Collagen Cross Linking in Keratoconus

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Keratoconus is a degenerative, noninflammatory disease of the corneal stroma that is associated with decreased biomechanical strength of the tissue, probably caused by diminished intra- and interfibrillar cross-links of the collagen fibers. Usually the onset occurs at puberty. Incidence of keratoconus is 1/2000. It is progressive in 20% of cases and can be treated by lamellar or penetrating keratoplasty.

Recently, a new method has been developed for the treatment of progressive keratoconus, which currently is under clinical study: **Corneal collagen crosslinking with riboflavin / UVA.** The technique of corneal collagen cross-linking consists of photopolymerization of the stromal fibers by the combined action of a photosensitizing substance (riboflavin or vitamin B2) and UV light from a solid-state UVA source. Photopolymerization increases the rigidity of the corneal collagen and its resistance to keratectasia. Basically, cross-linking treatment markedly stiffens the cornea and increases the biomechanical strength by a factor of 4.5. To avoid potential irradiation damage to the corneal endothelium by UVA light, the technical parameters are set in a way that only the anterior 300 mm of the corneal stroma is treated.

We tried to find out how the above treatment could be optimally utilised for best results in patients of keratoconus. Dr. Gregor Wollensak **(GW)**, introduced the technique for the first time. Dr. Farhad Hafezi **(FH)** has worked on collagen cross linking and published lot of work on it. Dr. Sudhank Bharti **(SB)**, Dr. Mahipal S. Sachdev **(MSS)**, Dr. S.P.S.Grewal **(SPSG)**, Dr. J.S.Thind **(JST)**, Dr. Rishi Mohan **(RM)** and Dr. Ajay Khanna **(AK)** have been using the technique in India for past few years. These leading ophthalmologists were asked for their opinion regarding the use of collagen crosslinking in the treatment of keratoconus.

GW: Dr. Gregor Wollensak, Department of Ophthalmology, Vivantes-Klinikum Neukölln, Berlin, Germany, FH: Dr. Farhad Hafezi, Associate Professor of Ophthalmology, University of Zurich, Editorial Board Member of the Journal of Refractive Surgery and the Iranian Journal of Ophthalmology. SB: Dr. Sudhank Bharti, Medical Director and Chief Consultant, Bharti Eye Foundation, Delhi, MSS: Dr. Mahipal S. Sachdev, Former Associate Professor at R.P. Centre, AIIMS, and now Chairman and Medical Director, Centre For Sight, Delhi. SPSG: Dr. SPS Grewal, Former Associate Professor, PGIMER and now Director, Grewal Eye Institute, Chandigarh, JST: Dr. J.S.Thind, Lasik and Phaco Surgeon, Jalandhar, RM: Dr. Rishi Mohan, Director, MM Eyetech Institute, Delhi, AK: Dr. Ajay Khanna, Director, Vitreo-retina and Refractive Surgery Dr. Om Parkash Eye institute, Amritsar.

Dr. Shubha Bansal (SB) DNB, who is working as an Senior Research Officer at Dr. Rajendra Prasad Centre for Ophthalmic Sciences, All India Institute of Medical Sciences, New Delhi, interviewed them on the Collagen Cross Linking in Keratoconus.

SB: What is your criteria of selection of patients?

GW: The treatment should only be performed in patients with documented progression of keratoconus in the preoperative months.

FH: We have the following inclusion criteria:

- minimal corneal thickness (without the epithelium) of 400 µm
- documented progression (topographies)
- cornea not scarred
- optical rehabilitation with contact lenses or glasses is possible
- prior treatment of mechanical underlying reasons, i.e. excessive eye rubbing

SB: I would do Corneal Cross Linking in the following patients:

We now use hypotonic Riboflavin (diluted in distilled water) in patients with thinner corneas. This causes hydration and swelling of the cornea and protects the corneal endothelium from UV-A radiation.

- Keratoconus & Pellucid Marginal Degeneration showing progress over a 6 months period on Topography.
- Post LASIK ectasia.

