Effect of Previous Crosslinking on Intraoperative and Postoperative Outcomes and Complication Rates of Big-Bubble Deep Anterior Lamellar Keratoplasty for Keratoconus: A Comparative Study

Esin Sogutlu Sari, MD, Anıl Kubaloglu, MD,† Arif Koytak, MD,‡ Ali Nihat Ofluoglu, MD,§ and Gözde Sahin, MD¶*

Purpose: To compare surgical outcomes and intraoperative and postoperative complications of big-bubble deep anterior lamellar keratoplasty (DALK) in patients with and without a history of previous corneal collagen crosslinking (CXL) for keratoconus.

Methods: Patients with keratoconus who underwent DALK surgery with big-bubble technique between January 2013 and January 2018 were retrospectively reviewed. Operative findings, intraoperative and postoperative complications, and visual and refractive outcomes were recorded. Patients were divided into 2 groups: with previous CXL (CXL-DALK group: 27 eyes) and without previous CXL (DALK group: 50 eyes). All parameters were compared between groups.

Results: Big bubble was successfully achieved in 24 eyes (88.9%) in the CXL-DALK group and in 45 eyes (90.0%) in the DALK group ($P = 0.87$). Type 1 bubble was obtained in 22 eyes (91.7%) in the CXL-DALK group and in 42 eyes (93.3%) in the DALK group ($P = 0.79$). Intraoperative microperforation occurred in 3 eyes (11.1%) in the CXL-DALK group and in 5 eyes (10.0%) in the DALK group ($P = 1$). Visual and refractive outcomes were similar between groups. The mean endothelial cell loss rates were 5.7% ± 2.3 at 1 year and 10.2 ± 3.1 at 2 years in the CXL-DALK group and 6.4% ± 4.7 at 1 year and 10.9% ± 5.4 at 2 years in the DALK group. Postoperatively, persistent epithelial defect was the most common complication in both groups, and postoperative complication rates were similar between groups.

Conclusions: Our results have shown that previous CXL treatment does not influence the success of bubble formation and does not increase intraoperative or postoperative complication rates of DALK surgery for keratoconus. The improvement in visual acuity and refractive errors and endothelial cell loss rates were similar between CXL treated and untreated eyes after 2 years of follow-up.

Key Words: keratoconus, corneal collagen crosslinking, deep anterior lamellar keratoplasty

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Since corneal collagen crosslinking (CXL) was introduced to the practice of ophthalmology, several studies have demonstrated the stabilization effect of ultraviolet A–activated riboflavin on corneal ectasia, including keratoconus.[1–3] Despite favorable results, corneal steepening and thinning may continue after CXL, and keratoplasty may be needed because of poor visual acuity or contact lens intolerance.[4] Currently, big-bubble deep anterior lamellar keratoplasty (DALK) is accepted as the most successful technique of keratoplasty in patients with keratoconus with a healthy endothelium.[5]

Previous animal studies and human confocal microscopic studies reported that the corneal stability and rigidity significantly increased in the anterior 300 μm of the corneal stroma after CXL treatment, and posterior corneal layers seemed unaffected.[6,7] By contrast, Müller et al[8] recently analyzed histopathological results of postpenetrating keratoplasty specimens from patients with previous CXL and concluded that CXL causes permanent structural changes throughout the entire corneal stroma, including the posterior part.

Using deep stromal air injections in Anwar's big-bubble technique in DALK surgery, the surgeon always aims to achieve a separation plane between the posterior stroma and Descemet membrane (DM) or pre-Descemet layer to avoid interface irregularities.[9,10] CXL-related corneal biomechanical changes may alter this cleavage plane achieved by pneumatic dissection, and it may cause concern among corneal surgeons about performing big-bubble DALK on keratoconic eyes that have undergone CXL. The effect of previous CXL on DALK outcomes is not well known yet. In the literature, there are a very limited number of studies about this issue, and these studies do not provide sufficient

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From the *Department of Ophthalmology, Faculty of Medicine, Bursa Uludag University, Bursa, Turkey; †Department of Ophthalmology, Faculty of Medicine, Dunya Eye Hospital, Yeni Yuzyil University, Istanbul, Turkey; ‡Department of Ophthalmology, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey; §Department of Ophthalmology, Faculty of Medicine, Yeni Yuzyil Universit, Istanbul, Turkey; and ¶Department of Ophthalmology, Faculty of Medicine, Balıkesir University, Balıkesir, Turkey.

