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Corneal Crosslinking in Keratoconus

[Corneal Crosslinking av keratokonus]

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Summary of the Health Technology Assessment

Method and patient group

Keratoconus is a noninflammatory, asymmetrical, progressive corneal ectasia caused by biomechanical instability of the corneal stroma. Treatment modalities are primarily glasses or contact lenses. However, it has been estimated that one out of five patients will progress to such an extent that a corneal transplant is necessary to regain useful vision.

Question at issue

Is corneal crosslinking effective in stabilizing the cornea in keratoconus and in preventing the need for corneal transplants?

PICO

P = Patients (Caucasian) with keratoconus who have not been surgically treated

I = Corneal crosslinking (CXL)

C = Contact lenses, no treatment, other treatment

O = Number of corneal transplants, curvature of the cornea (K max, K average, corneal radius), visual acuity, complications, side effects.

Studied risks and benefits for patients of the new health technology

The systematic literature search identified two randomised, controlled trials (RCTs) and five non-randomised, controlled observational studies reporting the effects of CXL on keratoconus. The follow-up ranged from three to 24 months. The RCTs were of low-to-moderate quality. One of the controlled observational studies was of moderate and the other four were of low scientific quality.

No studies have reported the incidence of corneal transplants in CXL treated patients.

During 3 – 24 months follow-up the studies have reported a stabilisation of the cornea, and a slight improvement of uncorrected and corrected visual acuity (UDVA and CDVA) in paired analyses, i.e. within treatment group before and after CXL. However, this has not been confirmed in statistical comparative analyses when treated eyes are compared with non-treated eyes. The level of evidence in support of blocking the progression of keratoconus, as well as of improvement of the visual acuity, by CXL is very low (GRADE ⊕).

Ethical questions

If CXL proves to be effective in preventing, or postponing, a corneal transplant in a young patient this will be a substantial benefit for the patient.

Currently, there is a risk of overtreatment since we do not know at the present time which patients should be selected for CXL.

Economical aspects

The direct costs for the health care system for the treatment of keratoconus patients is lower with CXL treatment in comparison to the present costs of corneal transplantation.

Which health technology or method will be assessed?

1a Who posed the question?

Majvor Martinsson, Head, Department of Ophthalmology, Sahlgrenska University Hospital, Göteborg, Sweden

1b Work group

Ulf Stenevi, Professor, Department of Ophthalmology, Sahlgrenska University Hospital, Göteborg, Sweden; Project leader

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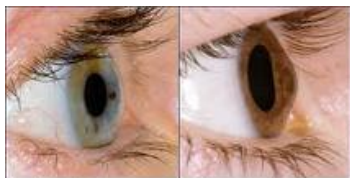
Bertil Lindblom, Professor, Department of Ophthalmology, Sahlgrenska University Hospital, Göteborg, Sweden

1d Are there any conflicts of interest for the proposer or any of the participants in the work group?

None of the participants has any conflict of interest with regard to this project.

Disease/disorder of Interest and Present Treatment

2a Disease/disorder of interest and its degree of severity



Normal cornea Keratoconus

Keratoconus is a noninflammatory process in which the cornea deforms in association with thinning and biochemical weakening. Due to optical changes caused by a progressive distortion and bowing of the cornea the patient usually needs rigid contact lenses of complex curvature to correct his/her vision.

Keratoconus is a bilateral disorder, but it is usually asymmetrical with one eye more severely affected than the fellow eye. It typically presents at puberty, and may progress over the second to fifth decades of life to such an extent that the visual acuity no longer can be corrected by contact lenses. At this late stage the patient will be subject for corneal transplantation. However, the rate of progression of keratoconus varies both between individual subjects and within the same individual over time, and may even stop to progress in the mid 30s in many subjects. Thus, most patients will never reach this advanced stage of corneal distortion.

- Risk of premature death
- Risk of permanent illness or damage, or reduced quality of life
- Risk of disability and health-related quality of life

2b Prevalence and incidence of the disease/disorder

The incidence of keratoconus is reported to be approximately one in 2000 (Rabinowitz 1998). The need for corneal transplantation is estimated to approximately 10% - 20% of all cases (Tuft et al 1994). It should be noted that these epidemiological studies were performed before modern corneal topography was introduced. No Swedish study of the incidence and prevalence of keratoconus has been performed.

2c Present treatment of the disease/disorder in the outpatient setting/ in-patient setting.

Patients with keratoconus are seen by ophthalmologists for two reasons:

1. To establish the diagnosis.
This normally occurs in the second decade of life. At this time glasses and/or contact lenses are prescribed.
2. When the disorder has progressed to such an extent that glasses or contact lenses no longer can give useful vision the patient is evaluated for surgical treatment, i.e. a corneal transplant.
There are also other treatment alternatives available, such as intracorneal stromal rings (ICRS) and conductive keratoplasty. However, these are rarely considered as therapeutic options in Sweden. The corneal transplants (i.e. penetrating keratoplasty, PKP) are performed at the Ophthalmology Clinics at the University hospitals. In the case of PKP the time from surgery to final evaluation ranges from 18 – 24 months.

2d Number of patients per year who undergo current treatment regimen?

About 100 PKPs are performed for keratoconus in Sweden each year according to the Swedish Cornea Transplant Register. This has been fairly constant during the last 10 years.

At the Department of Ophthalmology, Sahlgrenska University Hospital, Göteborg, Sweden, the annual number of PKPs for keratoconus ranges from 20 – 25 during this time period.

2e The normal pathway of a patient through the health care system

The optical correction, glasses or contact lenses, for these patients is handled by opticians. Patients are referred for surgical treatment only at more advanced stages of keratoconus, when glasses or contact lenses no longer are useful.

2f Actual wait time in days for medical assessment /treatment

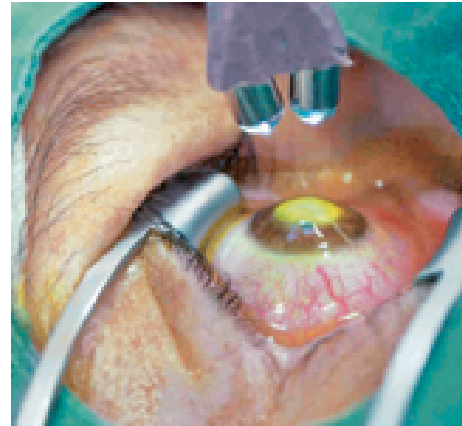
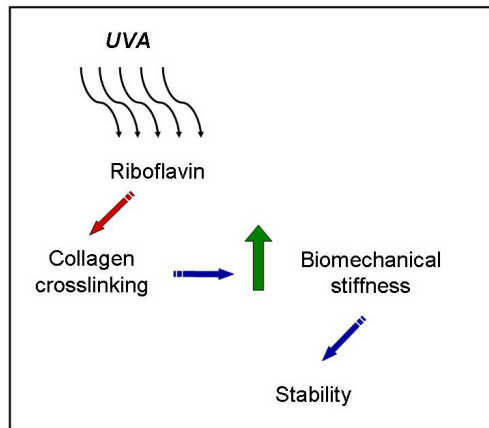
The waiting time between referral and an out-patient evaluation is usually less than three months.

The time to surgery varies between Ophthalmology Clinics and depends also on several other factors, such as available time in the operating room, the number of surgeons, and the availability of donor tissue. The average waiting time for surgery is about 3 – 12 months.

Present Health Technology

3a Name/description of the health technology at issue

Corneal collagen crosslinking (CXL) was proposed as a new therapeutic approach to treat patients with progressive keratoconus 15 years ago (Seiler 1996). In CXL riboflavin (vitamin B2) is administered in conjunction with ultraviolet A (UVA, 365nm irradiation), see figures below.



