Comparative Efficacy and Safety of Standard Versus Accelerated Corneal Crosslinking for Keratoconus: 1-Year Outcomes From the Save Sight Keratoconus Registry Study

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Purpose: The aim of this study was to compare the efficacy and safety of standard [Ultraviolet (UV) light power: 3 mW/cm², duration: 30 minutes] versus accelerated (UV power: 9 mW/cm², duration: 10 minutes) corneal crosslinking (CXL) for stabilizing keratoconus.

Methods: A total of 684 eyes (555 patients; mean age \pm SD, 25.0 \pm 7.9 years; women, 30.6%) from 24 international sites with epithelium-off CXL for keratoconus had follow-up data at 1-year and met the inclusion criteria. Two hundred sixty-six eyes (228 patients) had undergone standard CXL, and 418 eyes (327 patients) had undergone accelerated CXL. The outcome measures included changes in visual acuity, keratometry, minimum corneal thickness, and frequency of adverse events. The outcomes were compared using mixed-effects regression models adjusted for age, sex, visual acuity, keratometry, pachymetry, doctor, practice, and eye laterality.

Results: The adjusted mean changes (95% confidence interval) in outcomes were similar in standard and accelerated CXL in visual acuity [6.5 (2.0, 11.1) versus 5.5 (0.4, 10.6) logMAR letters, respectively], Kmax [-0.9 (-1.4, -0.3) D versus -1.2 (-1.9, -0.4) D, respectively], K2 [-0.4 (-0.9, 0.2) D versus -0.4 (-1.1, 0.3), D respectively], or minimum corneal thickness [-13.3 (-20.3, -6.3) µm versus -16.6 (-24.5, -8.6) µm, respectively] (all P > 0.05). The frequency of adverse events at the 12-month visit was also similar between the CXL groups (standard, 8.3% vs. accelerated, 5.5%; P = 0.21).

Conclusions: This real-world observational study found that both standard and accelerated CXL were similarly safe and effective in stabilizing keratoconus at 1-year postsurgery in the real-world setting. The findings support the adoption of accelerated CXL for time and convenience.

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Keratoconus is a chronic, progressive corneal disorder usually diagnosed in young adults, which leads to poor quality vision and reduction in quality of life.^{1,2} Corneal crosslinking (CXL), the only treatment to slow or halt keratoconus progression, has transformed the management of keratoconus. CXL is a minimally invasive procedure for stabilizing progressive keratoconus.³ It is a photochemical process, in which ultraviolet A (UVA) and riboflavin induce bonds in the corneal stroma to increase biomechanical strength and stability.^{4,5}

The standard (Dresden or conventional) protocol for CXL consists of irradiance of the corneal stroma with a cumulative energy dose of 5.4 J/cm² with 370 nm UVA wavelength at 3 mW/cm² intensity for 30 minutes.^{4,6} Recently, accelerated methods are in practice based on the Bunsen–Roscoe rule of reciprocity, which states that regardless of the time at which the energy dose is administered, a photochemical reaction is directly proportional to the total energy dose.^{4,6} However, biochemical change may not be the same as photochemical change.⁶

Accelerated CXL may improve patient comfort and reduce the rate of complications.^{4,7} However, the literature on its comparative effectiveness is somewhat divided. In a recent metanalysis, Wen et al⁴ reported standard crosslinking to be more effective in flattening Kmax but with a greater reduction in endothelial cell density and central corneal thickness than the accelerated protocol. However, in another review, Konstantopoulos and Mehta⁸ suggested similar efficacy of standard and accelerated protocols. There are only a few clinical trials that have compared the effectiveness of different protocols, and those studies are limited in sample size and follow-up duration.^{4,6,8} Besides, the clinical trials may not reflect the real-world situations; therefore, the results may not be directly applicable to routine clinical practice.⁹ The aim of this study was to compare the efficacy and safety of standard versus accelerated corneal CXL procedures for the treatment

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further research is required to compare the long-term efficacy and safety of the 2 procedures.

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REFERENCES

- Kandel H, Pesudovs K, Watson S. Measurement of quality-of-life in keratoconus. *Cornea*. 2020;39:386–393.
- Kandel H, Pesudovs K, Ferdi A, et al. Psychometric properties of the keratoconus outcomes research questionnaire (KORQ): a save sight keratoconus registry study. *Cornea*. 2020;39:303–310.
- O'Brart DP, Patel P, Lascaratos G, et al. Corneal cross-linking to halt the progression of keratoconus and corneal ectasia: seven-year follow-up. *Am J Ophthalmol.* 2015;160:1154–1163.
- Wen D, Li Q, Song B, et al. Comparison of standard versus accelerated corneal collagen cross-linking for keratoconus: a meta-analysis. *Invest Ophthalmol Vis Sci.* 2018;59:3920–3931.
- Greenstein SA, Fry KL, Bhatt J, et al. Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: scheimpflug and biomicroscopic analysis. J Cataract Refract Surg. 2010;36:2105–2114.
- Toker E, Çerman E, Özcan DÖ, et al. Efficacy of different accelerated corneal crosslinking protocols for progressive keratoconus. *J Cataract Refract Surg.* 2017;43:1089–1099.
- Sherif AM. Accelerated versus conventional corneal collagen crosslinking in the treatment of mild keratoconus: a comparative study. *Clin Ophthalmol.* 2014;8:1435.
- Konstantopoulos A, Mehta JS. Conventional versus accelerated collagen cross-linking for keratoconus. *Eye Contact Lens.* 2015;41:65–71.
- Sanson-Fisher RW, Bonevski B, Green LW, et al. Limitations of the randomized controlled trial in evaluating population-based health interventions. *Am J Prev Med.* 2007;33:155–161.
- Vandenbroucke JP, Von Elm E, Altman DG, et al. Strengthening the reporting of observational studies in Epidemiology (STROBE): explanation and elaboration. *PLoS Med.* 2007;4:e297.
- Watson S, Ferdi A, Nguyen V, et al. The long-term outcomes from corneal cross-linking: a save sight keratoconus registry study. *Clin Exp Ophthalmol.* 2019;47:36–37.