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Correspondence: Esin Sogutlu Sari, MD, Department of Ophthalmology, Faculty of Medicine, Bursa Uludag University, Görükle, Bursa 16059, Turkey (e-mail: dresinsogutlu@gmail.com).

comparative data, especially in intraoperative findings.[4,11,12] Therefore, we designed a comparative study aiming to clarify potential concerns. In this study, we compared CXL-treated keratoconic eyes with treatment-naive keratoconic eyes in intraoperative and postoperative complications and surgical outcomes of big-bubble DALK surgery.

MATERIAL AND METHODS

This is a retrospective and nonrandomized comparative study. Patients with keratoconus who underwent DALK surgery between April 2013 and November 2018 at Dunya Eye Hospital were retrospectively reviewed. The study was conducted in adherence to the tenets of the Declaration of Helsinki, and local ethical committee approval was obtained.[13] DALK surgery was performed if the keratoconus patient had poor visual acuity and/or contact lens intolerance. Patients with accompanying systemic or ocular diseases and a history of acute hydrops and intraocular surgery were excluded. The history of previous CXL treatment was recorded. All CXL procedures were performed at Dunya Eye Hospital. Standard Dresden protocol was used for all procedures.[14] In Dresden protocol, 0.1% riboflavin solution with 20% dextran was administered every 3 minutes for 30 minutes, and then, ultraviolet A of 3 mW/cm^2 was applied for 30 minutes with a cumulative dose of 5.4 J/cm^2. Patients who completed 2 years of follow-up after DALK surgery were included.

DALK surgery was performed using the big-bubble technique as previously defined. In this technique, the surgeon aimed to achieve a cleavage plane (big bubble) with intrastromal air injections. When multiple air injections failed to create the big bubble, a manual stromal dissection was performed. In case of an intraoperative microperforation, air was injected into the anterior chamber, and the surgeon proceeded with lamellar surgery. If the anterior chamber was not maintained by air or a macroperforation had occurred, the surgeon converted to full-thickness keratoplasty. Bubble type and number of air injections were also recorded for each DALK procedure.[15] Two suturing techniques (interrupted or running 10-0 nylon) were used in all eyes for fixation of donor corneal button. If a patient had peripheral corneal vascularization, interrupted sutures were used. Manual keratoscopy was used in all eyes for suture adjustment. All patients undergoing DALK received topical antibiotic, topical steroid, and artificial tear eye drops to be applied postoperatively, 6 times a day for a month. Artificial tear and prednisolone acetate eye drops were tapered off over the next 11 months.

All patients underwent ophthalmic examination including logarithm of the minimum angle of resolution corrected distance visual acuity, corneal topographic keratometry readings, spherical equivalent refractive error, biomicroscopic examination, and the mean endothelial cell density analyses (ECD, Topcon SP2000P; Topcon Corp, Japan) preoperatively and at 3, 6, and 12 months and 2 years postoperatively. Twenty endothelial cells were marked and averaged for ECD analyses. All complications were also noted.

All data were recorded in Microsoft Excel 2000 for Windows. For statistical analyses, data were divided into 2 groups: eyes with previous CXL (CXL-DALK group) and without previous CXL (DALK group). SPSS for Windows software (version 16; SPSS Inc, Chicago, IL) was used for statistical analyses. Normality of the data sets was assessed with the Shapiro-Wilk test. The Student *t* test for paired data or the Wilcoxon rank-sum test were performed for comparison between preoperative and postoperative data in both groups. The Student *t* test for unpaired data or Mann–Whitney *U* test were used for evaluating differences between groups. A *P* value less than 0.05 was considered statistically significant.