The interaction between riboflavin and UVA induces covalent bonds between collagen fibres, or between collagen fibres and interfibrillary matrix, and the result is stiffening of the corneal stroma. In the case of corneal ectasia such as keratoconus the progression of the disease is stopped or retarded.

The goal for CXL treatment is to stop the progression in order to avoid or postpone the need for a corneal transplantation (PKP), which is an expensive, cumbersome, and not always successful treatment.

3b The work group's understanding of the potential value of the health technology

Keratoconus is a noninflammatory, asymmetrical, progressive corneal ectasia caused by biomechanical instability of the corneal stroma. The result is induced myopia and irregular astigmatism leading to reduced vision. Treatment modalities are primarily glasses and or contact lenses. Most patients do well, and see well, and may never need further evaluation by an ophthalmologist once the diagnosis is established. However, it has been estimated that one out of five patients will progress to such an extent that a corneal transplant is necessary to regain useful vision.

If CXL can help the patients, who otherwise will progress to surgery, their quality of life will be affected in a positive way. Furthermore, surgical time, operating rooms and medical personnel can be allocated to other duties within ophthalmology. CXL is now being used in most countries in the developed world. Currently, seven Swedish clinics perform CXL. It does not cure keratoconus, but may stop or slow down progression of the disease so that a corneal transplant will not be needed to obtain useful vision. Thus, CXL has the potential to replace the PKP.

Presently our knowledge of CXL is limited. It works in the short-term, but neither do we know exactly by what mechanisms, nor do we know the long-term results and to what extent it may prevent the future need of corneal transplants.

The procedure has not changed since 1998. It is time consuming, and we can expect a rapid technical development in the next coming years, cutting primarily the time needed in the operating room.

The number of treatments needed in Region Västra Götaland (VGR, the Western Health Care Region of Sweden) is not known exactly, but can be estimated to approximately 50 per year. This estimation is based on the 25 patients that we presently operate each year, and an additional 25 patients that probably would need surgery.

Initially the focus will be on young patients with documented disease progression. Today the indication for CXL is a documented progress of keratoconus of more than 1 diopter over the last six to 12 months with keratometric readings. Other corneal ectasias such as peripheral pellucid degeneration and ectasia after refractive surgery may also be candidates for treatment. Other possible indications may include corneal melts and infectious keratitis.

3c The central question for the current HTA project in one sentence

Is corneal crosslinking (CXL) effective in stabilizing the cornea in keratoconus and in preventing the need for corneal transplants?

3d PICO

P = Patients (Caucasian) with keratoconus who have not been surgically treated

I = Corneal crosslinking (CXL)

C = Contact lenses, no treatment, other treatment

O = Number of corneal transplants, curvature of the cornea (K max, K average, corneal radius), visual acuity, complications, side effects.

3e Key words

Cornea, keratoconus, corneal transplantation

4 Summary of search strategy, study selection and references – appendix 3

During February, 2011, the library performed searches in PubMed, the Cochrane Library, EMBASE, CINAHL, Mosby Nursing Index and a number of HTA-databases. Reference lists of relevant articles were also scanned for additional references. A total of 247 articles were identified after removal of duplicates, of which 157 abstracts were excluded by the library. Another 39 articles were excluded by the library after having been read in full text. 51 articles were sent to the work group for assessment. 12 of these articles are included in the report, seven of which are controlled studies and have been critically appraised.

The appraisal of articles is based on checklists from SBU regarding randomized controlled trials, other checklists developed by Olle Nyrén, professor, Karolinska Institutet, Stockholm, and systematic reviews according to AMSTAR.

Search strategies, eligibility criteria and a graphic presentation of the selection process are accounted for in appendix 3. The literature search and exclusion of abstracts were made by two librarians (AL, YH) in consultation with the HTA-centre and the work group.

5a The present knowledge of the health technology

The systematic literature search identified two randomised, controlled trials (RCTs) and five non-randomised, controlled observational studies reporting the effects of CXL on keratoconus. The follow-up ranged from three to 24 months. Both RCTs were of low-to-moderate quality. One of the controlled observational studies was of moderate and the other four of low scientific quality.

Corneal transplantation

No study has reported the incidence of corneal transplants in patients with progressive keratoconus. There are no available long-term follow-up studies of patient series that can answer whether CXL will reduce the need of corneal transplants or not.

Curvature of the cornea (Appendix 1 – Table 1)

Two RCTs and four observational studies reported the effect of CXL on the distortion and bow of the cornea. A fifth observational study has reported the effect of CXL without prior removal of the corneal epithelium. The studies have used various measures of the curvature of the cornea (see Table 1, Appendix 1). All studies reported a slight improvement over time in treated eyes in paired analyses, i.e. in a statistical comparison of the status of the eye preoperatively with the status postoperatively after follow-up. In contrast, in the untreated control study groups (i.e. fellow eyes) the keratoconus progressed significantly in two out of four studies (paired analysis within group). Only two studies compared CXL-treated eyes with control eyes. In this latter comparison there was no difference between groups in the observational study in which CXL was performed without prior removal of the epithelium, whereas the other study (of low quality) reported a significant effect by CXL.

The level of evidence in support of blocked progression of keratoconus by CXL versus no treatment is very low (GRADE ⊕).

Uncorrected distance visual acuity (UDVA) (Appendix 1 – Table 2)

The effect on UDVA was reported in one RCT and three observational studies. All of them reported a slight improvement in UDVA over time in paired analyses, i.e. a statistical comparison of the UDVA of the eye pre- and postoperatively. Only the RCT studied the difference between CXL-treated eyes and control eyes. In this latter comparison there was no statistical difference between these two groups after a follow-up of three months.

The level of evidence in support of an improvement of UDVA by CXL compared to no treatment is very low (GRADE ⊕).

Corrected distance visual acuity (CDVA) (Appendix 1 – Table 3)

In two RCTs and four controlled observational studies, the effect on CDVA was reported. A slight improvement in CDVA over time was observed in all studies using paired analyses, i.e. a statistical comparison of the CDVA of the eye pre- and postoperatively. Only one RCT compared the difference between CXL-treated eyes and control eyes. In this analysis there was no statistical difference between the two groups after a follow-up of three months.

The level of evidence in support of an improvement of CDVA by CXL compared to no treatment is very low (GRADE ⊕).

Complications and adverse effects

Complications of CXL are rare. Two types of complications are reported:

1. Infections can occur, postoperatively, and are only reported in cases where a soft contact lens was used the first days after surgery. A corneal scar will result if the infection is left untreated with the risk of reduced vision.
2. Haze has been reported in some cases. Haze is due to a transient scar formation during the first postoperative month that gradually disappears during the following three to six months.

5b Outcome tables – appendix 1

5c Excluded articles – appendix 2

5d Ongoing research

A search in Clinicaltrials.gov (Mars 7th, 2011) using the search strategy (keratoconus OR Keratitis) AND (cross linking OR cross-linking OR crosslinking OR cross link OR cross-link OR crosslink OR x-link OR x-linking OR c3-R OR cxl OR ccl) identified 25 registered trials in the database. Only three of them are of interest for the specific question at issue of this report.

