· Clinical Research ·

Comparison of long-term results after manual and femtosecond assisted corneal trephination in deep anterior lamellar keratoplasty for keratoconus

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Abstract
● **AIM:** To compare long-term postoperative outcomes of manual and femtosecond assisted corneal trephination in deep anterior lamellar keratoplasty (FS-DALK) for keratoconus.
● **METHODS:** In the retrospective study, 17 consecutive eyes that underwent vertical side cut incision FS-DALK and 22 eyes that underwent trephine incision DALK were collected over a 2-year period. Main measurements included postoperative uncorrected-visual acuity (UCVA), corrected distance visual acuity (CDVA), refractive sphere and cylinder, manifest refraction spherical equivalent (MRSE), flat and steep corneal keratometry (K1 and K2), endothelial cell density (ECD), and time of epithelium healing and suture removal.
● **RESULTS:** Groups were comparable for diagnosis and preoperative visual acuity. Follow-up averaged 23mo (range, 12-36mo). At 12mo, the mean UCVA was better in the manual-DALK group (P=0.039), and the refractive sphere was lower in the FS-DALK group (P=0.040). MRSE between groups differed at 1, 6, and 12mo postoperatively (P=0.047, 0.025, 0.042, respectively). Mean CDVA, cylinder, K1, K2, corneal astigmatism, ECD, and time of epithelium healing were similar between groups. Stability of MRSE, ECD, and K1 returned sooner after FS-DALK. Initial loosened suture removal time was earlier in the manual-DALK group (P=0.042) while complete suture removal time was similar (P=0.122).
● **CONCLUSION:** Manual and femtosecond assisted corneal trephination in DALK are options for advanced keratoconus. FS-DALK do not result in improved visual acuity but it is more stable during the follow-up period. FS-DALK in the present form show limited benefit, so surgical design and parameters still need to be optimized and explored.
● **KEYWORDS:** femtosecond laser; manual technique; corneal trephination; deep anterior lamellar keratoplasty
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INTRODUCTION
Deep anterior lamellar keratoplasty (DALK) is becoming a more widely and provides better outcomes over penetrating keratoplasty (PKP) with respect to late graft rejection and corneal failure[1]. It can better preserve the structural integrity of the globe and reduces the use of postoperative steroid therapy, with comparable visual outcomes to those of PKP[2]. DALK is conventionally performed by a microkeratome and blade trephine manually; however, this method has failed to gain popularity because of the technical difficulties and the irregularity of the stromal interface. Recently, femtosecond (FS) laser-assisted corneal surgery has gained popularity and could overcome the problems associated with traditional methods. Theoretically, the laser is programmed to create precise corneal incisions, customized graft, lamellar planes of desired depths and diameters. Due to its precision and controlled size of the donor and recipient

cornea, it might make corneal transplantation a better and more controllable technique with favorable outcomes[3-4]. However, clinicians are more concerned with the practical application of FS laser, such as surgical operation, postoperative vision, refractive effect, and corneal endothelium recovery speed.

It is well known that visual performance after lamellar keratoplasty (LKP) was affected by the graft-host interface quality. Although the FS laser is effective in corneal surgery for creating lamellar ring cuts and peripheral side cuts, one drawback is that it may produce irregular surfaces when deep lamellar cuts ≥31% stromal thickness (approximately deeper than 200 μm)[5-7]. Previous studies suggested that the irregular stromal interface is also associated with levels of corneal hydration[8], corneal scarring[9], and parameters of the FS laser[10]. Possible compromises were to make the side cut only and then using the big-bubble technique[11] or using a manual technique to prepare the lamellar bed.

Some reports suggest that FS-DALK could improve uncorrected visual acuity (UCVA) and corrected distance visual acuity (CDVA)[9,12], but there are few studies compared this method with the manual DALK. Alio *et al*[13] suggested that FS-DALK (mushroom configuration) and manual-DALK were comparable in visual acuity and corneal cylinder at one year after surgery (big-bubble technique). Shehadeh-Mashor *et al*[14] showed comparable CDVA, refractive results after FS-DALK (mushroom configuration) and manual-DALK at 12mo postoperatively (Melles or Anwar big-bubble techniques). Li *et al*[15] insisted that FS-DALK (vertical) gain better visual acuity than manual-DALK at 1y postoperatively (diamond knife lamellar dissection). Salouti *et al*[16] found no significant difference between FS-DALK (polygonal or mushroom rim pattern) and manual DALK at 12mo and 24mo postoperatively (Melles techniques). Compared with these articles, we used the FS laser to make a vertical side cut which was closer to the manual-DALK. In this study, we aimed to evaluate the outcomes of FS and manual-assisted vertical corneal trephination in DALK from a long-term observation, and added the observation of corneal endothelial cell density (ECD), the time of epithelium healing, initial loose suture removal and the complete suture removal.