RESULTS

Demographic Data and Intraoperative Findings of DALK

Seventy-seven eyes of 77 patients with keratoconus were included. The CXL-DALK group consisted of 27 eyes with a median age of 24 years (range, 13–38 yrs), and the DALK group consisted of 50 eyes with a median age of 25 years (range, 14–47 yrs). The mean interval between CLX treatment and DALK surgery was 45.6 ± 21.07 months (range, 22–96 mo) in the CXL-DALK group. Big bubble was successfully achieved in 24 eyes (88.9%), and layer-by-layer stromal dissection was performed in 3 eyes (11.1%) in the CXL-DALK group. In the DALK group, big bubble and stromal dissection rates were 90.0% (45 eyes) and 10.0% (5 eyes), respectively. Type 1 bubble (between predescemetic layer and posterior stroma) was obtained in 22 eyes (91.7%) and type 2 bubble (between predescemetic layer and DM) was obtained in 2 eyes (8.3%) in the CXL-DALK group. In the DALK group, on the other hand, type 1 and type 2 bubbles were obtained in 42 eyes (93.3%) and 3 eyes (6.7%), respectively. Type 3 (mixed type) was not observed in any eyes in both groups. Intraoperative microperforation occurred in 3 eyes (11.1%) in the CXL-DALK group and in 5 eyes (10.0%) in the DALK group. In these eyes, microperforation was managed with the help of air injection into the anterior chamber. Conversion to penetrating keratoplasty was not needed in any eyes. Demographic features and preoperative and intraoperative findings of both groups were listed in Table 1.

Visual and Refractive Results after DALK

Table 2 demonstrates comparison of visual results in both groups at preoperatively and all postoperative visits. The mean logarithm of the minimum angle of resolution corrected distance visual acuity (CDVA) was significantly improved at all postoperative visits in both groups, compared with preoperative measurements ($P < 0.001$). CDVA was 20/100 or better in 7 eyes (25.9%) preoperatively and 20/40 or better in all eyes (100%) in the second postoperative year in the CXL-DALK group. In the DALK group, CDVA was 20/100 or better in 15 eyes (30.0%) and 20/40 or better in 49 eyes (98.0%) in the second postoperative year. There was no statistically significant difference between the CXL-DALK and DALK groups in UCVA and CDVA at any

TABLE 1. Demographic Features and Operative Data of Patients With Keratoconus Who Underwent DALK With Previous CXL (CXL-DALK Group) and Without Previous CXL (DALK Group)

Parameters	CXL-DALK Group (27 Eyes)	DALK Group (50 Eyes)	*P*
Age (yr)			0.21*
Median (range)	24 (13–38)	25 (14–47)	
Eye			0.84†
Right	14 (51.9%)	28 (56%)	
Left	13 (48.1%)	22 (44%)	
Patient			0.56†
Men	18 (66.7%)	30 (60.0%)	
Women	9 (34.3%)	20 (40.0%)	
Host–donor disparity			—
0.25 mm	27 (100%)	50 (100%)	
Suturing technique			0.95†
Interrupted	5 (18.6%)	9 (18.0%)	
Continuous	22 (81.4%)	41 (82.0%)	
Big-bubble DALK	24 (88.9%)	45 (90.0%)	0.87†
Manual DALK	3 (14.8%)	5 (10.0%)	
Type 1 bubble	22 (91.7%)	42 (93.3%)	0.79†
Type 2 bubble	2 (8.3%)	3 (6.7%)	
Type 3 bubble	0 (0%)	0 (0%)	
No. air injections			0.44*
Median (range)	1 (1–3)	1.5 (1–4)	

n (%).
*Independent samples *t* test.
†χ^2 test.

postoperative visits. In both groups, the mean maximum keratometry, keratometric astigmatism, and spherical equivalent refractive error values were significantly improved in both groups at all postoperative visits ($P < 0.001$). No statistically significant differences were observed between 2 groups regarding preoperative and postoperative refractive parameters ($P > 0.05$). Table 2 summarizes the refractive outcomes of both groups.