MSS: I recommend collagen cross linking for all patients with Progressive keratoconus as I have found it to be a very safe and effective technique to halt the progression of disease. Though traditionally it has been recommended that progression should be documented on successive topographies over 6 months or more, I rely on clinical assessment and even a single topography showing a progressive steepening or a repeated change in glasses/ contact lenses is an indication for collagen cross linking. During the procedure 0.1% Riboflavin eye drops (Figure1) in Dextran solution are applied to the cornea for 30 minutes followed by exposure to UV-A light (365 nm) at 3mW/cm^2 to achieve cross-linkage of the corneal collagen fibres. This increases the bio-mechanical strength of the cornea by upto 300% and arrests the progression of keratoconus.

SPSG: I would recommend collagen cross linking for a proven case of keratoconus between the age group 12 to 40 years. The thinnest corneal thickness should be more than 350 microns. It is strongly recomended in cases of keratoconus where Intacs of corneal graft is being planned.

JST: ***Selection Criteria*** – Post Refractive surgery Keratoconus, Progressive Keratoconus (Thinnest Cornea = / More than 400 microns), Pellucid marginal degeneration.

RM: The major indication for Corneal Collagen CrossLinking is Progressive Keratoconus. All patients with classic parameters of keratoconus are candidates. Unfortunately, documentation of progression is not always available as many patients have inadequate old records and one has to take into account the history of visual loss & increase in astigmatism on the glasses prescriptions or history of rapid changes in the contact lenses.

AK: I would do Corneal Cross Linking in the following patients:

- Progressive Keratoconus.
- Minimum corneal thickness 400 Microns or more (From 360 Microns to 400 Microns thickness, Corneal thickness is increased temporarily intra-operative with hydration using hypotonic solution).
- Steepest 'K' less than 65D.
- Progressive Iatrogenic Keratectasia.

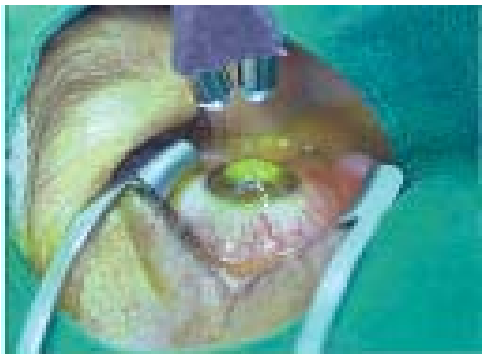


Figure 1: *Riboflavin/UV-A treatment in a patient with a double UV-A diode at 1 cm distance and the yellowish riboflavin on centrally abraded cornea.*

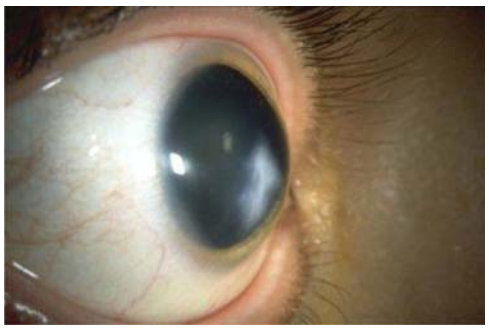


Figure 2: *Corneal scar in advanced keratoconus*

SB: What is your exclusion criteria?

GW: Preoperative pachymetry with less than 400mm stromal thickness.

FH: Any condition that does not meet the above mentioned criteria.

SB: Corneal thickness of less than 450 micron - because a minimum thickness of 400 micron is safe so that the ultraviolet light does not cause any harm to Retina. In cases where the original thickness is less than 450 microns, after removal of epithelium the target thickness is 400 microns and should be achievable with hydration of cornea either with distilled water or with aqueous riboflavin solution.

MSS: Patients with corneal thickness less than 400 µm and with significant apical scarring (Figure 2) were previously considered unfit for collagen cross linking. However we

now use hypotonic Riboflavin (diluted in distilled water) in patients with thinner corneas. This causes hydration and swelling of the cornea and protects the corneal endothelium from UV-A radiation, hence allowing the procedure to be carried out safely. Patients with significant apical scarring can also undergo collagen cross linking as it stabilizes the cornea without affecting the scarring thereby preventing or delaying the need for penetrating keratoplasty. I'm more aggressive in my approach and have successfully performed it in patients with advanced keratoconus with steeper and thinner corneas as well, as in any case we are strengthening the cornea and preventing further progression.

