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ORIGINAL PAPER

Comparison of pain after subepithelial versus conventional accelerated corneal collagen cross-linking for keratoconus

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Abstract

Purpose To compare the postoperative pain and epithelial healing time in conventional and subepithelial accelerated corneal collagen cross-linking (CXL) for progressive keratoconus.

Methods The medical records of 27 consecutive patients who underwent accelerated CXL for progressive keratoconus were retrospectively reviewed. Patients were divided into two groups: the conventional (n = 16) and the subepithelial accelerated CXL group (n = 11). Corneal epithelial layers with a diameter of 8.5 mm in central corneas were removed in the conventional group, while epithelial flaps with the same diameter were prepared in the subepithelial group before accelerated CXL procedures. Postoperative pain and epithelial healing time were evaluated within 1 week.

Results No complications developed in the subepithelial group, whereas peripheral corneal sterile infiltrate was observed in three eyes in the conventional group, which disappeared after treated with steroids for a week. The pain of patients in subepithelial group was significantly slighter than those in conventional group, with a significant difference in pain scoring 0, 1, 2 and 3 days postoperatively (P = 0.002, P = 0.001, P = 0.001, P = 0.001,

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respectively). Different from the fact that patients in subepithelial group had epithelium after operation, the healing time for epithelium in conventional group was 3–6 days, with an average of 4.64 ± 0.59 days.
Conclusions Subepithelial accelerated CXL significantly improved postoperative pain as well as reduced the epithelial healing time for the treatment of keratoconus.

Keywords Cross-linking · Epithelial flap · Keratoconus · Pain · Subepithelial

Introduction

Keratoconus is a type of bilateral corneal ectasia characterized by progressive corneal thinning and steepening, leading to high myopia, irregular astigmatism and occasionally corneal scarring [1]. It typically starts during the adolescent years [1, 2]. The prevalence in general population is 50–200 per 100,000 [3]. Corneal cross-linking (CXL) slows or stops the progression of keratoconus [4, 5]. Indeed, according to the Global Consensus on Keratoconus and Ectatic Diseases, CXL was strongly recommended no matter what age or level of vision (assuming the eye was an appropriate candidate) [6].

The conventional technique of CXL consists of an epithelial removal, after which riboflavin eye drops and ultraviolet-A (UVA) light are applied [4, 5]. The removal of the epithelium allows adequate penetration of riboflavin into the stroma to facilitate the cross-linking [7]. The disadvantage of epithelial removal is that it causes significant pain and discomfort during postoperative days, in addition to the risks of infection [8–10]. To circumvent these downsides of epithelium removal, a transepithelial CXL technique was developed [11–14]. However, transepithelial CXL, due to its retention of corneal epithelium, is less effective on controlling the progression of keratoconus than conventional CXL [15, 16].

In the laser subepithelial keratomileusis (LASEK) procedures, an epithelial flap is created and replaced after the laser ablation. The benefits of the creation of an epithelial flap include alleviation of discomfort in the early postoperative period as well as promotion of epithelial recovery [17, 18]. We hypothesized that an epithelial flap may also benefit in accelerated CXL procedures. The present study was performed to compare the postoperative pain and epithelial cell recovery time between conventional and subepithelial accelerated CXL.

Methods

Patients

The medical records of the patients who underwent accelerated CXL for progressive keratoconus at the Beijing Aier-Intech Eye Hospital between January 2016 and April 2016 were reviewed. Patients with corneal thickness less than 400 μm, ocular infections, or other contraindications such as pregnancy or breastfeeding were excluded. Patients who wore rigid gas permeable contact lens were told to take them off 2 weeks before operation. Twenty-seven eyes of 27 patients (17 men, 10 women) were ultimately included in the study. All patients and the guardians received explanation about characteristics of CXL and signed informed consent forms before surgery. Both conventional and subepithelial accelerated CXL were used concomitantly. Eleven patients accepted subepithelial accelerated CXL voluntarily and 16 patients who refused it were treated as a control conventional group. This study was approved by the Ethics Committee of Aier School of Ophthalmology of Central South university, and it adhered to the tenets of the Declaration of Helsinki.

Surgical procedures

All accelerated CXLs were performed by the same surgeon (Dr. Li). The ocular surface was anesthetized 5 times with topical 0.4% oxybuprocaine eyedrops. Cornea was imprinted by epithelial trephine with a diameter of 8.5 mm (A). Crescent blade was pressed tightly onto Bowman's lamina, and an intact epithelial flap was prepared with blunt dissection (B, C) in the subepithelial group (Supplementary Video 1, surgical procedures for an epithelial flap). Corneal epithelium was removed from the treatment zone using a crescent blade in conventional group. In both methods, after administration of 0.1% riboflavin every 1.5 min for 10 min, the corneal surface was rinsed thoroughly with 0.9% sodium chloride. Next, the cornea was exposed to 30 mW/cm^2 ultraviolet-A light for 4 min

