the duration of CXL effectiveness and ICER values is illustrated in Figure 2.

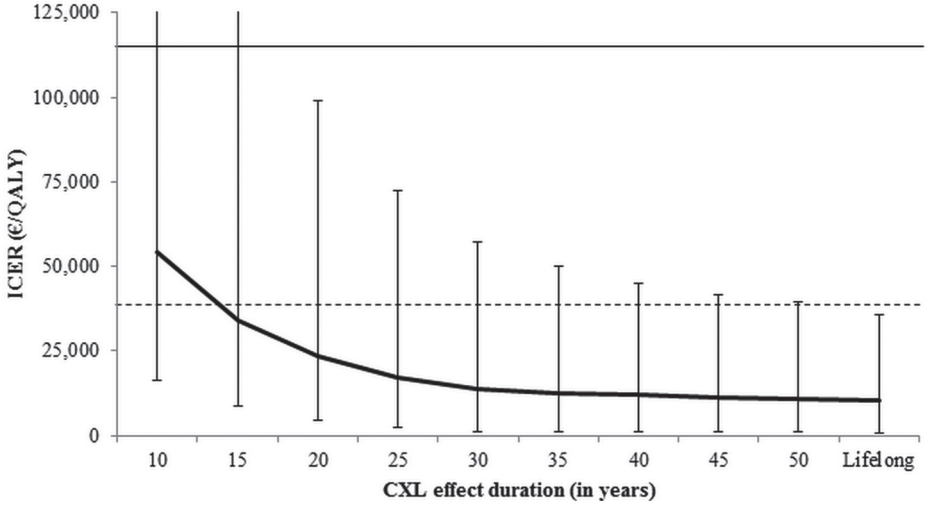

Figure 2. The relationship between the duration of CXL effectiveness and the ICER. The solid horizontal line indicates the willingness-to-pay (WTP) threshold of 3xGross Domestic Product (GDP) (€115,518/$127,070), and the dashed horizontal line indicates the WTP threshold of 1xGDP (€38,506/$42,356). The error bars show the limits of 95% of the simulations.

Scenario analyses and sensitivity analyses

Results of scenario analyses and sensitivity analyses are shown in Figure 3. Next to the duration of the stabilizing effect of CXL, the discount rate has the largest effect on ICER, with improved cost-effectiveness occurring below a discount rate of 3%.

Initial visual acuity also had a relevant impact on the ICER. We created a scenario of "better visual acuity to start with" by reducing the number of patients who were not in the bilateral "Good" category by 50% in order to determine the effect on the ICER if patients are diagnosed and treated in an earlier phase of the disease (i.e., prior to a decrease in visual acuity). In this scenario, the ICER decreases from €54,384/QALY ($59,822/QALY) to €44,191/QALY ($48,610/QALY).

A change in healthcare costs and the use of accelerated CXL can also have an impact on the ICER.[30] Because personnel costs associated with CXL decrease by 19.6% when accelerated CXL is performed, the ICER would decrease from

€54,384/QALY ($59,822/QALY) to €48,937/QALY ($53,831/QALY).[26] Other scenario and sensitivity analyses regarding parameter uncertainty had no major influence on the results (Figure 3).

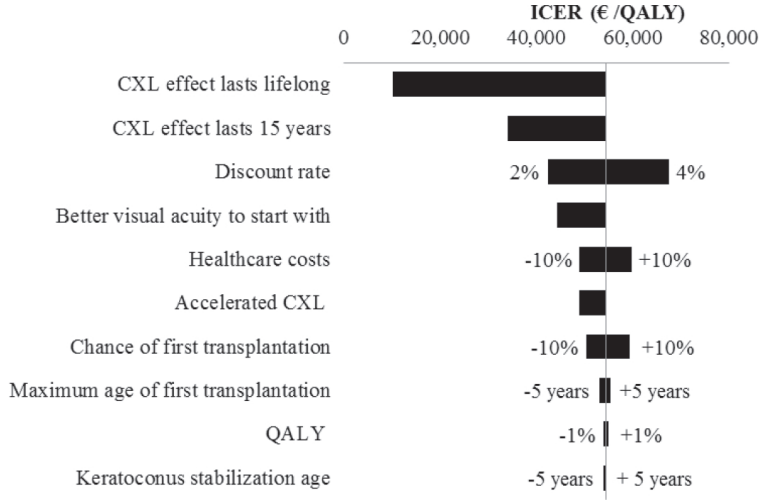

Figure 3. Tornado graph depicting the change in ICER following various scenario and sensitivity analyses. The magnitude of the bar relative to the vertical line represents the magnitude of the effect of varying a given parameter on the outcome. Bars to the left represent a lower ICER (and thus more favorable cost-effectiveness), and bars to the right represent a higher ICER (and thus less favorable cost-effectiveness). In the scenario "better visual acuity at baseline to start with", the number of patients not in the bilateral "Good" category was reduced by 50%. In the "healthcare costs" scenario, the costs associated with crosslinking and transplantation vary by ±10%. In the "accelerated CXL" scenario, the cost associated with the crosslinking treatment are reduced by 19.6%.[25]