1. “Riboflavin mediated corneal crosslinking for stabilizing progression of keratoconus” (NCT00626717); a study from the University Hospital Freiburg, Germany.
The study is an RCT with two parallel groups (CXL vs. sham treatment) with three years follow-up, and the primary outcome measure is keratoconus progression. The estimated enrolment is 130 subjects, and the completion date is estimated to be December 2012.
2. “Treatment of keratoconus using collagen cross-linking” (NCT00841386); a study from the University at Buffalo, New York, USA.
The study is an RCT with two parallel groups (CXL vs. sham treatment) with two years follow-up, and the primary outcome measures are “Best corrected visual acuity” and “The maximum corneal curvature”, i.e. progression of keratoconus.
The estimated enrolment is 150 subjects and the completion date is estimated to be December 2011.
3. “German corneal cross linking register” (NCT00560651); a study from St. Franziskus Hospital, Homburg and Münster, Germany.
The study is a prospective, observational study of patients treated with CXL. The estimated enrolment is 7 500 subjects. It started in November 2007 and the completion date is estimated to be November 2012.

6 Which medical societies or health authorities recommend the new health technology?

- The National Board of Health and Welfare
- Medical societies
- Other health authority

Which medical society or health authority?

The regional advisory board of ophthalmology in Region Västra Götaland (VGR)

Ethical aspects

7 Ethical consequences

There is a substantial patient benefit if CXL proves to be effective in preventing, or postponing, a corneal transplant in a young patient. However, until the long-term effects of CXL are known one may question the appropriateness to use the method in routine clinical practice. On the other hand, if CXL is not used in VGR many patients will probably be referred to other clinics outside the region. If CXL is introduced in the clinical routine in VGR it is not likely that other patient groups, or other treatments, will be negatively affected (i.e. pushed aside).

Organisation

8a When can this new health technology be put into practice?

The Department of Ophthalmology, Sahlgrenska University Hospital, has already the necessary equipment to perform collagen crosslinking. The procedure can be put into practice immediately after education and training of the personnel.

8b Is this technology used in other hospitals in Western Region of Sweden ?

The following Departments of Ophthalmology in Sweden use CXL today:

- Jönköping Hospital
- Linköping University Hospital
- S:t Eriks Eye Hospital, Stockholm
- Skåne University Hospital, Malmö/ Lund
- Umeå University Hospital
- Örebro University Hospital
- Uppsala University Hospital

8d Will there be any consequences for other clinics or supporting functions at the hospital or in the whole Western Region of Sweden?

The Department of Ophthalmology, Sahlgrenska University Hospital, is the only clinic in the VGR which can provide corneal transplantations (PKP), which currently is the gold standard for treatment of advanced stages of keratokonus.

Treatment with PKP includes an operation of approximately 1 hour and at least one pre- and several postoperative examinations over one to two years of follow-up. Large resources would be released if CXL is effective in obviating the need for PKP . Currently approximately 20 - 25 PKP procedures are performed each year in VGR (see 9a).

9a Present costs of currently used technologies

Approximately 100 corneal transplants (PKP) are performed annually in Region Västra Götaland in Sweden (VGR). All PKP are done at the Department of Ophthalmology, Sahlgrenska University Hospital. 20 - 25 of these PKP are performed for advanced keratoconus.

The average cost for one PKP, including hospitalization and follow-up, is 41 500 SEK.

One should bear in mind that many of these patients are relatively young, and might need one or more corneal re-transplants during their life-time.

9b Expected costs of the new health technology?

The equipment needed for CXL has already been acquired by the Department of Ophthalmology, Sahlgrenska University Hospital.

The cost of Riboflavin is approximately 1000 SEK per treatment.

The cost for teaching personnel is limited.

The average total cost for one CXL treatment, performed in the operating room, and including hospitalization and follow-up, is estimated to be 30 000 SEK. Once CXL has been established in the clinical routine the procedure will most likely be performed in the setting of an out-patient clinic, and not in the operating room. This will reduce the cost for one treatment considerably.

9c Total change of cost

The technique of CXL is predicted to reduce the cost of therapy of progressive keratoconus in Western Region of Sweden (VGR) by reducing the need for PKP. The net reduction in the total cost per one treated eye is estimated to be around 10 000 SEK (approximately 1050 €). For VGR this means an annual cost reduction of about 200 000 – 250 000 SEK.

9d Can the new technology be adopted and used within the present budget (clinic budget/hospital budget)?

Yes.

9e Are there any available analyses of health economy? Cost advantages or disadvantages?

No health economy analyses are available.

Unanswered Questions

10a Important gaps in scientific knowledge?

There are many important unanswered questions:

- What is the long-term effectiveness of CXL?
- How does CXL affect the physiology of the cornea?
- Are the corneal stem cells affected by CXL?
- How are the wound healing properties of the cornea affected by CXL?

10b Is there any interest in your own clinic/research group/organisation to start studies/trials within the research field at issue?

It would be of great importance to study the effect of CXL on the frequency of corneal transplants. This could be evaluated in a prospective, observational study by the use of the Swedish Corneal Transplant Register. This register is located at Sahlgrenska University Hospital,

Utlåtande och sammanfattande bedömning från Kvalitetssäkringsgruppen

”Corneal Crosslinking” av keratokonus

Frågeställning:

Stabiliserar ”corneal crosslinking” (CXL) hornhinnan hos patienter med keratokonus och kan behandlingsmetoden förebygga det framtida behovet av hornhinnetransplantation?

PICO

- P = Patienter (kaukasier) med keratokonus som tidigare inte behandlats med kirurgi
- I = ”Corneal crosslinking” (CXL)
- C = Kontaktlinser, annan behandling, ingen behandling
- O = Antal hornhinnetransplantationer, hornhinnans kurvatur (Kmax, Kmedel, hornhinnans radie), synskärpa, komplikationer, biverkningar.

Resultat av HTA-processen:

Metod och målgrupp:

Keratokonus är en asymmetrisk, degenerativ ögonsjukdom med en störning i hornhinnans tillväxt. Hornhinnan förtunnas på grund av biomekanisk instabilitet i dess stroma. Den buktar framåt och blir successivt alltmer konformad (”toppig”). Detta leder till ändrade brytnings-förhållanden och en alltmer försämrad syn med uttalad myopi och oregelbunden astigmatism. Keratokonus behandlas primärt med glasögon eller hårda kontaktlinser. Sjukdomen debuterar vanligen i mitten av tonåren och fortskrider långsamt för att hos flertalet patienter avstanna i 35-årsåldern. Emellertid kan sjukdomen fortsätta att progrediera så mycket att hornhinnans buktning blir så uttalad att en hornhinnetransplantation är enda möjligheten att återfå tillräcklig syn. Man uppskattar att detta sker hos var femte patient med keratokonus. ”Corneal crosslinking” (CXL) är en behandling som förstärker hornhinnans bindväv och kan få förändringen av hornhinnan att stanna upp.

Evidensläge:

Den systematiska litteratursökningen identifierade två randomiserade, kontrollerade studier (RCT) och fem icke-randomiserade, kontrollerade observationsstudier som har rapporterat behandlingseffekter av CXL hos patienter med keratokonus. Uppföljningstiden varierade i studierna från tre till 24 månader. Båda RCT var av låg-till-medelhög kvalitet. En av de kontrollerade observationsstudierna var av medelhög och de övriga fyra av låg vetenskaplig kvalitet.

Hornhinnetransplantation

Ingen studie har redovisat incidensen av hornhinnetransplantation hos patienter med progredierande keratokonus. Det saknas studier med tillräckligt lång uppföljning som kan besvara om CXL minskar behovet av hornhinnetransplantation eller inte.

