

Corneal Collagen Crosslinking for Keratoconus

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Interview with Raymond Stein, MD, FRCSC by Dr. Kevin Anderson



Dr. Raymond Stein is Medical Director of the Bochner Eye Institute, Assistant Professor of Ophthalmology at the University of Toronto, and Past President of the Canadian Society of Cataract and Refractive Surgery.

How long have you been performing collagen crosslinking?

We started Corneal Collagen Crosslinking for Keratoconus (CXL) in January 2008 at the Bochner Eye Institute in Toronto. We were the first centre in Canada to offer CXL and have been performing the procedure for over 21 months. The procedure has been available in Europe for the past 11 years. I followed the basic research literature from 1993 to 1998 and then the long-term clinical outcomes. From 2006 to 2007, I encouraged patients with progressive keratoconus to have CXL done in Europe. Five of my patients went to Europe for treatment and I followed them postoperatively. I was impressed with the outcomes using serial Pentacam analysis with difference maps to show that the procedure halts the progression of keratoconus.

Is crosslinking a significant advance in eye care?

CXL is a procedure that has the potential to help thousands of patients. For the first time in history, we now can offer our keratoconus patients a proven procedure that can improve vision, and potentially eliminate the need for a corneal transplant.

How much long-term safety and efficacy data is available for collagen crosslinking?

The first patients were treated in 1998, so at this point, we have 11 years of data on the safety and efficacy of the procedure. It is rare for a patient not to respond. In fact, it has been almost 2 years since we began offering CXL, and every case has responded favourably. Data from Europe suggests that a repeat CXL can be performed for the rare patient that does not respond.

How many procedures have you performed to date?

We have treated a total of 805 eyes across Canada and the United States. There were 771 eyes with keratoconus, 19 eyes with ectasia, and 15 eyes having post-radial keratotomies.

What is the age range of patients that you have treated?

The keratoconus patients have ranged from 11 to 60 years of age, though most have been under 45 years

of age. Keratoconus tends to slow down with age. Patients over 45 years of age that we have treated have had documented evidence of progressive ectasia.

Are there any contraindications to the procedure?

A minimal thickness of less than 300 μm indicates an absolute contraindication. If patients have corneal scarring that significantly interferes with best-corrected acuity, we would recommend a corneal transplant over CXL.

Is the procedure difficult for patients to undergo?

The procedure is relatively easy, but long. It takes an hour for one eye, and 1½ hours for both eyes. We encourage patients to bring their iPod so they can listen to their own music during the procedure. Most patients are relaxed and find the experience pleasant.

How do you make the diagnosis of keratoconus?

There are late-to-early clinical signs of keratoconus. Late clinical signs include Munson's sign, which is a bulging of the lower lid in downgaze, acute hydrops, which is a break in Descemet's membrane resulting in corneal edema, Vogt's striae, which are stress lines of the stroma, and apical scars. Earlier clinical signs include a scissors reflex on retinoscopy, inferior corneal steepening on computerized topography, and bulging of the posterior cornea on elevation topography. We can measure the thickness of the epithelial cells that may show areas of thinning and thickness suggestive of keratoconus. We can also look at biomechanical properties of the cornea that may show a reduction in rigidity.

Can you please describe your current technique?

We perform bilateral procedures 80% of the time. Preoperatively, we perform Pentacam analysis to determine the thinnest area of the cornea. If the cornea is 400 μm or greater, we will use the standard Riboflavin formulation at 0.1%. If the cornea is between 300 and 400 μm , we will use Riboflavin drops without dextran. This induces an average of 150 μm of transient swelling, to allow for a safe CXL procedure in thin corneas. The energy level of the UV-A laser is checked with a powermeter to be sure it is within a specific range. Pilocarpine drops are used preoperatively to constrict the pupil. Fourth generation fluoroquinolone drops e.g. Vigamox are instilled. Tetracaine eye drops are also used. The skin is prepped with a Betadine solution. We do not use a drape. A lid speculum is inserted. The Amoils rotary brush is used to remove 8 mm of epithelium. Riboflavin drops are instilled every minute for 30 minutes in one eye. UV-A light is then applied in one eye for

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30 minutes. At the same time, Riboflavin drops are instilled in the other eye. When CXL is completed in one eye, we move to the other eye. When both eyes are completed, a bandage SCL is inserted. Patients are encouraged to go home and rest. Postoperative follow-up is typically 1 day, 5 days for CL removal, then 2 weeks, 1 month, 3 months, 6 months, and 12 months. We allow our patients to resume CL wear after 2 weeks.

What factors might discourage surgeons from adopting this technique?