SPSG: There are two main exclusion criteria:

1. Extremes of Age(<12 years or >40 years).

2. Corneal thickness less than 350 microns.

JST: ***Exclusion Criteira*** - Thinnest Cornea less than 400 microns

- Diabetics
- Pregnancy
- Central Corneal Scarring
- Active or Healed Viral (Herpetic) Keratitis
- Maximum corneal curvature should not be more than 60 D.

RM: Patients with a stable power, a pachymetry of less than 375 microns at the thinnest point, a poor endothelial cell count, forme fruste and hydrops (both acute and healed with scarring) are excluded. Pregnancy should be inquired into in women of child-bearing age and lactating mothers should be excluded. Special precautions are recommended for patients with severe vernal catarrh and features of stem cell deficiency in whom there are wound healing concerns and in diabetics.

AK: Very early Keratoconus – Non progressive.

- Very advanced Keratoconus with Corneal Opacity.
- Steepest 'K' more than 65D.
- Minimum corneal thickness less than 360 Microns on Pentacam (From 360 Microns to 400 Microns thickness, Corneal thickness is increased temporarily intra-operative with hydration using hypotonic solution).

SB: **What is the cut off age for patients who can undergo the procedure?**

FH: There currently is no upper nor lower age limit for us. However, classic keratoconus almost never progresses after the age of 55 and only starts before puberty if excessive eye rubbing is the cause.

- On the other side, we have seen and treated patients as young as 11 years old (prepuberty) that had marked keratoconus due to eye rubbing and patients aged 60 and older with pellucidal marginal corneal degeneration, the latter NOT arresting at a certain age.

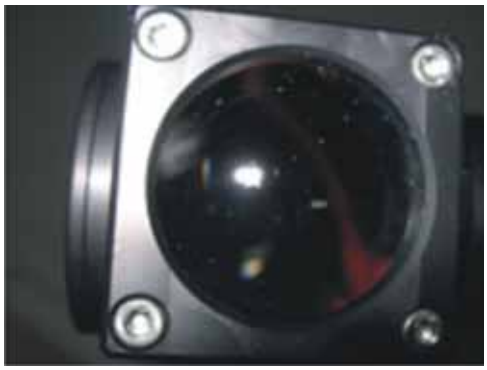


Figure 3: *Two views of the collagen cross linking machine*

SB: 30 years because natural crosslinks in the cornea become strong enough to retard/stop progression of keratoconus after this age.

MSS: Patients with progressive keratoconus can be taken up for collagen cross linking at any age. Younger patients are known to progress more and hence derive greater benefit from collagen cross linking while older patients usually have stable corneas and donot show much progression. However there is no contra-indication and collagen cross linking can be performed at any age.

SPSG: Patients with age less than 12 years or greater than 40 years are not candidates for this procedure.

JST: No cut off age as such but preferably below 50 years.

RM: There is no prescribed cut-off age for this procedure. The youngest I have done is at age 10 years and the oldest is 34 (the other eye has had a PKP). The issue in the older patient is the possible spontaneous cessation of progression as the cornea naturally cross-links as we age.

AK: There is no cut off age – minimum or maximum. It can be done if patient meets criteria & Keratoconus or Keratectasia is progressing.

SB: **How effective is the procedure in your settings – in terms of visual regain and time?**

GW: Collagen crosslinking might become the standard therapy for progressive keratoconus in the future diminishing

significantly the need for corneal transplantation. Preoperative pachymetry and individual control of the ultraviolet A-irradiance before each treatment are mandatory.

FH: When the inclusion criteria are respected, we can expect a regain of VA to the preoperative values at 10-12 weeks after surgery. Before, haze might lower VA for 1 or 2 lines when compared to the preop state.

SB: I am extremely satisfied with the results in terms of visual recovery and cessation of progression of the disease. Most of my patients regain vision in a week's time. In cases where I have performed PRK with collagen cross linking , the results have been more heartening.