Hornhinnans kurvatur

Två RCT och fyra observationsstudier har rapporterat effekterna av CXL på distorsion och buktning av hornhinnan. En femte observationsstudie har rapporterat effekten av CXL utan sedvanlig förbehandling med borttagande av hornhinneepitelet. Studierna har använt olika mått på hornhinnans kurvatur. Samtliga studier har rapporterat en viss förbättring efter behandlingen i behandlade ögon i parade analyser, dvs. statistisk jämförelse mellan status i samma öga före och efter CXL-behandlingen. I motsats till detta resultat rapporteras att graden av keratokonus progredierat i de obehandlade ”kontrollögonen”, som vanligen är det minst drabbade ögat hos en och samma individ. Endast två studier har gjort statistiska jämförelser mellan CXL-behandlade ögon med ”kontrollögon” i oparade analyser. Vid denna typ av jämförelse kunde man inte påvisa någon skillnad mellan grupperna i den observationsstudie som behandlade patienterna med CXL utan sedvanlig förbehandling med borttagande av hornhinneepitelet, medan den andra studien (av låg kvalitet) fann en signifikant skillnad till fördel för CXL-behandlingen.

Det föreligger ett otillräckligt stöd för att CXL leder till stabilisering av hornhinnan och hejdad progress av keratokonus (Otillräckligt vetenskapligt underlag GRADE ⊕).

Okorrigerad synskärpa

Bara en av RCT har jämfört CXL-behandlade ögon med obehandlade ögon. Man observerade inte någon skillnad mellan grupperna tre månader efter interventionen. Tre observations-studier rapporterade en viss förbättrad okorrigerad synskärpa i parad analys, dvs. då man jämför synstatus före och efter CXL-behandlingen i samma öga.

Det föreligger ett otillräckligt stöd för att CXL förbättrar okorrigerad synskärpa vid progredierande keratokonus (Otillräckligt vetenskapligt underlag GRADE ⊕).

Korrigerad synskärpa

Bara en av RCT har jämfört CXL-behandlade ögon med obehandlade ögon. Man observerade inte någon skillnad mellan grupperna tre månader efter interventionen. Fyra observations-studier och en RCT rapporterade en viss förbättrad korrigerad synskärpa i parad analys, dvs. då man jämför synstatus före och efter CXL-behandlingen i samma öga.

Det föreligger ett otillräckligt stöd för att CXL förbättrar korrigerad synskärpa vid progredierande keratokonus (Otillräckligt vetenskapligt underlag GRADE ⊕).

Komplikationer och biverkningar:

Postoperativa infektioner kan inträffa hos enstaka patienter som använder mjuka kontaktlinser de första postoperativa dagarna. Ett övergående dis av synen kan uppträda under den första postoperativa månaden. Båda dessa komplikationer är sällsynta.

Etiska aspekter:

Om CXL visar sig vara en effektiv behandlingsmetod att förhindra framtida hornhinne-transplantationer hos unga patienter skulle detta innebära avsevärda vinster för dessa patienter. För närvarande finns en risk för överbehandling då det inte är klart definierat vilka patienter som ska väljas för CXL och vilka som inte kommer att ha nytta av behandlingen.

Ekonomiska aspekter

De direkta kostnaderna för en behandling av progredierande keratokonus är lägre för CXL-behandling jämfört med de nuvarande kostnaderna för en hornhinnetransplantation.

Sammanfattning och slutsats

“Corneal crosslinking”, CXL, är en enkel och relativt billig behandlingsmetod som är förenad med en låg frekvens av icke allvarliga komplikationer. Evidensläget för den positiva effekten av CXL att stabilisera progredierande keratokonus är otillräcklig (GRADE ⊕). Det saknas för närvarande helt dokumentation om CXL kan förhindra framtida hornhinnetransplantationer.

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Summary Statement from the HTA centre of the Region Västra Götaland in Sweden
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Corneal Crosslinking in Keratoconus

Question at issue:

Is corneal crosslinking (CXL) effective in stabilizing the cornea in keratoconus and in preventing the need for corneal transplants?

PICO

- P = Patients (Caucasian) with keratoconus who have not been surgically treated
- I = Corneal cross linking (CXL)
- C = Contact lenses, no treatment, other treatment
- O = Number of corneal transplants, curvature of the cornea (K max, K average, corneal radius), visual acuity, complications, side effects.

Summary of the health technology assessment:

Method and patient category:

Keratoconus is a noninflammatory, asymmetrical, progressive corneal ectasia caused by biomechanical instability of the corneal stroma. The result is induced myopia and irregular astigmatism leading to reduced vision. Treatment modalities are primarily glasses and or contact lenses. However, it has been estimated that one out of five patients will progress to such an extent that a corneal transplant is necessary to regain useful vision. Corneal crosslinking (CXL) is an intervention that strengthens the corneal tissue and, thereby, can block progression of keratoconus in the progressive phase.

Level of evidence:

The systematic literature search identified two randomised, controlled trials (RCTs) and five non-randomised, controlled observational studies reporting the effects of CXL on keratoconus. The follow-up ranged from three to 24 months. Both RCTs were of low-to-moderate quality. One of the controlled observational studies was of moderate and the other four were of low scientific quality.

Corneal transplantation

No study has reported the incidence of corneal transplantations in patients with progressive keratoconus. There are no available long-term follow-up studies of patient series that can answer whether CXL will reduce the need of corneal transplants or not.

Curvature of the cornea

Two RCTs and four observational studies reported the effect of CXL on the distortion and bow of the cornea. A fifth observational study has reported the effect of CXL without prior removal of the corneal epithelium. The studies have used various measurements of the curvature of the cornea. All reported a slight improvement over time in treated eyes in paired analyses, i.e. in statistical comparisons of the status of the eye preoperatively with the status postoperatively after follow-up. In contrast, in the untreated control study groups (i.e. fellow eyes) the keratoconus progressed significantly in two out of four studies (paired analysis within group). Only two studies compared CXL-treated eyes with control eyes.

In this latter comparison there was no difference between groups in the observational study in which CXL was performed without prior removal of the epithelium, whereas the other study (of low quality) reported a significant effect by CXL. The level of evidence in support of blocked progression of keratoconus by CXL versus no treatment is very low (GRADE ⊕).

Uncorrected distance visual acuity (UDVA)

Only one RCT compared the difference between CXL-treated eyes and control eyes. There was no statistical difference between these two groups after three months of follow-up. Three observational studies reported a slight improvement in paired analyses, i.e. within the treated before and after CXL.

The level of evidence to support an improvement of UDVA by CXL compared to no treatment is very low (GRADE ⊕).

Corrected distance visual acuity (CDVA)

Only one RCT compared the difference between CXL-treated eyes and control eyes. There was no statistical difference between these two groups after three months of follow-up. Four observational studies and one RCT reported a slight improvement in paired analyses, i.e. within the treated before and after CXL.

The level of evidence to support an improvement of CDVA by CXL compared to no treatment is very low (GRADE ⊕).

Side effects and complications:

Postoperative infections have been reported at a low incidence in patients where a soft contact lens has been used the first days after surgery. Transient haze may occur during the first postoperative month. Both of these complications are rare.

Ethical aspects:

There is a substantial patient benefit if CXL proves to be effective in preventing, or postponing, a corneal transplant in a young patient.

There is a risk of over treatment since at the present time adequate patient selection for CXL is not defined.

Economical aspects

The direct costs for the health care system for the treatment of keratoconus patients is lower with CXL treatment in comparison to the present costs of corneal transplantation.

Concluding remarks

Corneal crosslinking is simple, rather inexpensive, and associated with a very low frequency of complications that are not severe. The level of evidence of a potential beneficial effect of CXL to stabilise progressive keratoconus is very low (GRADE ⊕). There is no documentation on whether CXL may prevent the need for future corneal transplants.

On behalf of the Regional HTA Centre of the Western Region in Sweden
Göteborg, Sweden, 2011-04-27.