Although the procedure is a major breakthrough, the only negative is that it is time-consuming, and healing can be similar to PRK. We do find that most patients are comfortable during the postoperative period. It is important to have a sharp edge of epithelium to promote reepithelialization. Using a blade or alcohol for epithelial removal may not achieve the same level of postoperative comfort or healing.

Are you using crosslinking as a first step in corneal rehabilitation? For example, stabilizing corneas with crosslinking and then performing refractive surgery to correct vision?

We are doing some combined treatments with PRK. The goal is to enhance UCVA, but not to weaken the cornea. We try not to remove more than 50 μm of tissue. A topographically-linked laser ablation has great potential to reduce irregular astigmatism in mild-to-moderate cases of keratoconus. More significant cases of keratoconus require the corneal ring procedure to induce significant flattening. We can do both CXL and PRK at the same time. The goal of a topographically-linked laser ablation is to reduce the irregular astigmatism so that patients can wear glasses or a soft contact lens. We can also do CXL and an intrastromal ring procedure at the same time. Additionally, we have done the adjunct procedure at a later date as well as at an earlier date, with satisfactory results.

Do you see new indications for collagen crosslinking down the road?

I believe that the treatment of RK eyes has the potential to be a breakthrough procedure which can help thousands of patients. Long-term data after RK has shown that some patients develop progressive hyperopia, and in addition, a high percentage have diurnal fluctuation in vision. Our early data over the past 21 months in 15 eyes has been impressive in stabilizing corneas and reducing fluctuation in vision. I believe that when the RK corneas are stable, the outcomes will be better with PRK, phakic IOL, refractive lens exchange, or cataract surgery. When I look back over the past 20 years, in dealing with RK outcomes following other procedures the results have not been as good as virgin eyes. I believe this may be related to unstable corneas. Another application is the treatment of refractory corneal infec-

tions. When infections do not respond well to intensive antibiotic therapy, CXL may be a valuable option to kill organisms. Another area of interest and concern are patients with ectasia after LASIK or PRK. I think it is important to follow our past laser vision correction patients with computerized topography, and preferably, elevation topography. If we see the earliest sign of ectasia, consideration can be given to CXL. Patients do best when the disease is mild or diagnosed in the early stages. If the diagnosis of ectasia is made late in the disease process, the prognosis for visual rehabilitation is guarded. In addition to CXL, patients may require a corneal ring procedure and/or a phakic IOL.

What complications could occur with this procedure?

Complications have been extremely rare – in 805 eyes, we have seen 1 sterile infiltrate, and a few cases of delayed epithelial healing taking longer than 5 days. We have not seen any cases of infection. Patients typically will develop a mild corneal haze that peaks at 6 months and gradually fades away by 12 months. This haze does not interfere with best-corrected vision, and this is a positive sign that the CXL was effective in stimulating cross-linking between the collagen fibers to enhance rigidity. With RK eyes, one has to be careful not to open the incisions that could induce irregular astigmatism. The LASIK cases that have previously had RK are the trickiest to deal with, as the flap essentially acts like a pie cut up into pieces. One has to take care not to dislocate the fragments. I am careful in dealing with these complicated eyes, and have not seen any problems to date.

What advice would you offer co-managing doctors who want to start offering collagen crosslinking?

It is important that patients have the proper expectations. They need to know that the main goal is to prevent progressive ectasia, and hence, reduce the risk of a corneal transplant. The vision can worsen in the first 1-2 months before it improves. The corneal epithelium undergoes maturation to smooth the corneal curvature. This results in epithelial thinning over the cone and thickening over the base, which enhances the quality of vision. Most patients show flattening on topography in 2-4 months. The best way to appreciate change is using a difference map that subtracts the preoperative map from the postoperative map. Sixty percent of our cases have shown an improvement in BCSVA in 6-12 months. Younger patients or those with less severe ectasia have a better prognosis. Those who are treated with a corneal scar will still have scars postoperatively. Ideally, the patients with less severe disease and clear corneas will have the best chance of quality of vision. Today, I believe that all patients with keratoconus should be informed of the CXL procedure and the potential benefits of halting the disease process.

COS: 41st Sally Letson Symposium Uveitis 2009: Diagnosis and Treatment

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The Canadian Ophthalmological Society (COS) recently hosted the 41st Sally Letson Symposium at the Westin, Ottawa, in conjunction with the Sally Letson Foundation and the University of Ottawa Faculty of Medicine. The event was a COS-sanctioned educational event, and ophthalmologists in attendance were entitled to up to 19 credits. 15 faculty members represented institutes, universities, and medical and research centres from Canada, the US, Australia, and France. The symposium was very well attended, with no fewer than 600 participants, including ophthalmologists, residents, allied health personnel, and fellows, among others. Dr. James Rosenbaum, the 2009 RCPSC Lecturer, said it was “arguably the most successful uveitis symposium in the world.”