SUBJECTS AND METHODS

Ethical Approval The Institutional Review Board, Qingdao Eye Hospital, approved this study protocol, which adhered to the tenets of the Declaration of Helsinki. All study patients were candidates for DALK and provided informed consent for surgery.

Patients In total, 39 consecutive eyes of 38 patients diagnosed with advanced keratoconus according CLEK[17] were enrolled in this study. Exclusion criteria included eyes with scarring involving the posterior 200 μm of corneal stroma, total corneal pachymetry <300 μm, clear stromal bed <120 μm on anterior segment optical coherence tomography (AS-OCT; RTVue, Optovue, Fremont, USA)[18], and less than 12mo follow-up. The FS-DALK group was matched by age and similar pre-/postoperative comorbidities with the conventional manual trephination DALK group (manual-DALK).

As variability in stromal thickness in eyes with advanced keratoconus may limit the FS laser to produce a uniform lamellar plane, we used the FS laser only to create the side cut both in donor and recipient corneas. We divided the patients into two groups according to the technique used to perform the side cut in the donor and recipient cornea. The donor tissue used for the two groups were the same quality, thickness and hydration status. One expert surgeon (Xie LX) at Shandong Eye Institute, Qingdao, Shandong, China performed the surgeries.

Operative Technique In the FS-DALK group, 17 eyes of 16 patients underwent vertical side cut in the donor and recipient cornea from August 30, 2013 to June 1, 2016. The surgery was performed in 2 steps. The first step was conducted in the laser room, using the Wavelight FS200 system (Alcon Laboratories Inc, Ft Worth, TX, USA) with a 200 kHz repetition rate. The donor cornea was mounted on an artificial anterior chamber with epithelium removed and then brought to the FS laser, which was programmed to perform a side cut with angles of 90° with total corneal thickness. On the recipient eyes, preoperative corneal thickness was obtained using the AS-OCT to determine the depth of the posterior side cut. The FS laser parameters were as follows: donor graft size was 8.24±0.27 (range, 7.8-9.0) mm and recipient graft size was 7.92±0.27 (range, 7.5-8.7) mm. Laser settings were 1.40 μJ pulse energy with spot and line separation of 6 μm. The donor cornea was oversized in diameter by 0.3 mm in all cases. The second step was performed in the operating room. After the lamellar was cut with a diamond knife along the stromal fibers layer by layer, the recipient corneal button was lifted, and the donor lenticule minus the endothelium and Descemet's membrane was placed on the recipient residual corneal stromal bed and sutured with 16 interrupted stitches using 10-0 nylon sutures under retrobulbar anesthesia.

In the manual-DALK group, 22 eyes of 22 patients underwent blade trephine incision DALK from June 25, 2013 to August 16, 2017. For manual-DALK, we used the standardized Hessburg-Barron vacuum trephine technique to perform side cut. The donor trephination was made by a Barron punch with endothelial side up. The donor graft size was 7.98±0.15 (range, 7.75-8.25) mm, and the recipient graft size was 7.68±0.14 (range, 7.50-8.00) mm. The donor cornea was oversized in diameter by 0.25 mm in all cases. The lamella was cut with a diamond knife along the stromal fibers as same as the lamellar

Table 1 Preoperative and postoperative data of conventional manual-DALK and FS-DALK case series