DISCUSSION

Our analysis shows that the incremental cost-effectiveness ratio associated with CXL for progressive keratoconus is €54,384 ($59,822) per QALY gained. We found that cost-effectiveness is strongly influenced by the assumption of CXL effectiveness duration, which was set at ten years in the base-case scenario, as this is the longest follow-up period for CXL in literature.[11] However, long-term follow-up studies suggest that the stabilizing effect of CXL does not appear to diminish over time, and indeed many studies found continued improvement in both topographic and visual parameters.[11,31] Therefore, it is plausible to assume that the stabilizing effect of CXL is well beyond ten years.[16] Such an increase in the stabilizing effect of CXL would result in lower ICER (i.e., higher cost-effectiveness); specifically, increasing the stabilizing effect of CXL from 10 years to the patient's lifespan decreases the ICER from €54,384/QALY ($59,822/QALY) to €10,149/QALY ($11,163/QALY).

Salmon et al. reported that crosslinking is highly likely to be cost effective for management of progressive keratoconus.[15] We believe that our cost-effectiveness model has a number of advantages over the previously reported model. Treatment effects and disease progression in this study were based on individual patient data from two randomized controlled trials, allowing to model disease progression and CXL effectiveness in a way that mimics clinical practice.[9,10] Transplantation rates were based on real clinical data of the longitudinal CLEK study, with more than 8,000 patient years of data on visual acuities, QoL and corneal transplantation rates. Graft failure rates from the Australian graft registry were used.[20] As we used international data on clinical effectiveness and disease progression, our findings should be generalizable to most developed countries. Finally, disease progression was modeled using three distinct categories of visual acuity, rather than using keratometry readings. This approach enabled us to calculate cost-effectiveness taking into account outcomes that matter most from the patient's perspective. This is an important point, given that corneal curvature is considered an intermediate clinical outcome to patients; moreover, because corneal curvature is not directly related to the patient's visual acuity, it has relatively little association with the patient's QoL.[6]

Our cost-effectiveness analysis was performed from a healthcare perspective, as it included only costs associated with the healthcare system (e.g., the costs associated with outpatient care, crosslinking treatments, and corneal transplantation). Thus, costs incurred outside of the healthcare system (e.g., costs associated with travel, visual aids such as spectacles/contact lenses, care provided by friends and family, and loss of productivity) were not taken into account. This was done in order to obtain conservative values for the cost-effectiveness of CXL. Precise data regarding the loss of productivity associated with keratoconus are not available, although a reduction in visual acuity can result in loss of productivity.[32] Had we included loss of productivity in our analysis, the ICER value due to CXL might have been more favorable. Costs associated with visual aids were also not included in our analysis, as no data are available regarding the effect of CXL on the use of visual aids; moreover, we assumed that patients with keratoconus generally require a visual aid irrespective of whether they undergo CXL. Therefore, we believe that incorporating the use and/or costs associated with visual aids into our model would have had little—if any—impact on cost-effectiveness.

Another important consideration is that our modeling approach is based on bilateral keratoconus. Treating unilateral keratoconus in a patient with good visual acuity in the unaffected eye is unlikely to be cost-effective if QALYs are based on visual acuity in the unaffected eye, as treating the affected eye would

not result in a significant increase in QALYs.[33] This essentially holds true for most ocular conditions and reflects a fundamental flaw inherent to calculating cost-effectiveness in the field of ophthalmology, because visual acuity in the worse eye has shown to be able to affect vision-related QoL, particularly in ocular conditions that affect the peripheral visual field.[34]

It is important to note that all of the patients in the clinical studies upon which we based our modeling had a documented progression of keratoconus. If the indication for CXL treatment were less stringent (i.e., if treatment were to occur in the absence of documented disease progression), our cost-effectiveness estimates would likely decrease, as the number of preventable corneal transplants will be reduced as non-progressive eyes are unlikely to deteriorate to a stage at which transplantation would be indicated. Conversely, cost-effectiveness could increase if patients are selected based on having a high risk of visual deterioration and a subsequent need for corneal transplantation. Therefore, identifying which eyes are most likely to progress, as well as developing effective algorithms that ensure that only these eyes undergo CXL, could greatly maximize cost-efficiency.

Several clinical observations were not included in the progression model, including complications following crosslinking. However, CXL-related adverse events are relatively rare, and their effect on visual acuity and disease progression are largely unknown; moreover, published evidence regarding CXL-related complications is anecdotal at best.[35] Another clinical observation is that CXL can provide long-term improvements in both corneal shape and visual acuity, even years after treatment. Improved visual acuity years after treatment might further reduce the rate of transplantation in the CXL cohort. Finally, our model does not discriminate between anterior lamellar and penetrating procedures. Currently, anterior lamellar surgery is considered the treatment of choice for keratoconus.[36] This preference is based on a presumed increase in graft survival. Nevertheless, penetrating surgery remains popular,[20] and data regarding graft longevity are unequivocal.[23,24] The probability of graft survival that we used in our model is based on data obtained from the Australian Graft Registry, and their data regarding anterior lamellar surgery do not indicate improved graft survival, further supporting our decision to exclude this type of surgery as a major factor when determining cost-effectiveness.[37]

CONCLUSIONS

Our analyses revealed that the introduction of corneal CXL for progressive keratoconus is cost effective at a willingness-to-pay threshold of three times the

GDP per capita. Cost-effectiveness is strongly influenced by the assumption of CXL effectiveness duration, which was set at ten year in the base-case scenario. If CXL would have a stabilizing effect on keratoconus of fifteen years or longer the treatment would be under the one time GDP per capita threshold and thus very cost effective.