Uveitis 2009: Diagnosis and Treatment was chaired by Dr. Emmett T. Cunningham Jr., who is the Director of The Uveitis Service at the California Pacific Medical Centre and Adjunct Clinical Professor of Ophthalmology at the Stanford University School of Medicine. It was co-chaired by Dr. William Hodge, who is Ophthalmologist-in-Chief at the Ivey Institute of Ophthalmology, University of Western Ontario.

The symposium had stated aims for the attendees, namely that they should leave the symposium able to:

1. List the clinical features of uveitis.
2. Discuss the natural history and the major causes of uveitis.
3. Describe the use of laboratory testing and imaging studies to diagnose uveitis.
4. Compare and contrast various approaches to treating uveitis, including the use of corticosteroids, non-corticosteroid immunosuppressive agents, and surgery.

Several presenters were quite active at the meeting, including Dr. Debra Goldstein, who gave numerous lectures. During her first lecture on the Thursday morning, she reminded everyone of the importance of accurate classification for work ups, differential diagnosis, treatment, disease course, and prognosis. She also warned against making a diagnosis too quickly, and suggested that once you find an indicator of a particular type of uveitis, you should continue to look for other signs indicating that you are right or wrong.

The symposium's chair, Dr. Emmett T. Cunningham Jr. also gave several lectures, including one on appropriate laboratory testing for diagnosing uveitis. He warned that uveitis can masquerade as other diseases, and that an accurate diagnosis helps to predict history, associated disorders, and response to therapy. He suggested a 4-step process for accurately diagnosing uveitis:

1. Obtain a thorough history from the patient.
2. Do a thorough review of systems.
3. Perform a complete dilated eye exam.
4. Conduct a focused systemic exam.

As there are more than 30 tests available, his general rule of thumb is: test when it's *not* simple anterior uveitis; do not test when it *is* simple anterior uveitis, or when the diagnosis is already known. The most common reason to test is to support a suspected diagnosis. He said to stop testing when a diagnosis is known, or when all indicated tests have been completed. Re-test when the pattern of disease changes.

Of the more than 30 available tests, he believes that the following six tests are the most useful: Chest Xray/CT; TB test (PPD/y – interferon); FTA-ABS/MHA-ABS; VDRL/RPR; serum ace; serum lysozyme.

Dr. James P. Dunn, who discussed testing with intraocular fluids, suggested that such testing only be used as confirmatory and when appropriate, as there are negatives associated with the procedure. These include risk of infection, false positive or negatives, and a high per-test cost.

Despite their potential drawbacks, Dr. Bahram Bodaghi also mentioned the importance of intraocular fluids. He discussed acute retinal necrosis (ARN) and reviewed appropriate treatments and dosages. He emphasized the fact that ARN is a sight-threatening emergency.

During question periods, many of the inquiries focused on treatment; attendees wanted to know what options the panelists were using in their respective countries.

Dr. Phil Hooper presented a helpful seminar on uveitis in the elderly, a population of growing concern for Canadians in particular, because of demographic changes. He encouraged attendees to consider diagnostic and management issues. As patients age, their pupil ages and becomes smaller, so it is more difficult to see what is important. At the same time, fundus changes, age-related changes, and disease-related changes make it harder to interpret what one sees.

When a diagnosis is made, one must remember that the physical limitations of elderly patients may dramatically affect their ability to follow treatment as prescribed – disease management thus becomes difficult. Disease complications (organ function, medication tolerance) can further compound disease management in the elderly.

Dr. Bahram Bodaghi's lecture on uveitis in children was an interesting contrast to Dr. Hooper's lecture. 10 percent of all uveitis cases occur in children. Treatment

is interesting because, as Dr. Bodaghi says, in certain cases, the problem is not so much the surgery itself as the treatment of inflammation pre and post-operatively. In France, LFM (laser treatment) is quite popular as it is non-invasive. He emphasized the benefits of multi-disciplinary collaboration and early treatment, saying that one should not under-treat children, or allow smoldering inflammation.

The featured lecturers were highlights of the symposium, and these included Dr. James Rosenbaum, who gave the Royal College of Physicians and Surgeons of Canada lecture. He was an enthusiastic and captivating speaker who began his career as a rheumatologist, and found ophthalmology later in his career. He spoke about using the eye to image immune response, and offered cutting-edge information on GFP technology that is being used to see how cells 'communicate'.

In all, the organizers are to be congratulated for a well-run symposium that provided excellent coverage on uveitis diagnosis and treatment.

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Disclosure: Jil Beardmore also acts as copy editor for *Eye Care Review*.