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Editorial

Ionotophoresis for corneal collagen crosslinking

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Corneal collagen crosslinking has rapidly become standard of care for progressive keratoconus. The prompt treatment of patients with standard corneal collagen crosslinking (S-CXL) also known as the Dresden protocol (epithelium-off, 30 minutes soak with riboflavin and 30 minutes of treatment with UVA light at 3mW/cm2) (ref 1) can reliably and safely halt progression (ref 2). Worldwide experience and limited trials have confirmed efficacy and lead to regulatory approval and widespread adoption of the technique (ref 3).

However, issues remain with the Dresden protocol. It is a long procedure for both the patient and the surgeon, and the patients suffer considerable discomfort post operatively. The large epithelial defect required for riboflavin penetration exposes patients to the small but definite risk of microbial keratitis and scarring.

Numerous methods have been proposed to improve the efficiency and safety of the procedure, including accelerated protocols with reduced soak times and increased UVA intensity. Epithelium-on treatments have been tried, albeit with reduced riboflavin penetration and reduced efficacy. (Ref 4) Ionotophoresis (I-CXL) is a non-invasive technique that can deliver riboflavin across the epithelium through use of a small electric current. This not only leaves the epithelium intact, but also reduces treatment time. (Ref 5)

Despite innumerable publications presenting results from these various modifications to the standard procedure, very few have reached the gold standard of randomised controlled trial (RCT) to prove equivalence. Most of the studies published have had small numbers, limited follow up and inadequate controls to unequivocally show equivalence let alone superiority. (Ref 6)

Meta-analysis seeks to overcome some of these shortcomings with a pooled analysis of the existing data. Wan et al have compiled the available literature in a comprehensive and rigorous analysis (ref 7). The authors found I-CXL has a more favourable safety profile, as evidenced by the available literature, with less thinning at the minimum pachymetry and reduced risk of complications, while achieving

comparable effects on visual, refractive, topographic, aberrometry, and morphological outcomes as S-CXL. However, the authors acknowledge the clinical and methodologic heterogeneities across the comparative studies, suggest that the overall efficacy of I-CXL should be appreciated with caution, and call for more studies.

The shortcomings of the data used for the analysis are considerable. The trials have considerable variability in study design, with differences in ion flux, soak time, treatment time and follow-up interval. The inclusion criteria are not well defined in the literature. Only patients with progressive keratoconus stand to benefit from treatment and so including large numbers of cases that have already stabilised will naturally distort the results. There is a real unmet need for standardizing the cut-off parameters to define keratoconus progression. However, a recent Delphic Consensus meeting was unable to agree on even a definition of keratoconus, let alone to provide guidance on progression. (ref 8)

Should you change your protocols based on imperfect data? This is a dilemma that faces all doctors as new procedures promise tangible advantages over standard and well proven approaches.

Safety of S-CXL is high, with very limited complications, and it is highly effective over the long term. Short term follow-up gives only limited indication of whether progression has indeed been halted. This, studies with short follow-up may not provide useful information on long term efficacy.

The reduction in complications reported is as expected, given maintenance of the epithelium, and is encouraging. However, it appears most studies did not report any complications from either technique. Is that a failure of the study or an indication of the general safety of S-CXL? The complete absence of complications reported for I-CXL is unlikely to remain the case in general clinical practice.

The authors have called for more RCTs. Rigorous placebo-controlled masked studies are impractical and probably unethical given the widespread uptake of CXL. Non-inferiority studies are possible, but are slow, expensive and can be difficult to recruit. An alternate strategy is the use of real-world data through outcome registries such as the Keratoconus International Consortium or the Save Sight Keratoconus Registry. (ref 9) This may be the most practical way of providing additional reassurance that the new technique is indeed an advance on the current state of the art.

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