

Current Perspectives in Keratoconus

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Keratoconus is a bilateral, progressive, non inflammatory thinning of the cornea stroma. It has a reported prevalence rate of 20 in 10,000^{1,2} to 1 in 500,000.³

The disease is multifactorial and is influenced by genetic, environmental and biochemical factors. Again although both genders are affected, men seem to

be more commonly involved.

Various grading systems have evolved. The Amsler - Krumeich classification system, Ectasia Risk Scoring Systems, Maeda and Klyce Keratoconus Prediction Index, KISA % of Rabinowitz and Rasheed are naming a few of the standard practicing norms.

The biomechanical weakening of the cornea pervades all the layers with its characteristic disruption of bowman's layer, collagen fragmentation, fibrillation and fibroblastic activity.⁴

Clinically, the early onset of the disease with presentation in teens with progressive visual blur and distortion secondary to myopia and high astigmatism is a disabling event.

The breakthrough to the disease entity and its ambiguities came with the evolution of CXL and the biomechanical strengthening it seemed to offer to halt the disease progression. The standard accepted Dresden protocol of CXL which relied on the interaction of UVA at a wavelength of 370 nm and the topical riboflavin releasing singlet oxygen and enhancing the covalent bonding among the collagen fibrils gained footage. Wollensak et al observed a 328.9% increased corneal rigidity and complimented by various studies, CXL came to be the accepted modality of treatment of KC if there was evidence of progression with a minimum CCT criteria of 400µ.

Hypoosmolar riboflavin was considered for CCT less than 400 u abetted by novel approaches of contact lens assisted CXL and the smile lenticule assisted CXL⁵ which augmented the thickness of these thinner corneas. The trans epithelial Crosslinking had a small window for treating thinner corneas, Paediatric KCs with severe allergic manifestations and epithelial breakdowns.

The positive change came with the accelerated protocols of CXL which lent reasoning to the alternate method of high fluence energy with commensurately reduced UV irradiation times.

Various protocols emerged and the 3 MW and the 9 MW protocols gained wider acceptance abetted with the electron microscopy and confocal studies which elaborated on the more effective crosslinking in these ranges.

As we continued to understand that the oxygen free radicals were critical for crosslinking and the rapid depletion was not in tandem with the reformation, pulsed irradiation came into vogue with pulsed on off times to better replenish free oxygen radicals during the rest periods for a more effective crosslinkage.

There has been an ongoing study of Customised CXL which further looked at the concept that Keratoconus was a focal disease and driving high fluence over the focal cone with lesser energy to the surrounds capitalized interest for evaluation as one more approach to customised CXL. Having discussed the various modes of crosslinking in vogue, we are still not clear as to which modality of crosslinking is the best way forward. We do have the ORA and Corvis but we are not able to acquire any standardized valuation of corneal hysteresis or its biomechanics. In other words, although we accept that there is a presumed increase in corneal rigidity and progression of KC has stalled, we do not have any authentic measure of which crosslinking works best. We realize that in accelerated crosslinking, 3MW and 9 MW work best by assessing the electron microscopic and confocal studies and the evidence of demarcation lines at the right depth and it getting patchy at higher fluence levels. These throw light on the validity of these lower fluence levels working better than the higher 30 MW and 45 MW levels. but we are also now talking about adaptive fluence for different thickness of corneas as one more novel more approach to consider. We are talking of customised crosslinking on the surmise that the disease has a focal propensity and hence could do better with higher focal energy delivery. This is augured by Brillion microscopy studies of higher viscosity in the surrounding area of the affected cone as compared to the area of cone which corroborates you the understanding of a focal disease process⁶.

But again no measure is fool proof and we are left with conjectures. We believe that progression of Keratoconus is far more rapid in Paediatric age group and that should expediate us to treat these eyes on primary diagnosis of KC but again the protocols are not defined. We also are realistic that crosslinking in the young with a more plastic cornea may not be too effective

and further progression of KC is a possibility with the need of repeat crosslinking⁷. So here again that's a quandary. While so much was happening, in this era of crosslinking, what also came to light was the need to regularize the corneal distortion and the need to improve BCVA and not a mere stiffening and strengthening of the corneal lamellae was sufficient. This set the stage for the inception of Topoguided PRK with CXL with proponents like Kanellopoulos and Binder and many more fixing the criteria for treating early to moderate Keratoconus⁸.

The essential dictums for combining cxl with Topoguided regularization was a CCT of at least 450u and a clear cornea, largely centered cones with a maximum ablation of 50u to reshape the corneal curvature and enhance the quality of vision. This was a bimodal approach with a combination of central myopic ablation to flatten the cone and a mid-peripheral hyperopic ablation to steepen the flatter areas and thus provide a larger flatter cone which could better withstand the biomechanical stress combined with crosslinking. But again was 50 u of tissue ablation the clear margin for safety or do we transgress a bit more? Are we completely and irrevocably sure that removal of this 50 u of tissue was not going to be hazardous in this already weakened corneas?? These elemental doubts did remain but there were many articles that came forth substantiating the intent of Topoguided PRK combined with CXL and its safety and efficacy. However, there were some questions that loomed in the background. Do we perform both in the same sitting or do we fall back on sequential treatment. The pros for simultaneous treatment came up with the discussion that it made no sense to crosslink a tissue and then ablate it later to regularize it? The purpose of cxl was defeated. Again there were no nomograms fixed for laser ablation on a cross linked tissue. And further more, doing Topoguided treatment first and then crosslinking in the same sitting made sense as the Bowman's layer was disrupted and this allowed better perfusion of riboflavin. Again do we perform Topoguided treatments only for centered cones or did it perform well for mildly decentered cones?