Christina Bergh, Professor, MD.
Head of the HTA Centre of Region Västra Götaland, Sweden

Appendix 1 - Table 1: Outcome variable = Progression/stabilisation of keratoconus, i.e. change in curvature of the cornea (K readings, radius).

A reduction of K-value (dioptres) and an increase in radius (mm) indicate a stabilisation/ stopped progression of keratoconus.

Author, year	Country	Study design	Number of eyes n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention	Control		
Hersh, 2011	USA	RCT	71 (controls, sham + fellow eyes: 71)	Not reported	<u>K max (Diopter)</u> $\Delta = - 1.7$ (sd 3.9) (p < 0.01) ¹ (No statistical difference vs controls)	<u>K max (Diopter)</u> $\Delta = + 0.3$ (sd 1.2) (p = 0.18) ¹	Follow-up: 3 months.	Low- moderate
Wittig-Silva, 2008	Australia	RCT	33 (controls: 33)	1 in each group	<u>K max (Diopter)</u> $\Delta = - 1.5$ (sd 1.0) (p = 0.002) ¹	<u>K max (Diopter)</u> $\Delta = + 1.3$ (sd NR) (p < 0.001) ¹	Follow-up: 12 months No statistical inference tests performed between groups	Low
Caparossi, 2010	Italy	Prospective non-randomised, observational study	44	Not reported	<u>K mean (Diopter)</u> $\Delta = - 2.1$ (sd 0.7)	<u>K mean (Diopter)</u> $\Delta = + 2.2$ (sd 1.2)	Follow-up: 24 months The eye with a more advanced stage and stronger progression of KC was treated and the fellow-up with less severe KC served as control (fellow-eye). No statistical inference tests performed between groups or within groups.	Low
Coskunseven, 2009 (J Cataract Refract Surg 35:2084)	Turkey	Prospective non-randomised, observational study	48	Not reported	<u>CXL group</u> <u>K mean (Diopter)</u> 52.5 (sd 4.0) ↓ 51.6 (sd 4.0) $\Delta = - 0.9$ (sd NR) (p < 0.001) ¹	<u>ICRS group</u> <u>K mean (Diopter)</u> 52.1 (sd 4.9) ↓ 49.1 (sd 4.6) $\Delta = - 2.9$ (sd NR) (p < 0.001) ¹	Follow-up: 7 months The study was an RCT with two sequences of treatments in different order; 1 st 7 months either CXL or ICRS 2 nd 8-13 months ICRS or CXL in reversed order as 1 st period. Only data from first treatment period is presented in the table; i.e. in the parallel groups No statistical inference tests performed between groups	Low

Footnotes: 1. p-value in paired analysis within group, i.e.comparison between the preoperative measurement and the postoperative follow-up measurement.

Abbreviations: RCT = randomised, controlled trial; CXL = corneal crosslinking; ICRS = intrastromal corneal ring segment; NR = not reported.

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Author, year	Country	Study design	Number of eyes n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention	Control		
Coskunseven, 2009 (J Refract Surg 25:371)	Turkey	Prospective non-randomised, observational study	8	Not reported	<u>K max (Diopter)</u> 54.0 (sd 4.2) ↓ 52.5 (sd 4.0) $\Delta = - 1.6$ (sd 1.1) (p < 0.01) ¹	<u>K max (Diopter)</u> 48.3 (sd 3.0) ↓ 48.3 (sd 3.3) $\Delta = + 0.04$ (sd 1.3) (p = 0.44) ¹	Follow-up: 5 -12 months The eye with a more advanced stage and stronger progression of KC was treated and the fellow-up with less severe KC served as control (fellow-eye). No statistical inference tests performed between groups	Low
Koller, 2009 (Cornea 28(5):510-515)	Italy	Prospective non-randomised, observational study	42 (controls, fellow eye: 42)	Not reported	<u>Minimal curvature radius</u> 6.14 mm ↓ 6.21 mm $\Delta = + 0.07$ (sd 0.10) (p = 0.01) ¹ (p < 0.001 vs control)	<u>Minimal curvature radius</u> 6.94 mm ↓ 6.86 mm $\Delta = - 0.08$ (sd 0.10) (p = 0.002) ¹	Follow-up: 12 months The eye with a more advanced stage and stronger progression of KC was treated and the fellow-up with less severe KC served as control (fellow-eye).	Low
Leccisotti, 2010	UK	Prospective non-randomised, observational study	51 (controls, fellow eye: 51)	13	<u>K apex (Diopter)</u> 54.3 (sd 8.8) ↓ 54.8 (sd 4.9) $\Delta = + 0.5$ (sd 7.8) (non-significant) ¹ (No statistical difference vs controls)	<u>K apex (Diopter)</u> 51.7 (sd 6.4) ↓ 53.3 (sd 7.7) $\Delta = + 1.6$ (sd 6.3) (non-significant) ¹	Follow-up: 12 months The eye with a more advanced stage and stronger progression of KC was treated and the fellow-up with less severe KC served as control (fellow-eye). CXL was performed as a transepithelial CXL and not after prior removal of the epithelium	Moderate

Footnotes: 1. p-value in paired analysis within group, i.e.comparison between the preoperative measurement and the postoperative follow-up measurement.

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A reduction of K-value (dioptres) and an increase in radius (mm) indicate a stabilisation/ stopped progression of keratoconus.

Author, year	Country	Study design	Number of eyes n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention	Control		
Leccisotti, 2010 cont.					<u>K average (Diopter)</u> 46.6 (sd 2.9) ↓ 46.5 (sd 3.2) $\Delta = - 0.1$ (sd 1.4) (non-significant) ¹ (No statistical difference vs controls)	<u>K average (Diopter)</u> 44.6 (sd 2.2) ↓ 45.5 (sd 2.9) $\Delta = + 0.9$ (sd 2.4) (non-significant) ¹		

Footnotes: 1. p-value in paired analysis within group, i.e.comparison between the preoperative measurement and the postoperative follow-up measurement.

Abbreviations: RCT = randomised, controlled trial; CXL = corneal crosslinking; ICRS = intrastromal corneal ring segment; NR = not reported.

Appendix 1 - Table 2: Outcome variable = Uncorrected distance visual acuity (UDVA) measured as logarithm of Minimum Angle of Resolution (logMAR) or Snellen lines.

Log MAR = 0 equals Snellen 20/20 and logMAR 0.30 equals Snellen 20/40. Thus, the lower the logMAR-value the better visual acuity, and a positive change in Snellen lines also indicates improved visual acuity.

Author, year	Country	Study design	Number of eyes n=	With drawals - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention	Control		
Hersh, 2011	U.S.A.	RCT	71 (controls, sham + fellow eyes: 71)	Not reported	<u>logMAR</u> $\Delta = - 0,07$ ($p = 0.04$) ¹	<u>logMAR</u> <i>Sham group (at 3 months)</i> $\Delta = - 0.08$ ($p = 0.03$) ¹ <i>Fellow eyes group (at 12 months)</i> $\Delta = - 0,04$ ($p = 0.17$) ¹	Follow-up: 3 months.	Low- moderate
Caparossi, 2010	Italy	Prospective non- randomised, observational study	44	Not reported	<u>Snellen lines</u> $\Delta = + 2.8$ (sd 0.8)	<u>Snellen lines</u> Not reported	Follow-up: 24 months The eye with a more advanced stage and stronger progression of KC was treated and the fellow-up with less severe KC served as control (fellow-eye). No statistical inference tests performed between groups or within groups	Low

Footnotes: : 1. p-value in paired analysis within group, i.e.comparison between the preoperative measurement and the postoperative follow-up measurement.

