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CONTROVERSY

Is accelerated corneal collagen cross-linking for keratoconus the way forward? No

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Collagen cross-linking (CXL) was introduced in the late nineties and was later adopted as a treatment option for keratoconus, pellucid marginal degeneration, and post-LASIK ectasia in 2003.[1–3] CXL is the only treatment modality for these conditions that addresses the underlying stromal weakening and thus halts disease progression. Recently, accelerated CXL was proposed as an alternative technique, whereby corneal stiffening can be achieved with higher fluence and reduced overall exposure time.[4]

The Bunsen–Roscoe reciprocity law, the basis for accelerated CXL, is valid within a certain range.[5] Determining what this range is for the cornea and how it translates to treatment settings and outcomes is still not known. Wernli *et al*[6] performed an *ex vivo* study and found that at illumination intensity of 45 mW/cm^2 and time exposure of <2 min, no corneal stiffening was achieved. On the basis of the experimental data presented by Richoz *et al*,[7] CXL requires the presence of oxygen for corneal stiffening to occur. Time exposure is perhaps more significant than we initially suspected, as at reduced time exposure, where oxygen utilisation is compromised, corneal stiffening is in turn hindered.[6,7] Moreover, the safety of a higher fluence, even for a short duration, is yet to be demonstrated and there is concern of long-term irradiation toxicity and greater risk of endothelial damage.[8,9] In the short term, more keratocyte apoptosis has been observed in corneas that have undergone accelerated CXL compared with conventional CXL.[10] The clinical significance of this is still unknown but suggests that as a procedure, accelerated CXL is harsher to the cornea.

In conventional CXL, a demarcation line, which demonstrates the depth of treatment, is seen at 300–350 μm.[11] A confocal microscopy study by Touboul *et al*[10] showed that with accelerated CXL, the demarcation line lies anterior at an average depth of 100–150 μm, considerably less than that in conventional CXL. With keratoconus being a posterior corneal disease, at least in its early stages, the CXL depth reached by accelerated CXL may not suffice for effective treatment.[12] In paediatric patients, treatment with conventional CXL is advocated early before established disease progression, as conventional CXL has been found to be safe and effective.[13–15] There is no literature available, at least at present, reporting the use of accelerated CXL in paediatric patients.

Perhaps the greatest concern regarding accelerated CXL is that the evidence for its efficacy is powered by case series and small studies, with shorter follow-up than conventional CXL.[10,16–18] The evidence supporting conventional CXL is extensive, including its successful use in thin corneas (<400 μm) with the recommended use of hypoosmolar riboflavin.[17–20] O'Brart *et al*[21] published long-term results for conventional CXL that reported similar treatment efficacy and safety to the Siena Eye Cross study but also noted that the cornea continues to flatten up to 4 years post treatment.[17,18] We do not have such studies for accelerated CXL and cannot be certain of its continuing effect. It can be postulated that such an effect of continued flattening may not be observed in accelerated CXL due to its comparatively shallow depth of treatment.

It is clear that accelerated CXL is still in its infancy as the treatment parameters have yet to be defined and standardised. There is great variability in treatment settings across studies

suggesting that the optimal fluence and timing for accelerated CXL has not been determined. The settings for accelerated CXL differ across studies and also in accordance to the treatment indication. Celik *et al*[23] reported the outcomes of accelerated CXL as an adjuvant treatment to LASIK, using 30 mW/cm^2 for 3 min, whereas Kanellopoulos used a setting of 10 mW/cm^2 for 3 min as prophylactic treatment in conjunction with LASIK, but used 7 mW/cm^2 for 15 min in the treatment of keratoconus,[16,22]. More research is needed to determine and standardise the most effective and safe treatment parameters for accelerated CXL. Once this is established, randomised controlled trials would prove invaluable in determining the true efficacy of accelerated CXL and whether accelerated CXL provides at least equal results to conventional CXL.

Conflict of interest

The authors declare no conflict of interest.

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