Post Lasik ectasia was another enigma. In fact, crosslinking itself was not claimed to be as efficient as the pathophysiology of these eyes were questioned and also the diffusion rate of riboflavin and of course the challenge of these corneas being thinner.

But while we could discuss unending on Cxl, we also need to remember the ingress of cxl with LVC and the arguments for and against it. We claimed to better augmentation of corneal rigidity by combining low fluence cxl with LVC with no compromise of refractive result but had no absolute fool proof evidence that it was the only way to go in borderline topographies.

Then again, there had to be a solution for the decentered cones in KC and a solution of sorts to better capitulate an acceptable BCVA.

Therein clamoured a solution for eccentric cones and the intracorneal ring segments combined with cxl drew large acceptance.

Four types of ICRS are available for Keratoconus management .1- Intacs 2- Intacs SK 3- Ferrara Rings 4- Kerarings.

Table of intracorneal ring segments ...

The characteristics of the most popular intracorneal ring segment implants.

Characteristics	INTACS	Ferrara Ring	Keraring
Arc length/degree	150	160	90,120,160,210,240
Cross section	Hexagonal	Triangular	Triangular
Thickness/mm	0.25-0.45 (0.05 increments)	0.20-0.35 (0.05 increments)	0.15-0.30 (0.05 increments)
Internal diameter/mm	6.77	4.40	5.0
External diameter/mm	8.10	5.60	6.0

The popular choices were the intacs which came as the standard 150 arc length PMMA segments, hexagonal in cross section and various sizes ranging from 0.210-0.450mm which were chosen based on the amount and type of refractive errors. Nomograms were evolved to choose between symmetric and asymmetric ring segments for centered and decentered cones. New smaller arc segments of 90 degrees came in when a more focal astigmatism needed to be corrected. Largely these segments were placed in channels created manually or by femtosecond lasers at 70% depth of the thinnest pachymetry.

As if challenging the scene which was already caught in the fray of controversies, Cxl pushed its way to enhancing the results of intacs by the favoured argument of simultaneous cxl with intacs placement. Herein the keratoconic cornea was displaced to a more physiological position by the intacs placement and further strengthened with cxl. This seemed to improve the BCVA and an augmented strengthening of the cornea.

There were always parallels and controversial statements floated whether a simultaneous or a sequential treatment could be done and each had its study comparisons with its arguments. Out of this discussion what came to light was the simultaneous intacs placement combined with cxl was more effective possibly potentiated by exaggerated effect of flattening by the pooling of riboflavin along the intacs segments

While a solution was being derived for strengthening corneas and reshaping, with ICRS and cxl, there were a subset of eyes with significant residual myopia and astigmatism which demanded a corrective measure.

Phakic Iols which were largely meant for treating larger refractive errors with its own stringent criteria came into the scenario but was questioned for treating the irregular KC corneas and their dubious outcomes. Early KCs,

topographically regularised corneas or centered cones came under the purview of Phakic Iols. A wait of 6 months to stabilize the topography and refraction following cxl seemed the ideal requisite to venture to debulk the residual refractive errors following Keratoconus progression with Phakic Iols and a larger stage was set for better KC management.

While contact lenses with their varied options remained as the preliminary options for KC management while watching for progression, they underwent reinvention with their hybrid options, piggy back contact lenses, Rose K lenses for smaller residual errors following ICRS and Phakic Iols too. The goal was to give the best to these visually hampered Keratoconus eyes and every nuance was better addressed.

Lots of thoughts, arguments and discussions fragmented the consistency and surities of KC management when proponents came forth suggesting that rubbing of eyes was a major factor for KC progression and abstaining from rubbing was sufficient in controlling the disease.

There were these allergic eyes of young children wherein it became necessary to include topographic evaluation as a critical protocol to rule out KC and a whole new diversion / aggression in treatment strategy became necessary if KC was diagnosed .Some of these eyes came with limbal stem cell deficiency in advanced stages wherein one wondered whether cxl was possible at all unless we protect the limbus and not to mention the challenges of epithelial surface breakdown which challenged us to reconsider trans epithelial Crosslinking as the only possibility in these select cases.

Then came the last frontier when the visual axis was not clear in a KC patient with corneal scarring, highly distorted thin corneas and hydrops which needed corneal lamellar procedures. DALK in the present settings and its well established protocols came in to visually rehabilitate this lot of patients.

The results have been very encouraging with minimal risk of graft rejection but again the time of suture removal, how to visually rehabilitate these patients were the ongoing challenges.

Having said it all, today with the algorithm that is evolved for KC management, we are definitively on the right crossroad to a more optimal BCVA in these challenging eyes.

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Studies suggest a low risk of COVID-19 transmission from tears

Investigators from Singapore studied viral shedding and infectivity of tears among COVID-19 patients. None of the 17 patients presented with ocular symptoms, but 1 developed conjunctival injection and chemosis during the hospital stay. Of 64 tear samples collected between day 3 and 20 from initial symptoms, neither viral culture nor RT-PCR detected SARS-CoV-2. This contrasts with findings from a prior 30-patient study in which 1 patient had conjunctivitis. Only that patient had virus particles in their ocular secretions. Collectively, these studies suggest conjunctivitis is an uncommon complication of COVID-19, and that risk of disease transmission through tears is low. *Ophthalmology*, in press; *Journal of Medical Virology*, in press