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14

Summary and discussion to this thesis

Daniel A. Godefrooij

The aim of this thesis was to provide evidence for clinical and policy decisions concerning the treatment of keratoconus. This summary and discussion is organized in sections following the three focus points of this thesis: epidemiology, treatment effects and economic evaluation.

EPIDEMIOLOGY

One of the aims of this thesis was to determine reliable and up-to-date estimates of the annual incidence and prevalence of keratoconus. **Chapter 2** reports on the current incidence and prevalence of keratoconus, based on the records of 4.4 million people from the largest health insurance provider in the Netherlands. The incidence and prevalence of keratoconus in our study are five-fold to ten-fold higher than previously reported,[1] suggesting that keratoconus is more common than previously suggested. These values provide insight in the extent of this disease and are essential for policy makers in order to estimate the true impact of keratoconus care on healthcare budgets. Previous studies found that Asian people are at an approximately ten times higher risk of developing keratoconus than Caucasian people, and do so at an earlier age.[2–4] Especially in young keratoconus patients, progression can be rapid and devastating; as a result, younger patients have a higher likelihood of requiring corneal grafting surgery.[5,6] Often the optician or optometrist has the first opportunity to suspect/diagnose a keratoconus when a patient suffers from progressive myopisation and/or (irregular) astigmatism. This suspicion is based on clinical symptoms. As computer-based technologies and imaging techniques have improved, the ability to diagnose keratoconus at a pre-clinical stage has evolved.[7–9] Despite the advances in crosslinking technology and subsequent increased clinical/research interest in keratoconus, clinical practice shows that many patients are not diagnosed in the earlier disease stages. Valuable eyesight might thus be needlessly lost. Therefore, screening for sub-clinical or early stage keratoconus might be beneficial in terms of preventing vision loss and healthcare costs such as corneal transplantations. Evaluating the efficacy and cost-effectiveness of such a screening program for keratoconus is one potential future perspective of keratoconus care. Whether this screening program should aim at the general population or at (high) risk groups (e.g. family members of keratoconus patients or patients with peri-ocular atopic disease) should be part of such an analysis.

Corneal surgery underwent major changes during the last decades with the event of (deep) anterior lamellar keratoplasty as one of the largest innovations for keratoconus surgery.[10–13] In (deep) anterior lamellar keratoplasty the host's

endothelium is preserved with the (theoretical) advantage of lower graft rejection compared to penetrating techniques. Because most keratoconus patients are relatively young, reducing graft failure is of paramount importance, particularly given that replacement transplants generally have worse clinical outcomes and shorter survival times.[14] In **Chapter 3** we investigated to what extent novel transplantation techniques have been implemented in the Netherlands over the last decade. Strength of this study is the use of an obligatory nationwide database which contained information on more than a thousand transplantations for keratoconus. One of the promises of deep anterior lamellar keratoplasty is the longer graft survival time. However, results are equivocal and since this new intervention has only been implemented several years ago, no solid conclusions on long term graft survival can be drawn at this moment.[15,16]

One of the future candidates to compete with corneal transplantations in the field of advanced corneal disease management is cell therapy. The goal of corneal cell therapy is to insert autologous living cells to replace or support affected cells, while leaving the unaffected cells and structures in place.[17] This would surpass many difficulties of transplantation that are related to surgical complications and allograft rejection. Different types of (stem) cells have been induced to express corneal cell characteristics in vitro[18] and in animal studies,[19] but to date there are no peer-reviewed publications on the treatment of corneal stromal cell diseases (e.g. keratoconus) in humans.[17] Keratoconus treatment is currently shifting towards intervening in the early stages of the disease process to prevent deterioration and the consequential need for a corneal transplantation. The next two sections of this summary and discussion are dedicated to this topic.

TREATMENT EFFECTS

At the time of the start of this research project the short term beneficial effect of crosslinking for progressive keratoconus in adults had been proven in three randomized controlled trials.[20–22] **Chapter 4** provided the results of our own cohort of children treated with crosslinking with a maximum follow-up of five years, which is the longest follow-up study on children after crosslinking to date. An interesting finding in this chapter is that the chance of progression despite treatment is much higher in children (22%) then in adults (2-10%).[22,23] This underlines the fact that evidence of crosslinking effects in adults might not be generalizable to children and stresses the importance of long-term follow-up in children. This chapter also provides a systematic overview of published results of different types of crosslinking in children. One of the difficulties in comparing

outcomes among studies is the range of different outcome measurements that are used, ranging from patient related outcomes such as visual acuity and quality of life to disease specific outcomes such as corneal thickness and curvatures. One of the future challenges in keratoconus research is to reach consensus on the most appropriate outcome measures and maybe to even create compound scores that incorporate the most relevant outcomes into sum scores, enabling comparison between studies and different disease entities. Such consensus should not only be reached among healthcare workers involved in ophthalmology, but should also comprise of extensive discussions with patient groups on outcomes that matter to patients. So far, outcomes are often reported in terms of technical measures, such as corneal curvatures and higher-order aberrations.[24] However, as was demonstrated in this thesis, the relationship between these technical measures and patient reported outcomes is not always coherent.