ECD after DALK

The mean endothelial cell losses were 5.7% ± 2.3 at 1 year and 10.2% ± 3.1 at 2 years in the CXL-DALK group and 6.4% ± 4.7 at 1 year and 10.9% ± 5.4 at 2 years in the DALK group. There was no statistically significant difference between groups at any postoperative visit ($P = 0.86$ at 1 yr, $P = 0.80$ at 2 yrs). Figure 1 shows preoperative and postoperative ECD measurements of both groups.

Postoperative Complications of DALK

The mean suture removal completion time was 17.89 ± 2.54 months (range, 14–21 mo) in the CXL-DALK group and 17.86 ± 2.35 months (range, 14–20 mo) in the DALK group ($P = 0.95$). All grafts were clear at 2 years, and no graft rejection episode occurred in any group. Persistent epithelial defect were observed in 4 eyes (14.8%) in the CXL-DALK group and in 2 eyes (4%) in the DALK group within 6 postoperative months. Traumatic graft detachment occurred in 1 eye (3.7%) in the CXL-DALK group and in 1 eye (2.0%) in the DALK group. Both cases were successfully managed with resuturing of the graft. Table 3 summarizes postoperative complications in both groups.

DISCUSSION

As the number of patients with keratoconus receiving CXL will increase over time, we can easily predict that corneal surgeons will be performing DALK on more CXL-treated eyes in the future than is performed today.[4,16] At the present time, there is no large comparative studies on the effect of previous CXL treatment on the surgical outcomes and complication rates of DALK surgery. This comparative study was designed to investigate the effect of previous CXL treatment on intraoperative and postoperative outcomes of big-bubble DALK for keratoconus.

It is widely accepted that intraoperative complications are less common with Anwar's big-bubble technique for

TABLE 2. Comparison of logMAR CDVA, Kmax, SE, and Kast Values of Patients With Keratoconus Who Underwent DALK With Previous CXL (CXL-DALK Group) and Without Previous CXL (DALK Group)

	CXL-DALK Group (27 Eyes)	DALK Group (50 Eyes)	*P**
Preoperative			
CDVA	1.30 (0.69 to 2.00)	1.15 (0.701.60)	0.56
Kmax	53.0 (47.0 to 56.0)	53.5 (47.0 to 60.5)	0.33
SE	−8.0 (−4.00 to 14.0)	−7.25 (−17.50 to 4.50)	0.21
Kast	7.2 (2.6 to 13.5)	7.4 (1.6 to 12.6)	0.77
Third mo			
CDVA	0.40 (0.15 to 0.70)	0.40 (0.15 to 0.52)	0.94
Kmax	46.4 (45.0 to 52.0)	46.8 (43.7 to 50.0)	0.21
SE	−2.75 (−12.50 to 1.50)	−3.00 (−9.00 to 2.00)	0.72
Kast	5.50 (2.4 to 6.0)	5.0 (0.8 to 9.4)	0.13
Sixth mo			
CDVA	0.30 (0.10 to 0.70)	0.22 (0.10 to 0.52)	0.19
Kmax	46.2 (44.0 to 51.8)	46.4 (43.7 to 48.0)	0.09
SE	−2.50 (−12.00 to 1.00)	−3.25 (−6.10 to 2)	0.71
Kast	4.2 (1.6 to 5.4)	3.7 (0.8 to 6.5)	0.32
First yr			
CDVA	0.22 (0.00 to 0.80)	0.22 (0.00 to 0.52)	0.66
Kmax	46.0 (44.0 to 51.6)	46.4 (43.7 to 48.2)	0.12
SE	−2.50 (−12.00 to 1.00)	−3.15 (−5.25 to 1.50)	0.63
Kast	4.8 (1.4 to 8.0)	3.75 (0.8 to 6.8)	0.42
Second yr			
CDVA	0.22 (0.00 to 0.52)	0.15 (0.00 to 0.70)	0.76
Kmax	46.4 (44.5 to 48.6)	46.6 (44.0 to 48.6)	0.33
SE	−2.80 (−7.00 to 0.50)	−2.90 (−7.00 to 1.00)	0.11
Kast	3.3 (1.5 to 6.8)	3.3 (1.1 to 6.8)	0.83

Median (range).
*Mann–Whitney *U* test.
Kast, keratometric astigmatism; Kmax, maximum keratometry; logMAR, logarithm of the minimum angle of resolution; SE, spherical equivalent refractive error.

