IONTOPHORESIS ASSISTED CORNEAL *CROSSLINKING*

CT2016/03

Spanish full text

Introduction: keratoconus (KC) is a degenerative disease of the cornea of unknown etiology. It is characterised by a progressive thinning of the cornea, which adopts an irregular cone-like shape, causing substantial visual deterioration. Currently, the available therapeutic options offer a temporary correction of the refractive error but do not address the underlying problem of the cornea's biomechanical integrity or the possibility of reducing and/or halting the progression of the disease. Iontophoresis corneal collagen cross-linking (I-CXL) is a non-invasive transepithelial technique, which seeks to increase the cornea's biomechanical stability by combining a riboflavin (vitamin B_2) ophthalmic solution and ultraviolet-A radiation. To boost riboflavin diffusion through the intact epithelium, a local low-intensity electric field is applied. This procedure is proposed as a therapeutic option capable of halting or reducing disease progression.

Objectives: assess the clinical effectiveness and safety of I-CXL as a therapeutic technique in the treatment of corneal ectasias and other corneal diseases

Methods: we performed a systematic review of health literature until may 2016, in relevant health databases: Medline, Embase, Centre for Reviews and Dissemination (CRD), HTA (Health Technology Assessment), International Network of Agencies for Health Technology Assessment (INAHTA), ECRI, Cochrane Plus Library, ISI Web of Science, as well as a specific search of ongoing clinical trials. This process was completed by a manual review of the bibliographic references cited in these papers, and additional searches using meta-search engines, such as Google Scholar, and websites of national and international organisations and assessment agencies, to provide all relevant information of interest. Two independent investigators, selected and reviewed the articles according to pre-established selection criteria, with any disagreements being settled by consensus. The information was synthesized in evidence tables, using a systematic methodology. The studies were classified according to their methodological quality, on the basis of the recommendations of the Spanish Network of Health Technology Assessment Agencies and National Health System Services (*RedETS*) guidelines for the drawing-up and adaptation of fast-track health technology assessment reports.

Results: the review included one randomised clinical trial (RCT) and 4 case series. Overall, 234 procedures in 204 patients were described, and I-CXL was used in all cases for treatment of progressive KC. The RCT's results indicated that I-CXL was an effective method for stabilising or halting KC progression at 2 years, without significant improvements being obtained in visual or topographic parameters. Although it succeeded in achieving adequate B_2 concentration in the corneal stroma, I-CXL proved less effective than classical CXL. The I-CXL failure rate was 1.3% *versus* 0% for classic CXL. No significant differences were observed in corrected

visual acuity, and non-corrected visual acuity remained stable in both groups without significant differences. The presence and depth of the corneal demarcation line was superior with CXL. Despite maintaining the corneal epithelium intact, I-CXL was neither a complication- nor a pain-free treatment. Most of the adverse effects were mild and transient, and the technique appeared to cause less pain in the first 3 days post-intervention.

Discussion: the studies display certain methodological limitations which could affect the efficacy and safety. Among others, these limitations included: the undertaking of studies on heterogeneous populations; the use of different disease-severity grading scales; a lack of uniformity in the definition of disease progression; and variability in the determination of topographic parameters. Most of the data came from observational studies, without comparison group. Not only is the available evidence limited, with 234 procedures on 204 patients being described, but in most cases it was drawn from preliminary studies with short follow-up periods (up to 2 years). Nothing is known about the long-term efficacy and safety of I-CXL, or the efficacy of reintervention, if required. Similarly, there are no data on its possible impact on the need for a transplant. These uncertainties mean that no solid conclusions can be drawn in this regard, and that it would be advisable to wait until the results of ongoing RCTs have been published.

Conclusions: in the databases analysed in this review, I-CXL is judged to be capable of stabilising and/or reducing the progression of KC, with its efficacy being lower than that of classic CXL. It is considered to be a low-risk procedure, and most of the complications are transient and of scant severity. These outcomes must be interpreted with caution, since the existing evidence is very limited both in quantity and quality, and is based on some 200 patients treated worldwide. In the absence of comparative quality studies (CXL *vs* I-CXL) and in view of the uncertainty surrounding its long-term efficacy and safety, I-CXL cannot be said to improve on the outcomes of the classical technique.