Parameters	Operation	Preoperative	1mo	3mo	6mo	12mo	24mo
No. of eyes	Manual-DALK	22	22	20	20	20	20
	FS-DALK	17	17	17	16	16	16
UCVA (logMAR)	Manual-DALK	1.38±0.38	0.85±0.32	0.76±0.43	0.74±0.34	0.63±0.32	0.62±0.27
	FS-DALK	1.48±0.45	0.99±0.26	0.79±0.25	0.96±0.23	0.88±0.26	0.79±0.44
CDVA (logMAR)	Manual-DALK	0.82±0.52	0.52±0.19	0.46±0.17	0.45±0.31	0.39±0.26	0.28±0.35
	FS-DALK	0.99±0.52	0.69±0.34	0.46±0.16	0.47±0.13	0.53±0.30	0.35±0.15
Refractive sphere (D)	Manual-DALK	-7.42±4.78	2.03±4.10	1.87±2.60	1.33±3.06	1.22±2.38	0.19±4.46
	FS-DALK	-8.27±5.12	-1.75±3.91	1.00±3.76	-1.44±5.17	-1.76±5.19	-0.90±3.70
Refractive cylinder (D)	Manual-DALK	5.39±1.70	3.80±2.17	4.38±1.78	4.50±2.54	4.15±2.30	4.52±1.90
	FS-DALK	3.00±0.94	3.14±1.29	3.05±1.52	3.41±1.16	3.94±2.52	4.73±2.44
MRSE (D)	Manual-DALK	-9.93±4.28	1.46±5.52	2.22±4.82	1.21±3.84	-0.19±2.44	-1.91±3.93
	FS-DALK	-9.50±5.12	-2.89±4.29	0.18±3.93	-3.14±5.07	-3.29±5.32	-3.26±3.34
K1 (D)	Manual-DALK	56.30±4.54	39.03±2.98	35.08±5.72	37.16±5.29	38.63±3.58	41.79±3.72
	FS-DALK	57.17±9.21	40.74±5.06	38.32±4.12	40.38±6.72	39.65±4.90	42.75±2.50
K2 (D)	Manual-DALK	60.58±5.02	44.55±3.44	41.11±5.85	43.25±2.17	44.77±2.42	46.18±2.82
	FS-DALK	60.93±8.61	44.26±4.98	42.03±5.89	46.51±4.85	44.18±4.60	47.54±2.68
Gain lines of UCVA	Manual-DALK		4.9±6.7	7.3±5.6	6.2±6.7	6.1±6.6	6.0±4.0
	FS-DALK		6.2±2.7	8.6±5.3	7.0±4..7	6.7±4.9	7.6±6.9
Gain lines of CDVA	Manual-DALK		2.2±5.0	3.1±5.4	1.3±6.0	3.0±5.4	3.0±5.2
	FS-DALK		3.8±4.5	6.8±5.6	5.2±3.9	5.0±5.6	8.8±5.6
ECD (cell/mm²)	Manual-DALK	2936±511	2279±1019	3130±629	2482±756	2041±630	2376±788
	FS-DALK	3017±347	2093±964	2614±450	2922±684	2349±672	2595±421

DALK: Deep anterior lamellar keratoplasty; MRSE: Manifest refraction spherical equivalent; UCVA: Uncorrected visual acuity; logMAR: Logarithm of the minimal angle of resolution; CDVA: Corrected distance visual acuity; ECD: Endothelial cell density; D: Diopter.

cut in FS-DALK. The donor was sutured to the recipient with 16 interrupted sutures.

Postoperative Evaluations Postoperative follow-up was conducted at 1, 3, 6, 12 and 24mo. The following data were collected: 1) postoperative UCVA [recorded in logarithm of the minimum angle of resolution (logMAR)]; 2) postoperative CDVA (recorded in logMAR); 3) postoperative refractive sphere, cylinder and manifest refraction spherical equivalent (MRSE); 4) postoperative corneal curvature, including the flat corneal keratometry (K1) and the steep corneal keratometry (K2; Topconom-4); 5) postoperative ECD (Konan Specular Microscope XIII, NSP-9900 II, Konan medical, INC); 6) postoperative corneal thickness and morphology were measured by AS-OCT; 7) the epithelium healing time; 8) the time of initial loose suture removal and complete suture removal.

Statistical Analysis Study data were analyzed using statistical software SPSS (version 20.0; IBM Corp., Chicago, IL, USA). The normality of all data samples was verified using the Kolmogorov-Smirnov test. Changes in UCVA, CDVA, refractive sphere and cylinder, MRSE, K1, K2, and ECD over time were analyzed repeated-measures analysis of variance and the further pairwise comparison used least-significant difference (LSD). The postoperative epithelium healing times were compared using the independent-samples *t*-test. The suture removal time was compared between groups using the Mann-Whitney *U* test. For all analyses, *P* values <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics Long-term results of 39 consecutive eyes of 38 patients were analyzed. Follow-up averaged 23 (range, 12-36)mo. There were no significant differences in age, sex, MRSE, UCVA, BCVA, K1, K2, thinnest corneal thickness and ECD between FS-DALK and manual-DALK (*P*=0.465, 0.141, 0.816, 0.462, 0.294, 0.294, 0.901, 0.162, 0.973, respectively). Table 1 list the follow-up points in both groups and the number of eyes in which data were collected, including preoperative and postoperative UCVA, CDVA, refractive sphere and cylinder, MRSE, K1, K2, and the gain lines of UCVA and CDVA, and ECD.