MSS: We have found it extremely effective with improvement of vision by 1 to 3 lines in 30-40% patients and stabilization in the rest. The visual gain has remained stable over a 1 year follow up in all our patients. It also significantly reduces the Surface Asymmetry Index (SAI) and increases the glass/ contact lens tolerance of these patients.

SPSG: Procedure is extremly effective in terms of stabilizing the keratoconus and protecting further deterioration of keratoconus. My clinical experience shows the safety of the procedure. Some patients do gain visual acuity by 1-2 snellen lines post collagen cross linking but improvement in vision is not the prime objective of this procedure. BCVA remained stable at 1 year followup. There were no significant changes observed in mean anterior and posterior corneal curvature (horizontal and vertical) central and apical corneal thickness.

JST: Most of the patients show obligations with regression to tune of 0.50 D to 1.50 D in 2-3 months times.

RM: The procedure is done for providing stability and not for visual gain. This must be emphasized to the patient who may have unrealistic expectations. The vision regains slowly; we refract the patient at around the 10^{th} –14^{th} day and provide glasses. A fresh topo-assisted contact lens trial is done at around 4 - 5 weeks. Some patients complain of a slight haze but the majority recover fully and actually gain in BCVA. At 6 months all patients have achieved or exceeded pre-op BCVA.

AK: After about 3 months of collagen cross linking procedure, there is gain of 1-2 lines in visual acuity in few patients and decrease in steepening of 2-3 dioptres.

SB: **How many times it can be repeated and how often?**

GW: Where recurrence of keratoconus is present, a second crosslinking procedure might be a choice.

FH: Up to now, we never had to repeat a treatment. However, we know from earlier studies from literature that the turnover time of the corneal stroma is approx. 10-15 years. So, theoretically, there should be no more cross-linked stroma in a human cornea at 10 years after treatment and maybe, we will have to re-treat these patients after 10 years.

- Nowadays, the longest follow-ups available are 8 years, so we will know more in a few years
- Even if the human cornea will be entirely reorganized after 10 years these patients will also be 10 years older and we know that classical keratoconus progresses more slowly with age

SB: I have not repeated Crosslinking in any eye.

MSS: It can be repeated if required if progression is documented on corneal topography. However, in a 9 year follow up of patients after collagens cross linking, a re-treatment was not required. Theoretically the procedure can be done again without any sight threatening side effects.

SPSG: We have not repeated treatment in any of our cases so far. The first treatment should stabilize the keratoconus for lifetime.

JST: We have not repeated it yet, but can be repeated after 2-3 years if needed as collagen turn over in cornea is estimated to be between 2-3 years but only if disease is progressive.

We cover the eye with ofloxacin ointment and a therapeutic contact lens until the epithelium is healed, followed by fluorometholone eye drops twice daily for several days.

RM: The theoretical concern is that the crosslinked collagen may be replaced in time by defective collagen and the cone progression may re-start. Follow-up worldwide is in the range of 7 years and there are no reports of repeat procedures. In our series too there seems to be no cause for us to perform a re-do.

AK: It can be repeated but I have not found the need to repeat till date. After collagen cross linking, there is decrease in corneal thickness of about 20-40 Microns (as measured by Pentacam) in all the cases as the corneal lamellae become more compact after corneal collagen cross linking.

SB: **What procedure do you follow for removal of corneal epithelium?**

GW: The central 7mm of the corneal epithelium are removed to allow better diffusion of riboflavin into the stroma.

FH: We remove the epithelium completely

- At the 3rd international congress on corneal cross-linking in Switzerland (organized by our institute, IROC, www.iroc.ch), an italian group (Baiocchi et al.) has presented very interesting data where the concentration of riboflavin in rabbit corneas was measured at 30 minutes after riboflavin application with and without prior abrasio.
- Their results clearly demonstrated that the group with

intact epithelium had a 10-times lower riboflavin concentration when compared to the abrasio group.

SB: In cases where I do only collagen cross linking, I remove epithelium in the cross pattern with 5 horizontal and 5 vertical line of 1-2 mm breadth of de-epithelisation. With PRK + collagen cross linking I remove epithelium with a hockey knife in a 9 mm diameter.

MSS: The instrument I use to remove the epithelium is the hockey stick. I have also used alcohol to debride the epithelium in a couple of cases. A brush rotator can also be used for mechanical debridement.