RCT = randomised, controlled trial; FU = follow-up; CXL = corneal crosslinking; ICRS = intrastromal corneal ring segment

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					Intervention	Control		
Coskunseven, 2009 (J Cataract Refract Surg 35:2084)	Turkey	Prospective non- randomised, observational study	48	Not reported	<u>Snellen lines</u> <i>CXL group</i> $\Delta \approx + 1$ line ($p < 0.001$)	<u>Snellen lines</u> <i>ICRS group</i> $\Delta \approx + 1$ line ($p < 0.001$)	Follow-up: 7 months The study was an RCT with two sequences of treatments in different order; 1 st 7 months either CXL or ICRS 2 nd 8-13 months ICRS or CXL in reversed order as 1 st period. Only data from first treatment period is presented in the table; i.e. in the parallel groups No statistical inference tests performed between groups	Low
Coskunseven, 2009 (J Refract Surg 25:371)	Turkey	Prospective non- randomised, observational study	8	Not reported	<u>Snellen lines</u> $\Delta = + 0.06$ (sd 0.05) ($p < 0.01$) ¹	<u>Snellen lines</u> $\Delta = - 0.08$ (sd 0.12) ($p < 0.01$) ¹	Follow-up: 5 -12 months The eye with a more advanced stage and stronger progression of KC was treated and the fellow-up with less severe KC served as control (fellow-eye). No statistical inference tests performed between groups	Low

Footnotes: : 1. p-value in paired analysis within group, i.e.comparison between the preoperative measurement and the postoperative follow-up measurement.

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Author, year	Country	Study design	Number of eyes n=	With draws - dropouts	Result		Comments	Quality (may vary according to outcome)
					Intervention	Control		
Hersh, 2011	U.S.A.	RCT	71 (controls, sham + fellow eyes: 71)	Not reported	<u>logMAR</u> 0.35 (sd 0.24) ↓ 0.23 (sd 0.21) Δ = - 0.12 (p < 0.001) ¹	<u>logMAR</u> <i>Sham group (at 3 months)</i> No change <i>Fellow eyes group (at 12 months)</i> Δ = - 0.04 (p < 0.001) ¹	Follow-up: 3 months.	Low- moderate
Wittig-Silva, 2008	Australia	RCT	33 (controls: 33)	1 in each group	<u>logMAR</u> Δ = - 0.12 (p = 0.07) ¹	<u>logMAR</u> Δ = + 0.11 (p = 0.04) ¹	Follow-up: 12 months No statistical inference tests performed between groups	Low
Caparossi, 2010	Italy	Prospective non-randomised, observational study	44	Not reported	<u>Snellen lines</u> Δ = + 1.9 (sd 1.0)	<u>Snellen lines</u> Not reported	Follow-up: 24 months The eye with a more advanced stage and stronger progression of KC was treated and the fellow-up with less severe KC served as control (fellow-eye). No statistical inference tests performed between groups or within groups	Low

Footnotes: : 1. p-value in paired analysis within group, i.e.comparison between the preoperative measurement and the postoperative follow-up measurement.
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Coskunseven, 2009 (J Cataract Refract Surg 35:2084)	Turkey	Prospective non- randomised, observational study	48	Not reported	<u>Snellen lines</u> <i>CXL group</i> $\Delta \approx + 0,5$ line ($p = 0.14$)	<u>Snellen lines</u> <i>ICRS group</i> $\Delta \approx + 0,5$ line ($p < 0.001$)	Follow-up: 7 months The study was an RCT with two sequences of treatments in different order; 1 st 7 months either CXL or ICRS 2 nd 8-13 months ICRS or CXL in reversed order as 1 st period. Only data from first treatment period is presented in the table; i.e. in the parallel groups No statistical inference tests performed between groups	Low
Coskunseven, 2009 (J Refract Surg 25:371)	Turkey	Prospective non- randomised, observational study	8	Not reported	<u>Snellen lines</u> $\Delta = + 0.10$ (sd 0.14) ($p < 0.01$) ¹	<u>Snellen lines</u> $\Delta = - 0.06$ (sd 0.09) ($p < 0.01$) ¹	Follow-up: 5 -12 months The eye with a more advanced stage and stronger progression of KC was treated and the fellow-up with less severe KC served as control (fellow-eye). No statistical inference tests performed between groups	Low
Leccisotti, 2010	UK	Prospective non- randomised, observational study	51 (controls, fellow eye: 51)	13	<u>logMAR</u> $\Delta = - 0.04$ (sd 0.05) ($p < 0.05$) ¹ ($p < 0.05$ vs control)	<u>logMAR</u> $\Delta = + 0.04$ (sd 0.03) ($p < 0.05$) ¹	Follow-up: 12 months The eye with a more advanced stage and stronger progression of KC was treated and the fellow-up with less severe KC served as control (fellow-eye). CXL was performed as a transepithelial CXL and not after prior removal of the epithelium	Moderate

Footnotes: : 1. p-value in paired analysis within group, i.e.comparison between the preoperative measurement and the postoperative follow-up measurement.

RCT = randomised, controlled trial; FU = follow-up; CXL = corneal crosslinking; ICRS = intrastromal corneal ring segment

Study (author, publication year)	Reason for exclusion
Agrawal, 2009	Case series with too few cases according to predefined limitations- see Appendix 3
Arbelaez, 2009	Case series with too few cases according to predefined limitations- see Appendix 3
Baumeister, 2009	Case series with too few cases according to predefined limitations- see Appendix 3
Caporossi, 2006	Case series with too few cases according to predefined limitations- see Appendix 3
Doors, 2009	Case series with too few cases according to predefined limitations- see Appendix 3
El-Raggal, 2011	Not adequate intervention (KERARINGS followed by CXL)
El-Raggal, 2009	Case series with too few cases according to predefined limitations- see Appendix 3
Goldich, 2009	Case series with too few cases according to predefined limitations- see Appendix 3
Goldich, 2010	Case series with too few cases according to predefined limitations- see Appendix 3
Greenstein, 2010	Case series with too few cases according to predefined limitations- see Appendix 3
Grewal, 2009	Case series with too few cases according to predefined limitations- see Appendix 3
Hafezi, 2007	Case series with too few cases according to predefined limitations- see Appendix 3
Henriquez, 2011	Case series with too few cases according to predefined limitations- see Appendix 3
Herrmann, 2008	Patients with keratitis. Not applicable for final PICO.
Hoyer, 2009	Double publication

Study (author, publication year)	Reason for exclusion
Iseli, 2008	Patients with keratitis. Not applicable for final PICO.
Kanellopoulos, 2007	Case report of one single patient
Knappe, 2011	Case series with too few cases according to predefined limitations- see Appendix 3
Koppen, 2009	Patients with keratitis. Not applicable for final PICO.
Krueger, 2010	Case series with too few cases according to predefined limitations- see Appendix 3
Kymionis, 2010 J Ophthalmol	Case series with too few cases according to predefined limitations- see Appendix 3
Kymionis, 2010 J Cataract R	Case series with too few cases according to predefined limitations- see Appendix 3
Kymionis, 2009	Case series with too few cases according to predefined limitations- see Appendix 3
Kymionis, 2010 Invest Ophtal	Case series with too few cases according to predefined limitations- see Appendix 3
Makdoui, 2010	Patients with keratitis. Not applicable for final PICO.
Mazzotta, 2007 Clin Exp Ophtal	Case series with too few cases according to predefined limitations- see Appendix 3
Mazzotta, 2007 Cornea	Case series with too few cases according to predefined limitations- see Appendix 3
Mazzotta, 2010	Case series with too few cases according to predefined limitations- see Appendix 3
Moren, 2010	Patients with keratitis. Not applicable for final PICO.
Raiskup, 2010	Double publication