Visual Acuity A significant improvement in UCVA and CDVA was noted in both groups. UCVA was comparable between groups at 1, 3, 6, and 24mo, and CDVA was comparable between groups at 1, 3, 6, 12, and 24mo. UCVA and CDVA remained stable at 1 and 3mo postoperatively, respectively. At 12mo, mean UCVA in the manual DALK group was better than that in the FS-DALK group (logMAR: 0.63±0.32 *vs* 0.88±0.26, *P*=0.039). There were no significant differences in CDVA between both groups at any postoperative time point (Figure 1). The gain of lines of UCVA at 24mo after FS and manual DALK were 7.6±6.9 and 6.0±4.0, respectively

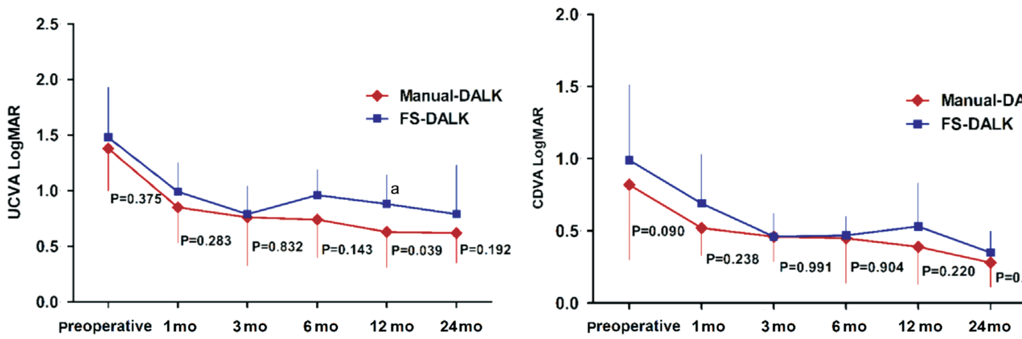

Figure 1 UCVA and BCVA preoperative and at the 1, 3, 6, 12, and 24mo follow-up period UCVA: Uncorrected visual acuity; logMAR: Logarithm of the minimum angle of resolution. [a]$P<0.05$.