SPSG: We use hockey stick knife, to remove linear streaks of the epithelium with few strokes, leaving the centre epithelium intact.

JST: I do not remove epithelium, but give scratch marks in epithelium in criss-cross fashion.

RM: Various modes of epithelial removal including mechanical debridement are being used. We use a commercially available filter paper swab soaked in 70% isopropyl alcohol, cut into a disc of 8 mm diameter and placed for 15 secs on the center of the cornea. The epithelium just peels off with a moistened sponge and the cornea is irrigated well with BSS before starting the riboflavin instillation.

AK: I usually remove epithelium manually with hockey – stick knife, only partial interrupted epithelium removal as it serves the purpose as well as causes early healing of epithelium.

SB: **Your post operative period management pertaining to pain. Any special precautions for herpes?**

FH: We cover the eye with ofloxacin ointment and a therapeutic contact lens until the epithelium is healed, followed by fluorometholone eye drops twice daily for several days

- In cases of severe pain we hand out 1:5 diluted oxybuprocaine 0.4% eye drops, but only in cases where we can trust the patient's compliance that he/she will not abuse on these drops (no more than once per hour, danger of prolonged epithelial healing)
- We take no special precautions for herpes

SB: I give Diclofenac 50 mg dispersible tablets on SOS basis. I also give 0.2% Xylocaine in lubricant every 2 hours for 2-3 days. A Vigamox impregnated Bandage CL is put at the end of procedure to be removed when slit lamp examination shows complete epithelization (Mostly 2-3 days).

MSS: We routinely prescribe antibiotic-steroid combination, NSAIDs & lubricating eye drops. A BCL (bandage contact lens) is placed for patient comfort and removed after 3-5 days depending on the healing and response. Patients with HSV are considered high risk for refractive surgery even though cases have been done without recurrence or problems. I have not encountered a case of Herpes with keratoconus so far.

SPSG: Pain is not an issue in the post operative period. I recommend liberal use of lubricating eye drops. Patient is followed up daily till the epithelial defect heals and bandage contact lens in removed.

JST: After the treatment we patch the eye for 24 hours, Orally NSAID (Combiflam) three times in a day for 2 days. Antibiotic eye drops QID (Vigamox) for 7 days, NSAID eye drops TID for one week, and Lubricating eye drops. We are not doing collagen cross linking in cases where we suspect herpes.

RM: The patient must be adequately counseled. Pain, discomfort, watering and foreign body sensation post-operatively are significant features. We now apply a bandage lens after the procedure is completed. Systemic ibuprofen & paracetamol are prescribed for 4 days. Lubricant drops 6 times daily help decrease the discomfort. We have not encountered any concern regards Herpes in our series.

AK: I place bandage contact lens on cornea and prescribe post-operative Ketarolac Eye drops (4 times a day) with lubricating and antibiotic drops & oral pain killer to be taken, if needed.

We don't need any precautions for herpes in case of normal Keratoconus / Keratectasia patient.

SB: **Your clinical experience with the above procedure. (Number of cases and results)?**

GW: Dresden clinical study shows that in all treated 60 eyes the progression of keratoconus was at least stopped ('freezing'). In 31 eyes there also was a slight reversal and flattening of the keratoconus by up to 2.87 diopters. Best corrected visual acuity improved slightly by 1.4 lines. So far, over 150 keratoconus patients have received crosslinking treatment in Dresden.

FH: We have now 5 years of clinical experience at IROC.

- Our preliminary study one-year follow up data confirm earlier results showing a stabilization of the keratoconus in all cases that met the inclusion criteria and slight increase in BSCVA of approximately one line.

SB: Over a period of 1 year and 2 months, I have done 102 eyes . 97 eyes have achieved either improvement or stability in the disease. 5 eyes have shown progression over 6 months. An improvement is appreciable in a weeks time when astigmatism shows tremendous reduction and keeps on getting better for next 6 – 12 months.