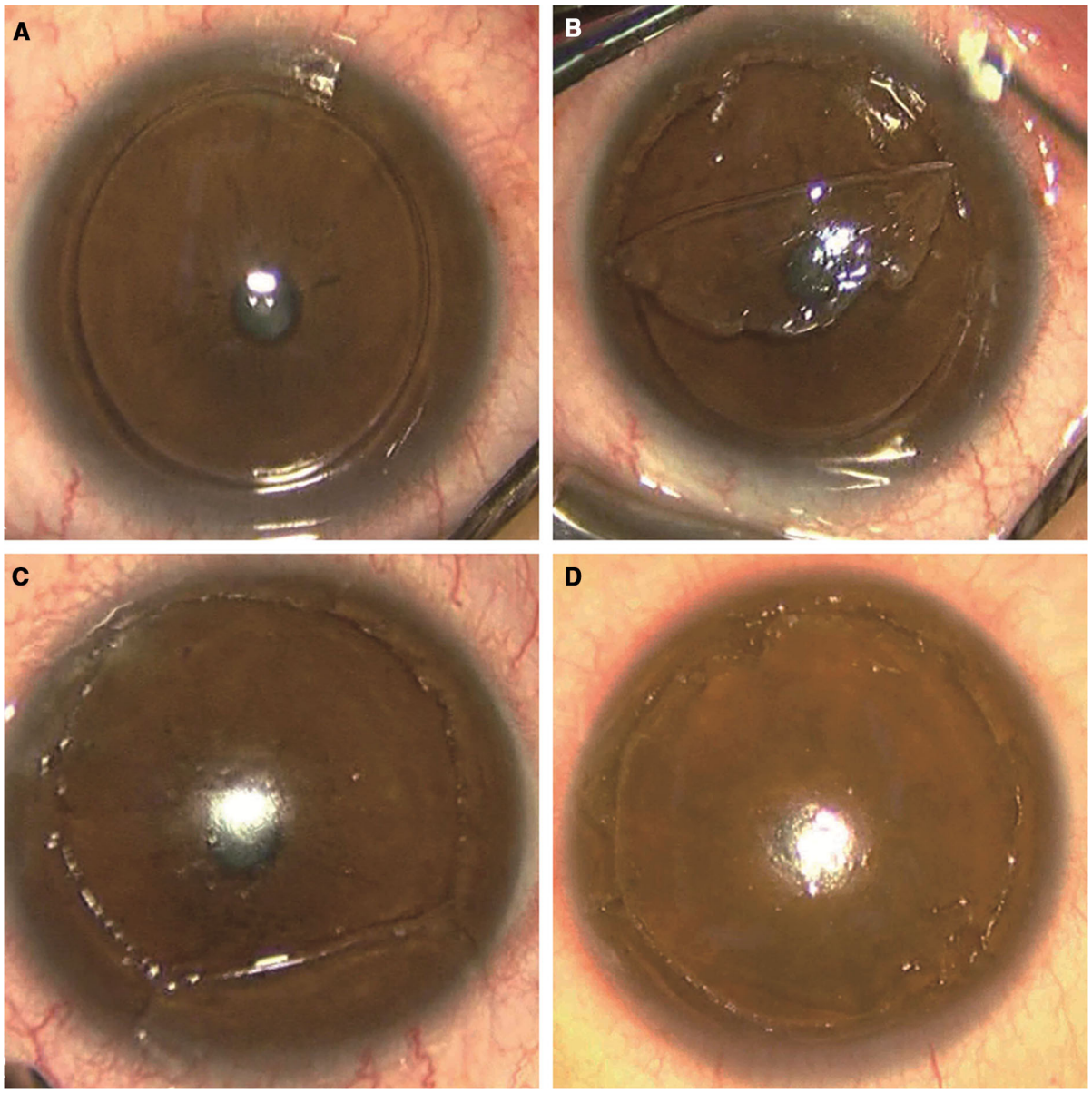

Fig. 1 Surgical procedures of subepithelial CXL. Cornea was imprinted by epithelial trephine with a diameter of 8.5 mm (**A**). Crescent blade was pressed tightly onto Bowman's lamina and an intact epithelial flap was prepared with blunt dissection (**B**, **C**) in the subepithelial group. The cornea was exposed to 30 mW/cm^2 ultraviolet-A light for 4 min at a distance of 5 cm from cornea surface (**C**). The epithelial flap was repositioned in the subepithelial group (**D**)

at a distance of 5 cm from cornea surface (KXL System from Avedro). The epithelial flap was repositioned in the subepithelial group (D) (Fig. 1). At the end of the procedure, a soft bandage contact lens was placed on the eye in both groups.

Postoperative management and follow-up

Postoperatively, 0.3% levofloxacin eyedrops were applied 4 times a day for a week. 0.1% fluorometholone eyedrops were administrated twice a day for 2 weeks and 0.3% sodium hyaluronate eyedrops were used 4 times a day for 4 weeks (all

from Santen Pharmaceutical, Japan). The soft bandage contact lenses were removed 1 week after surgery. The patients received the questionnaire forms after the surgery and were asked to record pain and irritation scores 2 h after the surgery and every morning in the following 3 days. Scorings were evaluated as followed: Score 0, no pain or discomfort; Score 1, slight discomfort; Score 2, medium level of twinge; Score 3, twinge that calls for analgesics; Score 4, constantly severe throe [19]. The analgesics used in the study is ibuprofen (300 mg/day, GSK, Tianjin, China). Postoperative edema (if any) of corneal stroma, corneal ulcer (if any), dissolution and haze were also analyzed.