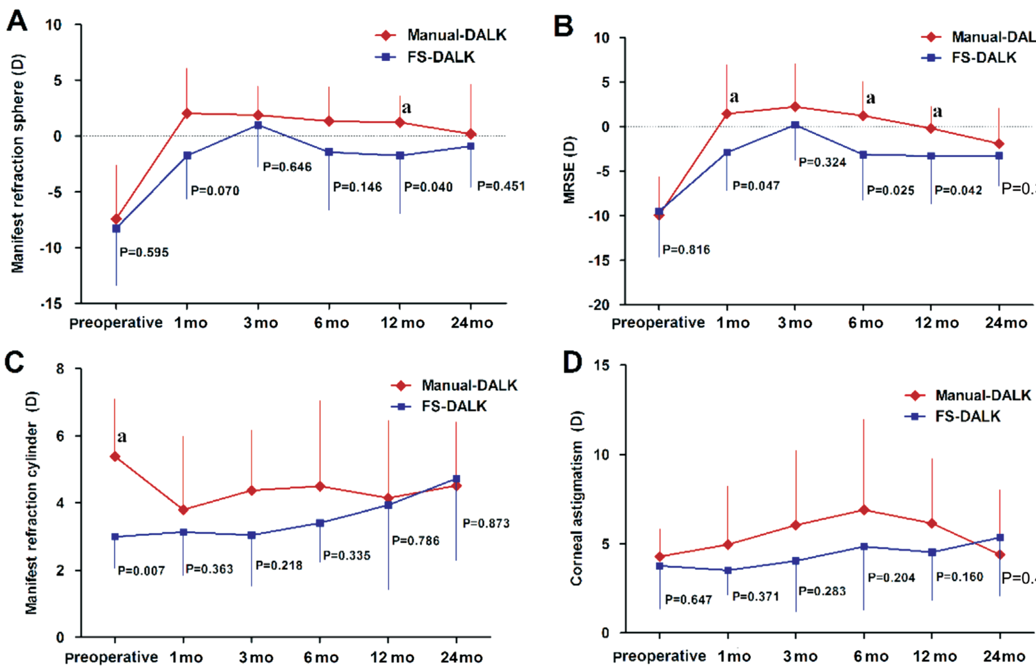

Figure 2 The mean manifest refraction sphere, MRSE, refractive cylinder and corneal astigmatism preoperatively and at the 1, 3, 6, 12, and 24mo after FS-DALK and manual-DALK, respectively [a]$P<0.05$.

(P=0.699), while the gain of lines of CDVA were 8.8±5.6 and 3.0±5.2, respectively (P=0.279).

Manifest Refraction Refractive sphere, cylinder, MRSE, and corneal astigmatism are shown in Figure 2. At 12mo postoperatively, the mean refractive sphere was lower in the FS-DALK group (-1.76±5.19 *vs* 1.22±2.38, P=0.040), but there was no significant difference at other follow-up time points (Figure 2A). The MRSE between both groups was different at 1, 6, and 12mo postoperatively (Figure 2B; 1.46±5.52 *vs* -2.89±4.29, P=0.047; 1.21±3.84 *vs* -3.14±5.07, P=0.025; -0.19±2.44 *vs* -3.29±5.32, P=0.042; respectively). The refractive cylinder was not different postoperatively (Figure 2C). Similarly, there was no significant difference in corneal astigmatism between two groups (Figure 2D). Comparison of the refractive sphere, cylinder, and corneal astigmatism in both groups showed no significant change at 1, 3, 6, 12, and 24mo (P>0.05). That is, they recovered stability 1mo postoperatively in both groups. Similarly, the MRSE became stable which was 1mo after FS-DALK and 6mo after manual-DALK.

Corneal Curvature The changes in corneal curvature including K1 and K2 are shown in (Figure 3). Mean K1 and K2 showed no significant difference between the two groups at any follow-up point. K1 became stable in FS-DALK at 6mo postoperatively and manual-DALK at 12mo postoperatively. The comparison of K2 in both groups showed no significant change at 6, 12, and 24mo (P>0.05). That is, K2 became stable at 6mo postoperatively in both groups.

Epithelium Healing and Angle of Trephination The mean time of epithelium healing was 5.00±1.60 (range, 2-7)d in the manual-DALK group and 4.56±1.59 (range, 2-7)d in the FS-DALK group; this difference did not reach statistical significance (P=0.410). The angles of trephination and graft-host interface after FS-DALK seems more regular and close to the theoretical values showed by OCT (Figure 4).

Suture Removal In the FS-DALK group, loose suture removal was initiated at a mean of 14.0 (range, 1-17)mo and

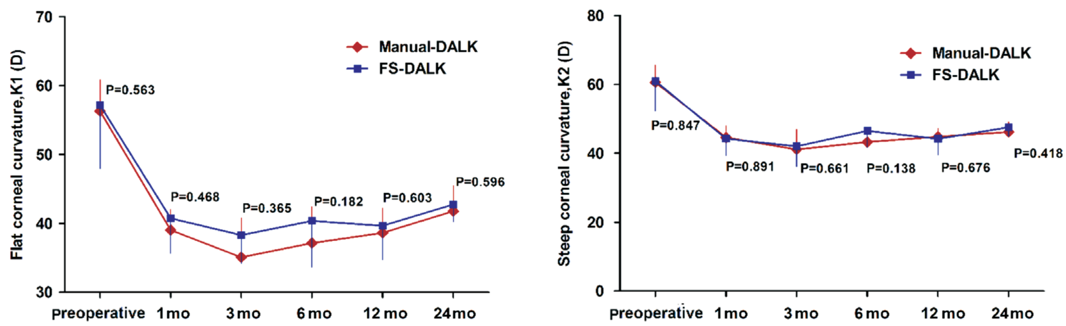

Figure 3 Mean K1 and K2 after FS-DALK and manual-DALK preoperative and postoperative Error bars show standard deviation of the mean.