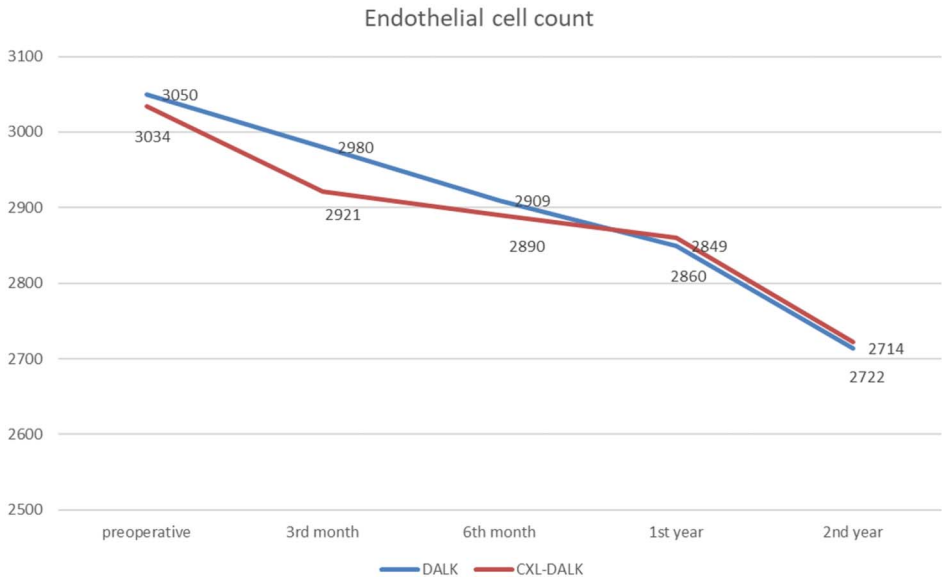

FIGURE 1. Mean ECD preoperatively and at 3 months, 6-months, 1 year, and 2 years postoperatively in patients with keratoconus who underwent DALK with previous CXL (CXL-DALK group) and without previous CXL (DALK group). (The full color version of this figure is available at www.corneajrnl.com.)

DALK and the surgery is safer when a type 1 bubble was achived.[10,17] Anwar's big-bubble technique allows a smooth cleavage plane for lamellar dissection and when a type 1 bubble forms, predescemetic layer provides additional strength to the host cornea, reducing risk for DM perforation.[17–19] Researchers are currently focused on identifying preoperative parameters of the eyes with keratoconus that may influence bubble formation during big-bubble DALK surgery.[17] In the literature, type 1 bubble was observed in more than 70% of the eyes without a history of previous CXL treatment.[15,17–20] In our study, type 1 bubbles were achieved in 91.7% of eyes in the CXL-DALK group and 93.3% of eyes in the DALK group; bubble success rates were 88.9% for the CXL-DALK group and 90.0% for the DALK group. There was no statistically significant difference between groups in bubble success rate and bubble type. Similar to our results, a bubble success rate of 56% to 82.4% was reported in eyes without a history of previous CXL treatment in previous studies.[21–24] Recently, our research group reported 3-year outcomes of DALK surgery for keratoconus with previous CXL treatment, where big bubble was successfully achieved in 80% of the eyes.[12] However, this study did not focus on the type of the bubble formation. In concordance with published studies, microperforation was the most common intraoperative complication of both groups, its frequency being reported as 11.1% for the CXL-DALK group and 10.0% for the DALK group. Regarding the postoperative complication rates, persistent epithelial defect was the most common, with a similar rate of occurrence in both groups. Suture-related complications, cataract and infectious keratitis were also observed, and there was no statistically significant difference between groups. In the literature, the report by Schaub et al. is a unique comparative study focusing on this issue.[11] They compared the outcomes of DALK surgery in a limited number of keratoconic eyes previously treated with CXL and the outcomes in previously untreated eyes. They concluded that previous CXL does not have a negative impact on clinical results and complication rates of DALK surgery. However, as the researchers mentioned, the main limitations of their study was the small size of the sample for eyes with CXL (8 eyes) that reduced the statistical meaning of its results.[11] Furthermore, they did not compare type of bubble formation between groups. Our study has shown that bubble success rate, bubble type, and intraoperative and postoperative complication rates of DALK surgery did not differ between eyes with and without previous CXL treatment. Consequently, previous CXL did not seem to be influence surgical success and complication rates of big-bubble DALK surgery. Our results may be explained with the confinement of the effect of CXL within the anterior 300 μm of corneal stroma, as reported previously, and may strengthen the assertion that CXL effect is not extend to posterior corneal layers where the big bubble forms.[6,7]