Study (author, publication year)	Reason for exclusion
Saffarian, 2010	Case series with too few cases according to predefined limitations- see Appendix 3
Stojanovic, 2010	Case series with too few cases according to predefined limitations- see Appendix 3
Tu, 2009	Case series with too few cases according to predefined limitations- see Appendix 3
Vinciguerra, 2010	Case series with too few cases according to predefined limitations- see Appendix 3
Vinciguerra, 2009 Ophthalmol	Case series with too few cases according to predefined limitations- see Appendix 3
Vinciguerra, 2009 Arch Ophthalmol	Case series with too few cases according to predefined limitations- see Appendix 3
Wollensak, 2008	Case series with too few cases according to predefined limitations- see Appendix 3
Wollensak, 2003 Am J Ophthalmol	Case series with too few cases according to predefined limitations- see Appendix 3
Wollensak, 2003 Ophthalmol	Case series with too few cases according to predefined limitations- see Appendix 3

Appendix 3, Search strategy, study selection and references

Question(s) at issue:

Is corneal crosslinking (CXL) effective in stabilizing the cornea in keratoconus and in preventing the need for corneal transplants?

P: Patients (Caucasian) with keratoconus who have not been surgically treated

I: Corneal crosslinking (CXL)

C: Contact lenses, no treatment, other treatment

O: Number of corneal transplants, curvature of the cornea (K max, K average, corneal radius), visual acuity, complications, side effects.

Initially the PICO included both patients with keratitis and keratoconus, because of that the search include both keratitis and Keratoconus. As it turned out that there were no comparative studies on keratitis, the PICO was revised to include only patients with Keratoconus.

Search strategies

PubMed 2011-02-14

keratoconus OR Keratitis

AND

cross linking OR cross-linking OR crosslinking OR cross link OR cross-link OR crosslink OR cross links OR cross-links OR crosslinks OR x-link OR x-linking OR x-links OR c3-R OR cxl OR ccl

Limits: English, German, Danish, Norwegian, Swedish, Publication Date from 1990

164 results

EMBASE (OVID SP) 2011-02-14

keratoconus.mp. OR exp Keratoconus / OR exp Keratitis / OR keratitis.mp.

AND

cross linking.mp. or exp cross linking/ OR cross-linking.mp. OR crosslinking.mp. OR cross link.mp. OR cross-link.mp. OR crosslink.mp. OR cross links.mp. OR cross-links.mp. OR crosslinks.mp. x-link.mp. OR linking.mp. OR links.mp. OR c3-r.mp. OR cxl.mp. OR ccl.mp.

Limits: Publication Date from 1990, English, German, Danish, Norwegian, Swedish,

186 results

The Cochrane Library 2011-02-14

MeSH descriptor Keratoconus explode all trees OR MeSH descriptor Keratitis explode all trees OR keratitis OR keratoconus **in** Title, Abstract or Keyword

AND

(cross link) OR cross-link OR crosslink OR x-link OR c3-r OR cxl OR ccl **in** Title, Abstract or Keyword

5 results

Cochrane reviews 0

Other reviews 0

Clinical trials 3

Technology Assessments 2

Economic evaluations 0

CRD 2011-02-14

Keratoconus OR keratitis OR MeSH Keratoconus EXPLODE OR MeSH Keratitis EXPLODE

AND

(cross AND linking) OR cross-linking OR crosslinking OR (cross AND link) OR cross-link OR crosslink OR (cross AND links) OR cross-links OR crosslinks OR x-link OR x-linking OR x-links OR c3-r OR cxl OR ccl OR

2 results

CINAHL (EBSCO) 2011-02-14

"keratoconus" OR (MH "Corneal Diseases+") OR "Corneal Diseases" OR (MH "Keratitis+") OR "keratitis"

AND

"cross linking" OR "cross-linking" OR "crosslinking" OR "cross link" OR "cross-link" OR "crosslink" OR "cross links" OR "cross-links" OR "crosslinks" OR "x-link" OR "x-linking" OR "x-links" OR "c3-r" OR "cxl" OR "ccl"

Limits: Publication Date from 1990, English, German, Danish, Norwegian, Swedish,

36 results

Mosby Nursing Index 2011-02-14

'keratoconus'/exp OR 'keratoconus' OR 'keratitis'/exp OR 'keratitis'

AND

(cross AND linking) OR 'cross linking'/exp OR 'cross linking' OR 'crosslinking'/exp OR 'crosslinking' OR (cross AND link) OR 'cross link'/exp OR 'cross link' OR 'crosslink'/exp OR 'crosslink' OR (cross AND links) OR 'cross links' OR crosslinks OR 'x link' OR 'x linking' OR 'x links' OR 'c3 r' OR cxl OR cxl OR ccl OR

13 results

SBU, Kunnskapssenteret, Sundhedsstyrelsen 2011-02-14

Nothing relevant to the question at issue was found

Eligibility criteria

Study design:

- Studies with some kind of control group
- Case series etc. if ≥ 100 patients
- No review articles