Statistics analysis

The results are expressed as the mean ± SD. All statistical analysis was performed using the SPSS Version 20 (IBM, Armonk, NY, USA). The statistical differences in the age and gender between the two groups were analyzed using Fisher's exact test. The Mann–Whitney *U* test was used for analyzing the recorded postoperative data. All tests were two-tailed, and $P < 0.05$ was considered significant.

Results

Patients

The 16 patients who received conventional accelerated CXL were a mean age of 20.1 (range, 14–27) years. Eleven patients who received subepithelial accelerated CXL had a mean age of 21.6 (range, 14–31) years. All operations went smoothly without any severe complications such as infection. In both groups, no eyes lost any Snellen lines on best corrected visual acuity (BCVA) at 1-week follow-up. Table 1 summarizes the demographic data of the study patients.

Scoring of pain

The pain scores of patients in conventional group at 0, 1, 2 and 3 days postoperatively are 2.97 ± 0.75, 2.09 ± 0.57, 1.76 ± 0.56 and 1.12 ± 0.54, respectively, while those in subepithelial groups are 2.23 ± 0.44, 1.38 ± 0.51, 0.85 ± 0.38 and 0.46 ± 0.52, and the differences were statistically significant ($P = 0.002$, $P = 0.001$, $P = 0.001$, $P = 0.001$, respectively) (Table 2). One patient in conventional group reported distinctive pain on the day of operation and was given 1 pill of oral analgesic.

Healing time of epithelium

The healing time for epithelium in conventional group was 3–6 days, with an average of 4.64 ± 0.59 days. All 11 eyes in subepithelial group experienced slight edema 1 day after operation, but epithelial layers were intact and gradually became transparent after 2–3 days. Three eyes in conventional group had pericorneal sterile infiltrate, which gradually disappeared after 1-week treatment of steroids.

Discussion

Nowadays, transepithelial CXL has received lots of attention mostly due to the fact that the preservation of epithelium reduces infection as well as pain and irritation symptoms [11–14], however, the cross-linking effects may decline [15, 16]. In this study, epithelium was temporarily separated during the CXL and repositioned after the treatment (i.e., using the same technique as in LASEK).

The epithelial flaps healed quickly after the operation. Different from the fact that it took 3–6 days for epithelium to heal in patients in conventional group, patients in subepithelial group only experienced mild edema. This indicates that the epithelial technique in

Table 1 Patient demographic data in the two groups

	Conventional (n = 16)	Subepithelial (n = 11)	P
Male/female, n	10:6	7:4	0.95
Age, y, mean (SD)	20.1 (4.1)	21.6 (5.9)	0.47

n number, y year, SD standard deviation

Table 2 Scoring of pain

Group	Pain score			
	Day 0	Day 1	Day 2	Day 3
Conventional (n = 16)	2.97 ± 0.75	2.09 ± 0.57	1.76 ± 0.56	1.12 ± 0.54
Subepithelial (n = 11)	2.23 ± 0.44	1.38 ± 0.51	0.85 ± 0.38	0.46 ± 0.52
P	0.002	0.001	0.001	0.001

LASEK can also be applied to CXL. Pericorneal sterile infiltration was noted in three eyes in the conventional group, and disappeared after treated with steroids for a week, without any complications. The traditional method caused severe postoperative pain as well as postoperative complications [20–23]. Researches revealed that if epithelium integrity in LASEK was not well preserved, the postoperative healing would delay with the same or even more pain as PRK [24]. Such phenomena were not observed in the subepithelial group, which might be attributed to dexterous skills and quick reposition of epithelial flaps.

Patients in subepithelial group experienced medium level of pains and irritation symptoms without any need for analgesics, which were significantly lighter than the pains of patients in conventional group. In surface ablation such as epipolis laser in situ keratomileusis (Epi-LASIK) and LASEK, the effect of epithelial flaps on reducing postoperative pain has been fully demonstrated [25].

We prepared epithelial flaps with crescent blades manually without using alcohol, which is widely used in the preparation of epithelial flaps in LASEK and toxic to corneal stroma [26]. It may cause protein coagulation of corneal stroma tissues, affect the penetration of riboflavin and aggravate postoperative pain and irritation symptoms [24]. This alcohol-free preparation of epithelial flaps poses a learning curve for surgeons.

There are some flaws in this study. The retrospective study sample is small. Moreover, the major results of this study are limited to the postoperative healing time of epithelium and the scoring of pain is not validated. Further perspective studies with larger sample size and longer follow-up need to be investigated.

In conclusion, subepithelial CXL significantly improved postoperative pain as well as reduced the epithelial healing time for the treatment of keratoconus.

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Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (the Ethics Committee of Aier School of Ophthalmology of Central South university) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Human and animal rights This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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