Although the transepithelial crosslinking technique was lauded by many for its potential beneficial effects, head-to-head comparison between the transepithelial technique and original technique with epithelium removal (epi-off) had not been performed at the start of this PhD project. **Chapter 5** reports on a randomized controlled trial comparing transepithelial crosslinking with the epi-off crosslinking. The transepithelial technique proved to be less effective in halting keratoconus progression than the epi-off treatment. Paradoxically, the transepithelial group did benefit more in terms of visual acuity. In **Chapter 6** we investigated whether this difference in visual acuity was related to changes in the complex optical refractive state of keratoconus corneas, expressed in higher-order aberrations. Higher-order aberrations can affect visual acuity and cause glare and halos. Because higher-order aberrations are correlated to disease severity and crosslinking improves corneal keratometry in general, we hypothesized that changes in higher-order aberrations could affect visual acuity after crosslinking.[25] However, changes in total higher-order aberrations did not differ between the two crosslinking groups; only horizontal trefoil differed significantly between the two groups, with a (paradoxically) more favorable outcome in the epi-off treatment group. Moreover, we found no independent relationship between the change in horizontal trefoil and visual acuity outcome. Therefore, we concluded that no clinically relevant differences exist between the two treatment entities with respect to the effects on higher-order aberrations. In the following years the scientific interest for transepithelial treatments waned because many patients that were initially treated with transepithelial crosslinking had to be re-treated with epi-off crosslinking in order to halt the progression of keratoconus.[26]

In **Chapter 7** we decided to focus on the changes in higher-order aberrations after the epi-off crosslinking treatment on visual acuity in a much larger

cohort (n=187). We found that crosslinking had limited effect on higher-order aberrations in general, but that changes in one specific type of higher-order aberration (horizontal coma) did have an independent effect on uncorrected visual acuity. However, two other studies with smaller sample sizes investigating this same relationship in epi-off crosslinking found no such association.[27,28] If we combine the outcomes of those studies on higher-order aberrations with the outcomes of chapter 6, we have to conclude that the effect of crosslinking on higher-order aberrations remains rather controversial. Even if additional studies were performed and this would lead to the conclusion that crosslinking indeed has a significant effect on higher-order aberrations, the effect is likely to be small and of little clinical relevance to patients. A more promising way to reduce the distorting effects of both lower and higher-order aberrations in keratoconus patients is combining crosslinking with refractive laser surgery. The application of refractive laser surgery in keratoconus patients is controversial because this treatment is based on tissue removal and could therefore lead to further weakening of the keratoconic cornea. An iatrogenic induced ectasia after refractive surgery is a rare but serious complication.[29] However, several research groups have investigated a combination of refractive laser surgery and crosslinking in patients with early stage keratoconus.[30-34] The positive effects on both lower and higher-order aberrations and visual acuity were unequivocal and the effect size was much larger than in crosslinking alone.[30-34] Whether more severe keratoconus cases can also be treated with a combination of refractive laser surgery and crosslinking, while maintaining long term mechanical stability of the cornea, is one of the future perspectives of keratoconus research.

Chapter 4 described that the average keratometry values and visual acuity of patients improved after crosslinking, but that some eyes deteriorated despite treatment. **Chapter 8** focusses on underlying factors that are related to treatment success and predictions of individual treatment outcomes. Since many baseline factors in keratoconus patients are interrelated (e.g. eyes with higher keratometry values tend to be thinner and have a lower visual acuity) we performed a multivariable analysis to identify independent relationships between baseline factors and treatment outcomes. We found that cone location is the only independent predictor of treatment success when looking at corneal curvature outcomes. With respect to corrected distance visual acuity, the only independent predictive factor was pre-treatment corrected distance visual acuity. We proposed a reliable model to predict individual visual acuity one year after treatment based on pre-treatment visual acuity (R^2 = 0.45). However, validation of such prediction models is essential before application in clinical practice. In **Chapter 9** we were able to validate the factors influencing treatment

success in a new treatment cohort. The previously postulated prediction model for visual acuity showed limited predictive value in the new cohort (R^2 = 0.15) and should therefore not be used for patient counseling. Unfortunately, creating a prediction model based on the validation cohort or the combined cohort proved to be cumbersome as well. This finding stresses the quintessential essence of validating predictive modeling studies.

