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Review

A review and meta-analysis of corneal cross-linking for post-laser vision correction ectasia

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Abstract

Purpose: The aim of this study was to review the safety and stability of cornea cross-linking (CXL) for the treatment of keratectasia after Excimer Laser Refractive Surgery.

Methods: Eligible studies were identified by systematically searching PubMed, Embase, Web of Science and reference lists. Meta-analysis was performed using Stata 12.1 software. The primary outcome parameters included the changes of corrected distant visual acuity (CDVA), uncorrected visual acuity (UCVA), the maximum keratometry value (Kmax) and minimum keratometry value (Kmin), the surface regularity index (SRI), the surface asymmetry index (SAI), the keratoconus prediction index (KPI), corneal thickness, and endothelial cell count. Efficacy estimates were evaluated by weighted mean difference (WMD) and 95% confidence interval (CI) for absolute changes of the interested outcomes.

Results: Seven studies involving 118 patients treated with CXL for progressive ectasia after laser-assisted in situ keratomileusis (LASIK) or photorefractive keratectomy (PRK) (140 eyes; the follow-up time range from 12 to 62 months) were included in the meta-analysis. The pooled results showed that there were no significant differences in Kmax and Kmin value after CXL (WMD = 0.584; 95% CI: −0.289 to 1.458; $P = 0.19$; WMD = 0.466; 95% CI: −0.625 to 1.556; $P = 0.403$, respectively). The CDVA improved significantly after CXL (WMD = 0.045; 95% CI: 0.010 to 0.079; $P = 0.011$), whereas UCVA did not differ statistically (WMD = 0.011; 95% CI: −0.055 to 0.077; $P = 0.746$). The changes were not statistically significant in SRI, SAI, and KPI (WMD = 0.116; 95% CI: −0.090 to 0.322; $P = 0.269$; WMD = 0.240; 95% CI: −0.200 to 0.681; $P = 0.285$; WMD = 0.045; 95% CI: −0.001 to 0.090; $P = 0.056$, respectively). Endothelial cell count and corneal thickness did not deteriorate (WMD = 12.634; 95% CI: −29.460 to 54.729; $P = 0.556$; WMD = 0.657; 95% CI: −9.402 to 10.717; $P = 0.898$, respectively).

Conclusion: The study showed that CXL is a promising treatment to stabilize the keratectasia after Excimer Laser Refractive Surgery. Further long-term follow-up studies are necessary to assess the persistence of the effect of the CXL.

Keywords: Cross-linking; Keratectasia; Refractive surgery; Meta-analysis

Introduction

Iatrogenic keratectasia is a rare sight-threatening complication of the laser refractive surgery. It is associated with progressive corneal steepening, an increase in myopia and astigmatism, and a decrease in uncorrected and corrected visual acuity.[1] Risk factors for its development are thin corneas, a thin residual stromal bed, deep ablations, and pre-existing abnormal corneal topography such as forme fruste keratoconus and pellucid marginal degeneration.[2,3] Until recently, treatment

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options were limited. In addition to rigid contact lenses, intrastromal corneal ring segments, penetrating or lamellar keratoplasty, and, more recently, cornea cross-linking (CXL) have been used to treat postrefractive surgery ectasia.[4−6]

CXL has emerged as an effective technique to slow or halt progression of keratoconus and postoperative ectasia. CXL is a new method to increase the biomechanical stability of the cornea by adding additional polymer bands between collagen fibers using a combination of riboflavin and ultraviolet A (UVA).[7−9] Over the past 10 years, more and more studies and meta-analysis published the encouraging outcomes in advanced keratoconus throughout the world.

However, studies about CXL for postoperative ectasia are rare, the results were controversial, and the studies were less convincing because of the small sample sizes and other research design limitations. Therefore, a meta-analysis is imperative for summarizing results from different studies.

The main objectives of this systematic review and meta-analysis were to evaluate the safety and stability of CXL for the treatment of keratectasia after Excimer Laser Refractive Surgery.

Methods

Search strategy

The clinical studies were identified through a systematic search of PubMed, Embase, Web of Science, and reference lists (all searches with no limitation to specific languages or years of publication were used). The search terms included: “cross linking”, “crosslinking”, “cross-linking”,“keratectasia after laser-assisted in situ keratomileusis (LASIK)”, “post-LASIK keratectasia,” and “Postoperative Ectasia”. Different search strategies were used for database in order to meet the different requirements of each database. The citations of related articles were screened for additional publications. Two reviewers (DW and HY) screened the titles and abstracts of the obtained publications and determined the trial eligibility independently. Then the full articles of the eligible publications were scrutinized.[10] Only trials meeting the following criteria were used in present meta-analysis.

Inclusion criteria and outcomes

We included studies that compared: (1) research design: randomized or non-randomized clinical studies; (2) population: patients with keratectasia after Excimer Laser Refractive; (3) intervention: corneal cross-linking (4) outcome parameters: the end points of topographic parameters, corrected distant visual acuity (CDVA), uncorrected visual acuity (UCVA), endothelial cell count, and corneal thickness.

Data extraction

Two reviewers (DW and HY) evaluated the quality of the citations and extracted data independently. Any disagreement was resolved by discussion.[10] The following information was extracted: the name of the first author, the year of publication, the trial location, the research design, the number of eyes, the mean age of patient, the sex proportion, the follow-up durations, and the sort of refractive Surgery.

Quality assessment

The Newcastle-Ottawa Scal (NOS) scoring methods of quality literature assessment was used for the prospective and retrospective studies that were selected for this analysis.[9] The quality assessment scale is composed of three main sections (Selection, Comparability, and Outcome). A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability. Studies with stars $\geq$5 were considered to have adequate quality.

Statistical analysis

Analyses were carried out using Stata SE software package (Version 12.1; Stata Corp, College Station, TX). For continuous outcomes, the weighted mean difference (WMD) and 95% confidence interval (CI) calculated for absolute changes of the interested outcomes. The outcomes were measured as mean ± standard deviation (SD). Heterogeneity across studies was estimated by using χ^2 and I^2 test (I^2> 50% indicating significant heterogeneity).[11,12] The overall effect was determined to be statistically significant with $P < 0.05$. Additionally, if significant heterogeneity existed among trials, a random model was used, and sensitivity analysis was conducted. Alternatively, results were combined using a fixed effect model.[13] Potential publication bias was assessed visually with a funnel plot and statistically with the Egger's and Begg's tests.[10,14,15]

Result

Characteristics of trials

The detailed steps of the study selection process and exclusion reasons are summarized in Fig. 1. Finally, this meta-analysis was based on seven studies[2,16−21] that met our inclusion criteria. Among these, 5 were prospective studies, and 2 were retrospective studies (Table 1). There were altogether 118 patients (with 140 eyes) diagnosed with post-lasercorneal ectasia, 134 eyes after LASIK and 6 eyes after photorefractive keratectomy (PRK), included in this meta-analysis. The sample sizes of these trials ranged from 10 to 40. These trials were performed in 6 countries (2 each in Switzerland; 1 each in Italy, Germany, China, Turkey, and Brazil). Three trials reported that their patients were followed up for 12 months after post-CXL. Four trials reported follow-up outcomes after more than 1 year.

Visual acuity outcomes

The outcomes of UCVA and CDVA are shown in Fig. 2. Visual acuity was recorded and analyzed as the logarithm of

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