MSS: We have done 42 eyes and found the procedure to be highly effective. On an average the BCVA improved by 1.4 lines and an average regression of 2.8 D took place in the keratometry. There was stabilization of keratoconus in all patients. There was an overall flattening of the corneal contour with a reduction of Sim K astigmatism between 0.2- 6.9 D with the effects being most apparent in on the anterior surface (ABFS). On an average the astigmatism reduced between 1.0 to 7.0 D.

SPSG: We have done collagen cross linking in about 150 eyes till date and all the eyes are doing well in terms of not only stability but also in maintaining good vision with help of contact lenses or glasses. Some cases have haze lasting for up to three weeks.

JST: We have done over 100 eyes, in almost all cases progression has stopped and some of them improved from 0.50 D to 1.50 D.

RM: My co-workers and I have performed over 140 procedures in the last 15 months. About 35 patients have completed 1 year follow-up. All treated eyes have achieved stabilization of cone progression. The other eye, in those who underwent one eye treatments, has progressed over the same period.

UCVA improved in 80%, BCVA has improved in over 2/3rd and contact lens tolerance in over 75%. Topographic flattening of the cone is observed in the majority with a reduction in corneal irregularities and decrease in corneal astigmatism. Some patients complain of visual haze till 4 months but this improves thereafter. No patient recorded a drop in BCVA.

AK: Till now, I have treated 18 eyes in last 11 months and I am quite satisfied with the procedure and in all the patients, Keratoconus is stabilized but long term follow-up is needed.

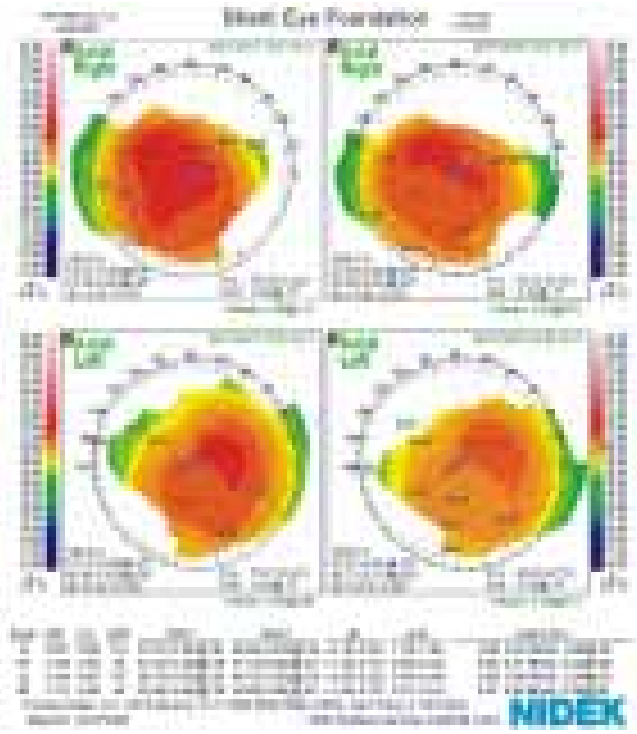
SB: **Other indications in which you are doing collagen cross linking as a line of treatment?**

FH: We have successfully established and published CXL for three further indications:

- LASIK-induced keratectasia
- PMD (pellucidal marginal degeneration)
- acute corneal melting processes
- I will attach the corresponding papers to the Email.

SB: As of now I am treating only conus and ectasias.

MSS: I have used collagen cross linking in patients with Pellucid marginal degeneration and Post-LASIK keractesia and found good results. I've also used it in conjunction with Kera Rings for patients with advanced keratoconus and along with Toric Implantable Contact Lens to correct myopic astigmatism and further improve vision after collagen cross linking.



Pre & Post Corneal Collagen cross linking topography of a patient (Courtesy: Dr. S. Bharti)

SPSG: We are doing collagen cross linking in cases having proven Post Lasik Ectasia and also in some patients with progressive pellucid margin degeneration.

RM: Any progressive ectatic corneal condition can in theory be benefited by crosslinking. Though the majority of our cases are of progressive Keratoconus, we have performed the procedure successfully in many cases of post-LASIK keratectasia and some patients with Pellucid marginal degeneration.

AK: Apart from progressive Keratoconus, other indication is progressive Iatrogenic Keratectasia.

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