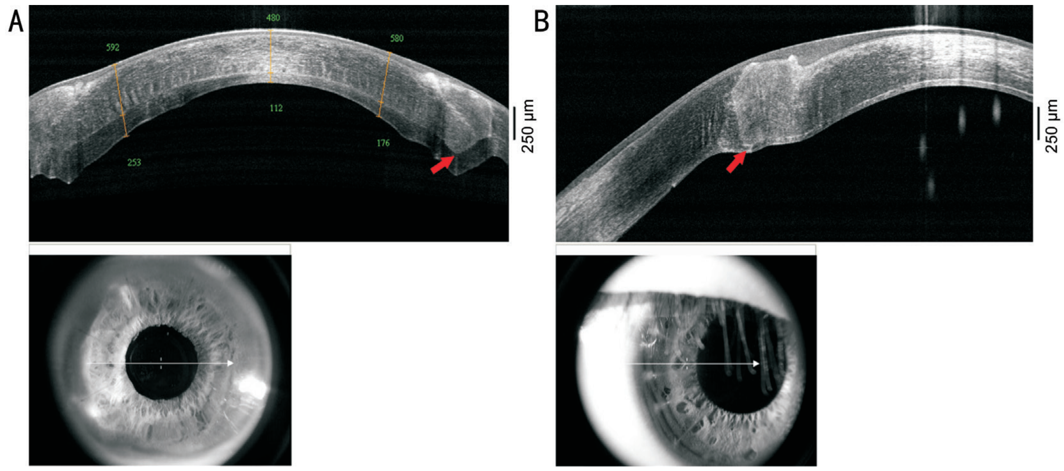

Figure 4 The corneal trephination angles of manual-DALK (A) and FS-DALK (B) at 2y postoperative The red arrow indicates the graft-host interface.

sutures were completely removed at 16.0 (range, 12-21)mo. In the manual-DALK group, loose suture removal was initiated at a mean of 6.0 (range, 1-19)mo, which was significantly earlier than FS-DALK group (*P*=0.042). All sutures were completely removed at 19.5 (range, 10-60)mo in the manual-DALK group, which was similar to the FS-DALK group (*P*=0.122). The incidence rate of loose stitches in manual-DALK and FS-DALK was 62.5% (10/16) and 22.2% (2/9), respectively.

Considering the complete sutures removal time in every patient varied, we selected 2mo after complete suture removal for comparison of refractive state between two groups to exclude the effect of suture removal. There were no significant difference between manual and FS-DALK in UCVA (logMAR: 0.78±0.45 *vs* 0.72±0.43, *P*=0.84), CDVA (logMAR: 0.34±0.21 *vs* 0.30±0.19, *P*=0.76), refractive sphere (2.00±1.79 D *vs* 0.35±5.02 D, *P*=0.51), cylinder (5.70±1.34 D *vs* 4.65±3.16 D, *P*=0.51), MRSE (0.25±3.73 D *vs* -1.97±4.40 D, *P*=0.41), K1 (41.41±1.52 D *vs* 41.06±2.35 D, *P*=0.78), and K2 (47.66±0.88 D *vs* 47.82±3.84 D, *P*=0.93).

Endothelial Cell Density The ECDs in the manual and FS-DALK groups were comparable at 1, 3, 6, 12 and 24mo postoperatively (*P*=0.527, 0.345, 0.318, 0.559 and 0.491 respectively). Comparison of ECD values in FS-DALK at different follow-up time points showed no change between 1, 3, 6, 12, and 24mo (*P*>0.05), while in the manual-DALK group, there was no change between 6, 12, and 24mo (*P*>0.05).

Complications No adverse events or complications occurred in any of the 22 patients in the manual-DALK group during the operation. Descemet's membrane perforation occurred in 1 eye in the FS-DALK group, but no conversion to PKP was required.

DISCUSSION

Theoretically, using an FS laser to create incisions may not only facilitate the DALK procedure, but also offer the advantages of precise creation of customized incisions, better donor-recipient fit and accelerated healing time[13,19]. However, clinicians are more concerned with the practical application of FS laser, such as surgical operation, postoperative visual acuity, refractive effect, impact on corneal endothelium and postoperative recovery speed from a long-term observation.