Study population: Mainly Caucasian

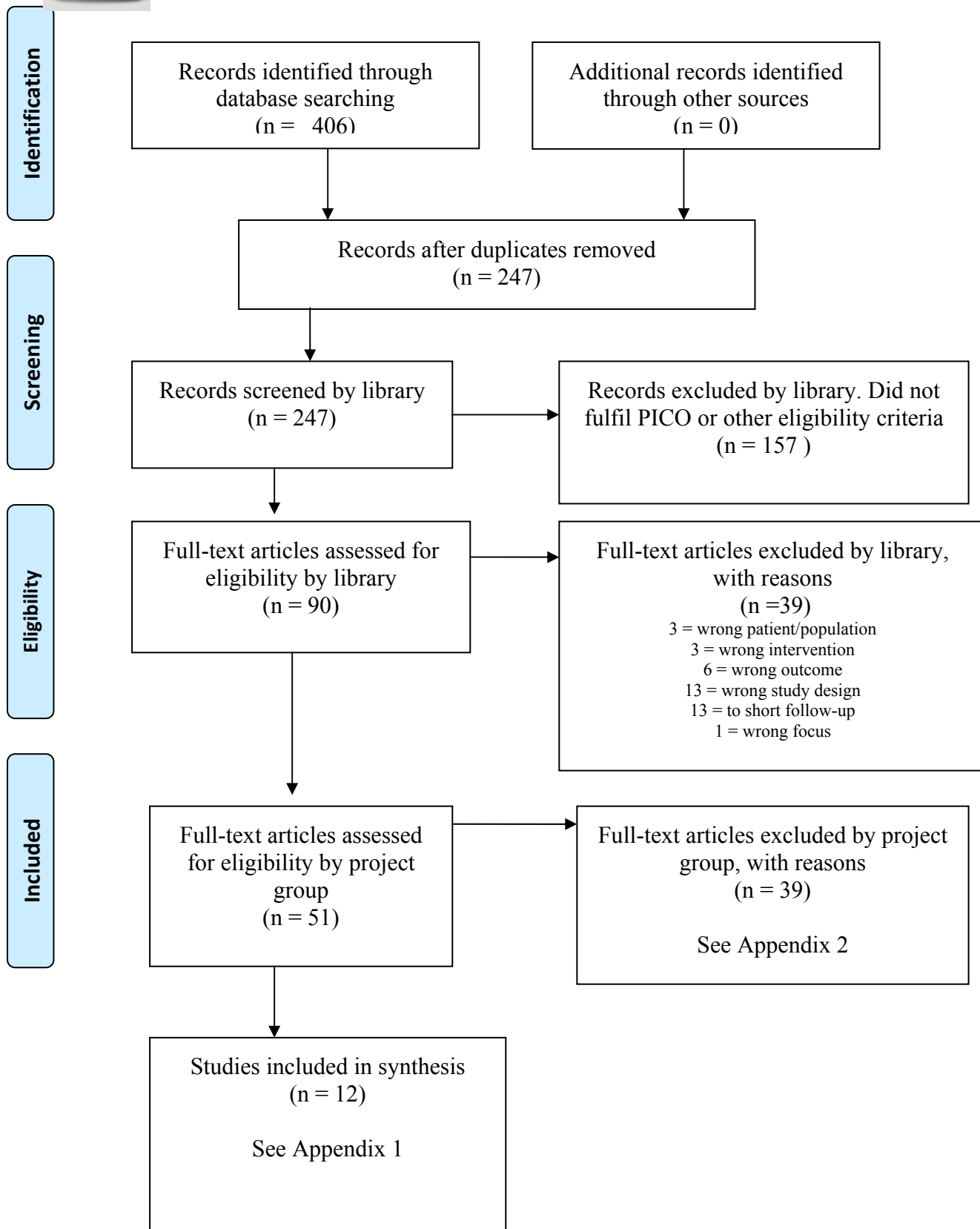
Time to follow-up: ≥ 6 months

Language:

English, German, Swedish, Norwegian, Danish

Publication date: 1990-

Selection process – flow diagram



Reference lists**Included studies:**

Caporossi A, Mazzotta C, Baiocchi S, Caporossi T. Long-term results of riboflavin ultraviolet a corneal collagen cross-linking for keratoconus in Italy: the Siena eye cross study. *Am J Ophthalmol*. 2010 Apr;149(4):585-93.

Coskunseven E, Jankov IMR, Hafezi F, Atun S, Arslan E, Kymionis GD. Effect of treatment sequence in combined intrastromal corneal rings and corneal collagen crosslinking for keratoconus. *Journal of Cataract and Refractive Surgery*. 2009 December;35 (12):2084-91.

Coskunseven E, Jankov MR, 2nd, Hafezi F. Contralateral eye study of corneal collagen cross-linking with riboflavin and UVA irradiation in patients with keratoconus. *J Refract Surg*. 2009 Apr;25(4):371-6.

Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: One-year results. *J Cataract Refract Surg*. 2011 Jan;37(1):149-60.

Hoyer A, Spoerl E, Pillunat LE. [Collagen cross-linking with riboflavin and UVA light]. *Klin Monbl Augenheilkd*. 2010 Sep;227(9):723-8.

Kanellopoulos AJ. Comparison of sequential vs same-day simultaneous collagen cross-linking and topography-guided PRK for treatment of keratoconus. *J Refract Surg*. 2009 Sep;25(9):S812-8.

Koller T, Iseli HP, Hafezi F, Vinciguerra P, Seiler T. Scheimpflug imaging of corneas after collagen cross-linking. *Cornea*. 2009 Jun;28(5):510-5.

Koller T, Mrochen M, Seiler T. Complication and failure rates after corneal crosslinking. *J Cataract Refract Surg*. 2009 Aug;35(8):1358-62.

Leccisotti A, Islam T. Transepithelial corneal collagen cross-linking in keratoconus. *J Refract Surg*. 2010 Dec;26(12):942-8.

Raiskup F, Hoyer A, Spoerl E. Permanent corneal haze after riboflavin-UVA-induced cross-linking in keratoconus. *J Refract Surg*. 2009 Sep;25(9):S824-8.

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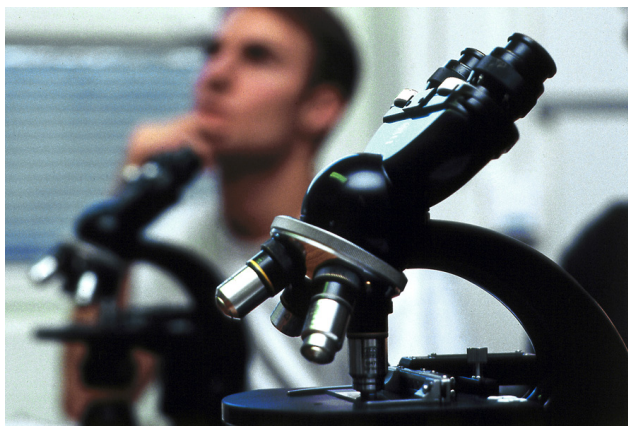
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Summary of Findings
Corneal crosslinking in patients with keratoconus

Outcome variable	Design	Study limitations	Consistency	Directness	Precision	Publication bias	Magnitude of effect	Relative effect (95%CI)	Absolute effect ⁱ	Level of evidence GRADE ⁱ
Number of studies										
Curvature of cornea										
6	2 RCTs 4 observational studies	Serious limitations (-1)	No important inconsistency	Uncertainty (-1)	Imprecision (-1)	Unlikely	Not relevant	-	Change in Kmax pre-to postop: -1.7 to -1.5 D	⊕ Very low
UDVA										
4	1 RCT 3 observational studies	Serious limitations (-1)	No important inconsistency	Serious uncertainty (-2)	Imprecision (-1)	Unlikely	Not relevant	-	Change in logMAR pre-to postop: -0.07	⊕ Very low
CDVA										
6	2 RCTs 4 observational studies	Serious limitations (-1)	No important inconsistency	Uncertainty (-1)	Imprecision (-1)	Unlikely	Not relevant	-	Change in logMAR pre-to postop: -0.12	⊕ Very low

Footnote: i. Includes only data from the RCTs

Abbreviations: D = diopter; log MAR = logarithm of Minimum Angle of Resolution; UDVA = Uncorrected Distance Visual Acuity; CDVA = Corrected Distance Visual Acuity



HTA

Health technology assessment (HTA) is the systematic evaluation of properties, effects, and/or impacts of health care technologies, i.e. interventions that may be used to promote health, to prevent, diagnose or treat disease or for rehabilitation or long-term care. It may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. Its main purpose is to inform technology-related policymaking in health care.

To evaluate the quality of evidence the Centre of Health Technology Assessment in Region Västra Götaland is

currently using the GRADE system, which has been developed by a widely representative group of international guideline developers. According to GRADE the level of evidence is graded in four categories:

High quality of evidence	= ⊕⊕⊕⊕	(Previously Level of evidence 1)
Moderate quality of evidence	= ⊕⊕⊕	(Previously Level of evidence 2)
Low quality of evidence	= ⊕⊕	(Previously Level of evidence 3)
Very low quality of evidence	= ⊕	(Previously Level of evidence 4)

In GRADE there is also a system to rate the strength of recommendation of a technology as either “strong” or “weak”. This is presently not used by the Centre of Health Technology Assessment in Region Västra Götaland. However, the assessments still offer some guidance to decision makers in the health care system. If the level of evidence of a positive effect of a technology is of high or moderate quality it most probably qualifies to be used in routine medical care. If the level of evidence is of low quality the use of the technology may be motivated provided there is an acceptable balance between benefits and risks, cost-effectiveness and ethical considerations. Promising technologies, but a very low quality of evidence, motivate further research but should not be used in everyday routine clinical work.

For diagnostic studies, the GRADE system is still under development and not yet ready for use. In the present report, we have evaluated the level of evidence for diagnostic accuracy according to the system previously used by SBU, (Swedish Council on Health Technology Assessment), briefly described below.

High level of evidence

At least two studies of high quality or a systematic review of good quality

Moderate level of evidence

One study of high quality and at least two studies of moderate quality

Low level of evidence

At least two studies of moderate quality

Very low level of evidence

Only studies of low quality

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