ECONOMIC EVALUATION

Before the introduction of crosslinking, approximately 10-20% of all keratoconus patients ultimately required a corneal transplant due to the development of severe astigmatism, scar formation and/or contact lens intolerance.[35,36] One of the promises of corneal crosslinking was that it would reduce the number of corneal transplantations, but this had not been formally evaluated. In **Chapter 10** we reported that the number of corneal transplantations for keratoconus decreased by 25% after the implementation of crosslinking. Although there is some degree of uncertainty when establishing a causal relationship in observational research, we tested several assumptions and concluded that it was reasonable to assume that the nationwide introduction of corneal crosslinking has played a major role in reducing the number of corneal transplantations. An interesting feature of this study was that the annual number of crosslinking treatments performed greatly exceeded the previous annual number of transplantations. This finding led to the question whether it is reasonable to treat such a large number of patients with crosslinking in order to prevent a much smaller number of corneal transplantations. An important factor in this equation is the costs that are associated with crosslinking treatment. **Chapter 11** reported on the costs of crosslinking, including pre-operative screening and postoperative consultations. A remarkable finding, related to the aim of shortening the treatment time in order to reduce costs and patient comfort, is that a decreased radiation time from thirty to five minutes would save only 8.0% of total costs. This relatively small decrease in costs is explained by the fact that the majority of costs incur during the pre-operative consultation and post-operative follow-up period. This finding suggests that further shortening of treatment time will have limited effect on the total costs of crosslinking treatment.

In **Chapter 12** we investigated the quality of life of keratoconus patients in various disease stages. Interestingly, we found no relation between keratometry values and quality of life in keratoconus patients. Keratometry is no clinical endpoint and its relationship with visual acuity is multifactorial and complex.

Visual acuity did correlate strongly with quality of life. This finding had major influence on the choices that we made in modeling the cost-effectiveness of keratoconus treatment. We indeed chose to base our cost-effectiveness estimated primarily on visual acuity and quality of life and not on keratometry values. **Chapter 13** reported on the cost-effectiveness of crosslinking for progressive keratoconus. The cost-effectiveness turned out to be strongly influenced by the assumption of crosslinking effectiveness duration. The longest documented stabilizing effect of crosslinking in literature is ten years.[37] When assuming no effect of crosslinking after ten years, the benefits in terms of gain in quality of life and prevented transplantations would be relatively small in relation to the costs of crosslinking (€54,384 per QALY). Depending on different settings and different countries crosslinking might or might not be cost-effective. However, long term follow-up studies on crosslinking efficacy showed no trend towards a diminishing effect over time, and a stabilizing effect beyond ten years is regarded probable and reasonable.[38] If a lifetime stabilizing effect of crosslinking was assumed crosslinking would be very cost-effective (€10,149 per QALY), and thus a good investment to secure more quality of life and less operations in the future. One of the scenario analyses demonstrated that treating patients with crosslinking in earlier disease stages would improve cost-effectiveness. This finding supports the rationale to evaluate the efficacy and cost-effectiveness of a screening program for keratoconus, because such a program could lead to treatment with crosslinking in an earlier diseases stage and thus improvement of cost-effectiveness.

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Addenda

NEDERLANDSE SAMENVATTING

De zorg omtrent keratoconus heeft het afgelopen decennium grote veranderingen ondergaan, met innovaties op het gebied van hoornvliestransplantatie technieken en met de introductie van crosslinking. Het doel van dit proefschrift is om bewijs te leveren voor beslissingen met betrekking tot de behandeling van keratoconus, met een speciale focus op crosslinking. Dit proefschrift omvat de epidemiologie van keratoconus, de behandeleffecten en een economische evaluatie.

EEN BEKNOPTE INLEIDING TOT KERATOCONUS

Keratoconus is een ziekte van het hoornvlies die meestal begint in de puberteit of op jongvolwassen leeftijd. De ziekte tast meestal beide ogen aan, hoewel het begin en de manifestatie niet altijd symmetrisch zijn. De oorzaak van keratoconus is een samenspel van genetische gevoeligheid, omgevingsfactoren en chronische inflammatie. Een typische keratoconus patiënt is een jonge man die frequent in zijn ogen wrijft vanwege allergische klachten. Het eerste symptoom van keratoconus zou een verslechtering van zijn gezichtsscherpte zijn als gevolg van progressieve bijziendheid en een toename van zijn cilindrische refractie afwijking. Aangezien het bij keratoconus vaak een onregelmatige cilinder betreft schiet correctie door middel van een bril vaak tekort en is een harde contactlens nodig om een adequate gezichtsscherpte te bereiken. Vergevorderde gevallen van keratoconus, waarbij de dikste laag van het hoornvlies (stroma) en de buitenste laag van het hoornvlies (epitheel) dunner worden, lopen een risico op het krijgen van littekens op het hoornvlies. In deze gevallen is een hoornvliestransplantatie de enige manier om de visuele functie te herstellen. Als patiënten hun contactlens niet goed kunnen verdragen kan dit ook een reden zijn om een hoornvliestransplantatie te verrichten. Het ondergaan van een hoornvliestransplantatie kan een aanzienlijke impact hebben op het leven van patiënten, aangezien er na de operatie frequente controles nodig zijn, patiënten dagelijkse oogdruppels moeten gebruiken en er een constant risico is op afstoting van het getransplanteerde hoornvlies. De meeste keratoconus patiënten krijgen hun eerste hoornvliestransplantatie tussen hun 20ste en 50ste levensjaar. Aangezien een getransplanteerd hoornvlies ongeveer 20 jaar mee gaat, zullen de meeste patiënten tijdens hun leven ook een tweede of zelfs een derde transplantatie moeten ondergaan. Daarom is het voorkomen van de noodzaak tot hoornvliestransplantatie één van de prioriteiten in de keratoconus zorg.