TABLE 3. Intraoperative and Postoperative Complications of Patients With Keratoconus Who Underwent DALK With Previous CXL (CXL-DALK Group) and Without Previous CXL (DALK Group)

Complications	CXL-DALK Group (27 Eyes) n (%)	DALK Group (50 Eyes) n (%)	*P**
Intraoperative			
Microperforation	3 (11.1)	5 (10.0)	1
Macroperforation	0 (0)	0 (0)	—
Conversion to penetrating keratoplasty	0 (0)	0 (0)	—
Postoperative			
DM detachment	0 (0)	1 (2.0)	1
Persistent epithelial defect	4 (14.8)	2 (4.0)	0.17
Loose sutures	2 (7.4)	3 (6.0)	1
Traumatic graft detachment	1 (3.7)	1 (2.0)	1
Keratitis	0 (0)	1 (2.0)	1
Interface opacity	1 (3.7)	0 (0)	0.35

*χ^2 test.

Although it is believed that some structural changes may occur in the posterior cornea after CXL treatment in keratoconus, these changes may not influence the success in achieving a bubble separation plane during DALK. However, further prospective studies are needed for making a definitive conclusion.

The main advantage of DALK surgery is the preservation of the healthy recipient corneal endothelium.[5,20–24] Studies have demonstrated that successful DALK surgery with minimum endothelial trauma and without any complication results in a low rate of postoperative endothelial cell loss.[23–25] ECD loss rates were reported as approximately 10% at 1 year and approximately 12% at 2 years in previous studies with big-bubble DALK for keratoconus without a history of CXL.[23–25] In the only study in eyes with a history of CXL, ECD loss rates were reported as 6.3% and 9.0% at 1 year and 2 years, respectively.[12] In this study, ECD loss rates were 5.7% and 6.4% at 1 year and 10.2% and 10.9% at 2 years in the CXL-DALK and DALK groups, respectively. There was no statistically significant difference between groups at any postoperative visit. All grafts were clear at the end of 2 years follow-up. According to this comparative study, previous CXL treatment did not cause a negative impact on the endothelial survival after big-bubble DALK surgery.

Our study has some limitations that should be mentioned. The main limitation is its retrospective and nonrandomized design. In addition, sample size of CXL-DALK group is relatively small because CXL treatment significantly reduces the indication for keratoplasty, which makes larger series difficult to obtain.

In conclusion, this study is the largest case series comparing big-bubble DALK outcomes between keratoconus patients with keratoconus with and without a history of previous CXL treatment. Our results show that previous CXL does not increase intraoperative or postoperative complication rates of DALK surgery, when compared with noncrosslinked eyes. Moreover, the improvement in visual acuity and refractive errors and endothelial cell loss rates were similar between CXL-treated and untreated eyes after 2 years of follow-up. Type 1 bubble was the most common type in both groups and CXL did not have a negative impact on the rate of successfully achieved bubble. According to the comparative results of this study, corneal surgeons can perform big-bubble DALK surgery as needed in patients with keratoconus with a history of CXL treatment without big concern.

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