- Watson S, Kandel H, Ferdi A, et al. Who is getting clinically significant haze after corneal cross-linking for keratoconus? A Save Sight Keratoconus Registry study. *Invest Ophthalmol Vis Sci.* 2020;61:4067.
- Ferdi A, Nguyen V, Kandel H, et al. 5-year outcomes of corneal crosslinking: a Save Sight Keratoconus Registry study. *Invest Ophthalmol Vis Sci.* 2020;61:2339.
- Ferdi A, Nguyen V, Kandel H, et al. Who needs cross-linking? Predictors of progression in untreated keratoconus: a Save Sight Keratoconus Registry study. *Clin Exp Ophthalmol.* 2019;47:100.
- Resnikoff S, Pascolini D, Mariotti SP, et al. Global magnitude of visual impairment caused by uncorrected refractive errors in 2004. *Bull World Health Organ.* 2008;86:63–70.
- Godefrooij DA, Roohé SL, Soeters N, et al. The independent effect of various cross-linking treatment modalities on treatment effectiveness in keratoconus. *Cornea*. 2020;39:63–70.
- Bates D, Mächler M, Bolker B, et al. Fitting linear mixed-effects models using lme4. J Stat Softw. 2014;67:1–48.
- Koller T, Pajic B, Vinciguerra P, et al. Flattening of the cornea after collagen crosslinking for keratoconus. *J Cataract Refract Surg.* 2011;37: 1488–1492.
- Greenstein SA, Hersh PS. Characteristics influencing outcomes of corneal collagen crosslinking for keratoconus and ectasia: implications for patient selection. J Cataract Refract Surg. 2013;39:1133–1140.
- Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. J Cataract Refract Surg. 2011;37:149–160.
- Brittingham S, Tappeiner C, Frueh BE. Corneal cross-linking in keratoconus using the standard and rapid treatment protocol: differences in demarcation line and 12-month outcomes. *Invest Ophthalmol Vis Sci.* 2014;55:8371–8376.
- Çınar Y, Cingü AK, Türkcü FM, et al. Comparison of accelerated and conventional corneal collagen cross-linking for progressive keratoconus. *Cutan Ocul Toxicol.* 2014;33:218–222.
- Hagem AM, Thorsrud A, Sandvik GF, et al. Collagen crosslinking with conventional and accelerated ultraviolet-A irradiation using riboflavin with hydroxypropyl methylcellulose. *J Cataract Refract Surg.* 2017;43: 511–517.
- Ng ALK, Chan TC, Cheng AC. Conventional versus accelerated corneal collagen cross-linking in the treatment of keratoconus. *Clin Exp Ophthalmol.* 2016;44:8–14.
- Sadoughi MM, Einollahi B, Baradaran-Rafii A, et al. Accelerated versus conventional corneal collagen cross-linking in patients with keratoconus: an intrapatient comparative study. *Int Ophthalmol.* 2018;38:67–74.
- Shetty R, Pahuja NK, Nuijts RM, et al. Current protocols of corneal collagen cross-linking: visual, refractive, and tomographic outcomes. *Am J Ophthalmol.* 2015;160:243–249.
- Shajari M, Kolb CM, Agha B, et al. Comparison of standard and accelerated corneal cross-linking for the treatment of keratoconus: a meta-analysis. *Acta Ophthalmologica*. 2019;97:e22–e35.
- Kobashi H, Tsubota K. Accelerated versus standard corneal cross-linking for progressive keratoconus: a meta-analysis of randomized controlled trials. *Cornea.* 2020;39:172–180.
- Hersh PS, Stulting RD, Muller D, et al. US multicenter clinical trial of corneal collagen crosslinking for treatment of corneal ectasia after refractive surgery. *Ophthalmology*. 2017;124:1475–1484.
- He M, Han T, Wang Y, et al. Effects of HGF and KGF gene silencing on vascular endothelial growth factor and its receptors in rat ultraviolet radiation-induced corneal neovascularization. *Int J Mol Med.* 2019;43: 1888–1899.
- Dhawan S, Rao K, Natrajan S. Complications of corneal collagen crosslinking. J Ophthalmol. 2011;2011:869015.
- Georgiou T, Funnell C, Cassels-Brown A, et al. Influence of ethnic origin on the incidence of keratoconus and associated atopic disease in Asians and white patients. *Eye.* 2004;18:379–383.

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