EPIDEMIOLOGIE

De meest geciteerde incidentie en prevalentie van keratoconus in de internationale literatuur zijn gebaseerd op een studie uit de Verenigde Staten die verricht werd in de periode van 1936 tot 1982. Deze studie schatte de jaarlijkse incidentie van keratoconus op 1 per 50.000 mensen en de prevalentie op ongeveer 1 per 2.000 mensen. In hoofdstuk 2 worden betrouwbare en up-to-date schattingen van de incidentie en prevalentie van keratoconus in Nederland gepresenteerd. Deze studie is uitgevoerd op basis van de gegevens van 4,4 miljoen mensen uit een zorgverzekeringsdatabase. De incidentie en prevalentie van keratoconus in deze studie zijn vijf tot tien keer hoger dan in veel geciteerde studies, wat suggereert dat keratoconus vaker voor komt dan doorgaans wordt aangenomen. Deze waardes geven inzicht in de omvang van het probleem en zijn van essentieel belang voor beleidsmakers om de impact van keratoconus op de kosten van onze gezondheidszorg te schatten.

Historisch gezien onderging ongeveer 10 tot 20% van alle keratoconus patiënten uiteindelijk een hoornvliestransplantatie vanwege de ontwikkeling van littekenvorming en/of intolerantie voor contactlenzen. Penetrerende keratoplasty (PKP) was lange tijd de meest gebruikte hoornvliestransplantatie techniek. Met deze techniek worden alle lagen van het hoornvlies van de patiënt – ook het gezonde endotheel – vervangen door donorweefsel. Behoud van het eigen endotheel is van belang omdat het merendeel van de afstotingsreacties na hoornvliestransplantatie gericht is op het endotheel van het getransplanteerde hoornvlies. Op dit moment wordt de diepe anterieure lamellaire hoornvliestransplantatie techniek (DALK) steeds meer toegepast, waarbij het aangetaste stroma wordt vervangen, maar het endotheel gespaard blijft. Eén van de beloften van DALK is dat getransplanteerde hoornvliezen langer mee gaan dan bij PKP. Dit is van groot belang omdat de meeste keratoconus patiënten relatief jong zijn en her-transplantatie over het algemeen een minder goede gezichtsscherpte oplevert en daarnaast ook weer sneller vervangen moet worden. Echter, de resultaten van DALK zijn niet eenduidig en aangezien DALK pas een aantal jaar wordt toegepast kunnen er nog geen conclusies over de lange termijn resultaten worden getrokken. Hoewel DALK een aantal voordelen heeft ten opzichte van PKP weten we weinig over de praktische uitvoering van deze en andere nieuwe transplantatie technieken. Hoofdstuk 3 beschrijft de implementatie van nieuwe transplantatie technieken in de afgelopen tien jaar in Nederland op basis van gegevens van de Nederlandse Orgaan Transplantatie Registatie.

BEHANDELEFFECTEN

Crosslinking is een relatief nieuwe behandeling die is gericht op het stoppen van de progressie van keratoconus. Tijdens de oorspronkelijke crosslinking procedure wordt de buitenste laag van het hoornvlies (epitheel) verwijderd (epi-off crosslinking). Hierdoor kunnen riboflavine oogdruppels doordringen in de dikste laag van het hoornvlies (stroma). Riboflavine is een molecuul dat reageert met UV-A straling waardoor er nieuwe verbindingen tussen collageenvezels worden gemaakt. Hierdoor wordt het hoornvlies sterker. Aan het begin van dit PhD traject waren de gunstige korte termijn effecten van crosslinking met betrekking tot het voorkomen van progressie van keratoconus aangetoond bij volwassenen. Tot op heden zijn er geen gecontroleerde studies uitgevoerd om de werkzaamheid bij kinderen aan te tonen. Het voorkomen van progressie bij kinderen is echter cruciaal aangezien kinderen vaak een veel snellere progressie laten zien dan volwassenen. Er was wel een aantal cohort studies over crosslinking bij kinderen gepubliceerd met een maximale follow-up van drie jaar. In hoofdstuk 4 geven we een overzicht van alle eerdere studies over crosslinking bij kinderen en daarnaast geven we de resultaten weer van een groep kinderen die is behandeld met crosslinking met een maximum follow-up van vijf jaar. Een interessante bevinding in dit hoofdstuk is dat de kans op progressie na behandeling met crosslinking bij kinderen veel groter is (22%) dan bij volwassenen (2-10%). Dit laat zien dat studie resultaten bij volwassenen niet direct generaliseerbaar zijn naar kinderen en dit onderstreept het belang van lange termijn follow-up studies over crosslinking bij kinderen.

Er zijn twee belangrijke doelen voor de verbetering van de huidige crosslinking behandeling: het verkorten van de behandeltijd en het intact laten van het epitheel tijdens de behandeling (transepitheliaal). Het verkorten van de behandeltijd heeft het voordeel van een hoger patiëntcomfort en lagere kosten voor de gezondheidszorg. Het intact laten van het epitheel heeft het voordeel van minder postoperatieve pijn en een lager risico op postoperatieve complicaties. Hoewel de transepitheliale techniek werd geprezen om potentiële gunstige effecten was er nog geen gerandomiseerde vergelijkende studie uitgevoerd tussen epi-off en transepithelial crosslinking. Hoofdstuk 5 doet verslag van de eerste gerandomiseerde studie op dit gebied. Alhoewel de transepitheliale techniek minder effectief bleek te zijn in het stoppen van progressie, bleek deze techniek wel meer verbetering op te leveren wat betreft gezichtsscherpte. Aangezien transepitheliale crosslinking een oppervlakkiger effect heeft dan epi-off crosslinking hebben wij de hypothese getest dat dit de grotere verbetering in gezichtsscherpte komt door het verschil in effect op hogere orde aberraties.

Hogere orde aberraties zijn optische verstoringen (meestal aan het oppervlak van de cornea) die veel vaker voorkomen bij keratoconus patiënten en die niet gecorrigeerd kunnen worden met een bril. Veranderingen in de totale hoeveelheid hogere orde aberraties verschilde niet tussen de transepitheliale groep en de epi-off groep; alleen één subtype van de hogere orde aberraties (horizontale trefoil) verschilde significant, waarbij paradoxaal genoeg een gunstig resultaat werd gezien in de epi-off behandelgroep. Bovendien vonden we geen relatie tussen het verschil in effect van transepitheliale en epi-off crosslinking op hogere orde aberraties en de gezichtsscherpte. Daarom hebben wij geconcludeerd dat er geen klinisch relevant verschil is tussen de twee vormen van crosslinking wat betreft het effect op hogere orde aberraties. In de jaren na deze studie is de wetenschappelijk interesse voor transepitheliale crosslinking sterk afgenomen omdat veel patiënten die met deze techniek waren behandeld vanwege progressie van de keratoconus opnieuw behandeld moesten worden met epi-off crosslinking.

In hoofdstuk 7 hebben we de relatie onderzocht tussen gezichtsscherpte en veranderingen in hogere orde aberraties na epi-off crosslinking in een grote groep (n = 187). We vonden dat epi-off crosslinking een beperkt effect heeft op hogere orde aberraties, maar dat veranderingen in één specifiek soort hogere orde aberratie (horizontale coma) een onafhankelijk effect had op de gezichtsscherpte. Echter, twee andere studies met minder patiënten hebben een dergelijke relatie niet gevonden. Als we de resultaten van die studies combineren met de conclusies van hoofdstuk 6 moeten we concluderen dat het effect van crosslinking op hogere orde aberraties klein is en waarschijnlijk weinig relevant is voor patiënten.

Veel vragen die worden gesteld door patiënten met progressieve keratoconus hebben betrekking op de prognose na crosslinking. Hoofdstuk 8 is gewijd aan factoren die veranderingen in de vorm van het hoornvlies en veranderingen in gezichtsscherpte kunnen voorspellen. We vonden dat de locatie op het hoornvlies waar de grootste vervorming door keratoconus heeft plaatsgevonden de enige voorspellende factor is voor het effect op de vorm van het hoornvlies. Met betrekking tot de verandering in gezichtsscherpte is de enige voorspellende factor de gezichtsscherpte voor de crosslinking behandeling. We stelden een model op waarmee de individuele gezichtsscherpte één jaar na de behandeling betrouwbaar voorspeld kon worden (R^2 = 0,45). Echter, in prognostisch onderzoek is het van essentieel belang om resultaten te valideren voordat ze worden toegepast in de klinische praktijk. In Hoofdstuk 9 waren we weliswaar in staat om de eerder gevonden voorspellende factoren te valideren in een nieuwe groep patiënten, maar het model om de individuele gezichtsscherpte te voorspellen

bleek van beperkte waarde in deze nieuwe groep patiënten (R^2 = 0,15). Dit model kan daarom niet worden gebruikt bij het voorlichten van patiënten. Deze bevinding benadrukt het belang van validatie in prognostisch onderzoek.

ECONOMISCHE EVALUATIE

Het voorkomen van de noodzaak van een hoornvliestransplantatie is één van de prioriteiten in de zorg omtrent keratoconus. De korte termijn effectiviteit van crosslinking is aangetoond in meerdere klinische trials. Echter, of crosslinking daadwerkelijk het aantal hoornvliestransplantaties vermindert was een onbeantwoorde vraag die nadere aandacht verdiende. In Nederland worden alle hoornvliestransplantaties geregistreerd in de Nationale Orgaan en Transplantatie Registratie en alle crosslinking behandelingen worden uitgevoerd in een klein aantal behandelcentra. In hoofdstuk 10 wordt beschreven dat het aantal hoornvlies transplantaties voor keratoconus met 25% is gedaald na de invoering van crosslinking. Hoewel er een bepaalde mate van onzekerheid is bij het vaststellen van een oorzakelijk verband in observationeel onderzoek hebben wij een aantal aannames onderzocht en geconcludeerd dat het redelijk is om te veronderstellen dat de landelijke invoering van crosslinking een belangrijke rol heeft gespeeld bij het verminderen van het aantal hoornvliestransplantaties. Een interessant aspect aan dit onderzoek is dat het jaarlijks uitgevoerde aantal crosslinking behandelingen veel groter is dan het aantal hoornvliestransplantaties dat voorheen jaarlijks werd uitgevoerd. Deze bevinding leidde tot de vraag of het aanvaardbaar is om een groot aantal patiënten te behandelen met crosslinking om een veel kleiner aantal hoornvliestransplantaties te voorkomen.

Crosslinking brengt evidente korte termijn kosten met zich mee in termen van diagnostiek, de behandeling zelf en postoperatieve controles en eventuele complicaties. Hoofdstuk 11 brengt deze kosten nauwkeurig in kaart. Een opvallende bevinding was dat het verkorten van de crosslinking behandeling van 30 naar 5 minuten slechts een kostenbesparing van 8% van de totale kosten met zich mee brengt. Deze relatief kleine besparing wordt verklaard door het feit dat de meeste kosten worden gemaakt tijdens de preoperatieve diagnostiek en de postoperatieve follow-up. Hoe verhouden deze evidente korte termijn kosten zich met het lange termijn behoud van kwaliteit van leven en met de verlaging van de kans op een hoornvliestransplantatie? Met andere woorden, moet de maatschappij op dit moment geld investeren in crosslinking om kwaliteit van leven te waarborgen en om lange termijn kosten te voorkomen? Om deze vraag te beantwoorden hebben we een kosten-batenanalyse uitgevoerd.

Hiervoor is het van groot belang om meer te weten over de kwaliteit van leven van keratoconus patiënten in verschillende ziekte stadia. Daarom hebben wij in hoofdstuk de kwaliteit van leven in verschillende ziekte stadia onderzocht op basis van metingen bij meer dan 1200 keratoconus patiënten. Hoofdstuk 13 geeft de resultaten van de kosten-batenanalyse voor crosslinking weer. De langst gedocumenteerde werking van crosslinking is tien jaar. Als er vanaf tien jaar na de behandeling wordt aangenomen dat de keratoconus progressie doorgaat alsof er geen behandeling heeft plaatsgevonden dan is de verhouding tussen de kosten en de baten nog steeds redelijk gunstig (€ 54.384 per QALY); de hoeveelheid gewonnen kwaliteit van leven en de vermindering van de lange termijn kosten staan in verhouding tot de korte termijn kosten van de crosslinking behandeling. Echter, in studies over de lange termijn follow-up na crosslinking wordt geen trend gezien richting een afname van de werking van deze behandeling. Daarom is het reëel om te veronderstellen dat de werking na crosslinking langer is dan tien jaar. Als er een werking van twintig jaar wordt verondersteld heeft crosslinking een zeer gunstige verhouding tussen kosten en baten (€ 10.149 per QALY). Crosslinking is dus een goede investering om kwaliteit van leven in de toekomst veilig te stellen. Een van de doorgerekende scenario's liet zien dat de verhouding tussen kosten en baten verder zou verbeteren als patiënten in een vroeger ziekte stadium zouden worden behandeld.

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CURRICULUM VITAE

Daniel Godefrooij was born on 19 November 1987 in the Diakonessenhuis in Utrecht and grew up with his parents Annelies Konincks and Peter Godefrooij. In September 2006 he started medical school at Utrecht University. During medical school he participated in national championships in athletics and won the national freshman eight competitions in rowing.

His academic career started with a research elective on hip prostheses at the Diakonessenhuis in Utrecht/Zeist (supervisor Dr. A. de Gast). During his clinical internships he decided to pursue a career in ophthalmology and dedicated most of his final year of medical school to this area of interest, with an elective clinical internship (supervisor Dr. R. Kalman) and an elective research internship (supervisor Dr. A. van der Lelij) at the ophthalmology department of the University Medical Center (UMC) Utrecht. During his graduation in November 2013 he was offered a PhD position at the UMC Utrecht by Dr. R.P.L. Wisse. Before accepting this great honor, he decided to start his career as a medical doctor at the emergency department of the Academic Hospital in Paramaribo, where he was promoted to supervisor after five months.

His PhD project began in September 2014, simultaneously with his post-graduate master in epidemiology (research methods and statistics), which he completed in the fall of 2016. Next to the research presented in this thesis he also initiated the Dutch Crosslinking for Keratoconus (DuCK) study: a prospective longitudinal multicenter study on treatment outcomes and quality of life of keratoconus patients. During his PhD he explored his interest in consultancy and entrepreneurship at the Utrecht University Business Course, where he won the start-up talent award and the ideation award. Near the end of his PhD he was awarded three grants that enabled him to make a working visit to the Royal Victorian Eye and Ear Hospital in Melbourne (supervisor Dr. E. Chan). He also wrote a successful grant application for future research on novel operation technology (iOCT).

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