The postoperative UCVA and CDVA were comparable between two groups except UCVA at 12mo postoperatively. Alio *et al*[13] reported that in a preliminary study of 50 eyes, the manual and FS-DALK with mushroom side cut showed comparable visual and refractive outcomes. There were no significant differences in UCVA and CDVA at 1, 3, 6, and 24mo between the two groups. In our study, the mean UCVA at 12mo was better in the manual-DALK group, which may be related with the earlier initial suture removal.

For the postoperative refractive sphere and cylinder, we found a lower refractive sphere in the FS-DALK group at 12mo (-1.76±5.19 D), but that difference was not present at other postoperative time points. The refractive sphere in the FS-DALK group at 12mo postoperatively was consistent with the study of Buzzoneti *et al*[20] who reported a mean postoperative myopia of -1.50±1.70 D at 12mo following FS-DALK with mushroom side cut incision combined with the big-bubble technique for keratoconus. The difference in refractive sphere between the two groups at 12mo may be caused by the different suture removal. Collectively, patients undergoing manual DALK generally tended to hyperopia while FS-DALK tended to myopia. Previous studies focused on the refractive sphere after PKP suggested that there were many influential factors including the size of donor and recipient[21-22], the axial length of eyeball[23], different suturing techniques[24], and suture tension. In this study, a reason for this difference may be that the suture tension was smaller in FS-DALK as it can achieve a better graft-host junction apposition. Moreover, it may be related with the donor-recipient size which was described by Girard *et al*[21]. They insisted that compared with the recipient diameter, the smaller the graft, the more decrease in postoperative myopia. In this study, the donor cornea was oversized in diameter by 0.25 mm in the manual-DALK group, and 0.30 mm in the FS-DALK group. Another, the postoperative corneal thickness may affect the refractive sphere and cylinder. This was a difficult variable to measure and requires further investigation.

Concerning corneal curvatures K1 and K2, there was no significant difference between groups with a flatter K1 in the manual-DALK group. As noted, the donor corneas were oversized in diameter by 0.25 mm and 0.30 mm in the manual and FS-DALK groups, which might lead to flatter keratometry in the manual-DALK. This was also consistent with the tendency of postoperative refractive sphere to hyperopia after manual-DALK.

Sutures were selectively removed dependent on loose stitches and postoperative astigmatism. In the present study, initial loose suture removal was earlier in manual-DALK than FS-DALK. Since the donor grafts in FS-DALK were mostly fresh corneal material kept in preservative (58.8%, 10/17) while grafts in manual-DALK were mostly kept in glycerol (59%, 13/22). Sutures were more prone to loosen in the manual-DALK group because donor graft edema was greater and sutures loosen as the graft edema subsided. However, complete suture removal was earlier in the FS-DALK group, which was consistent with previous studies. Alio *et al*[13] reported an better wound healing response to FS-DALK with mushroom configuration, which increased the contact area as well as increased laser-stimulated collagen fibrosis.

As for the mean healing time of the epithelium, we found a favorable trend in the FS-DALK group compared with the manual-DALK group, but this did not reach statistical significance (4.56±1.59d *vs* 5.00±1.60d). It has been suggested that using FS laser may accelerate suture removal and epithelium healing due to the better and closer donor-recipient fit and faster wound healing[14-15,25]. Li *et al*[15] investigated FS-DALK with vertical side cut incision and showed that the epithelium healed within approximately 3d in the FS-DALK group, faster than that of manual-DALK (approximately 6d). The reason for different rate of epithelial healing may be the angle of manual trephination on the host and donor. It may not be vertical but actually oblique or obtuse, which need further investigation. However, the surface between donor and recipient in FS-DALK was more regular. Furthermore, the ECD was comparable and showed the same change trend, indicating the FS laser does not affect ECD in clinical setting.

Although the postoperative visual acuity was comparable, the technique of FS-DALK was easier to master than conventional techniques. During the manual DALK procedure, a partial trephination of variable depths ranging from 50% to 70% of corneal thickness was initially performed, followed by layer-by-layer stromal removal using various types of lamellar dissectors[26]. It was a challenge for beginners to control the ablation depth and ensure a smooth cutting interface, and these factors inevitably affect the postoperative visual acuity. However, the FS-DALK computer-guided cuts allows precise, accurate, and reproducible placement of incisions at desired depths in the cornea, and this technique may be helpful to beginners.

Based on our analysis of long-term outcomes of both groups, we concluded that both manual and FS assisted corneal trephination in DALK were effective options for advanced keratoconus. It could provide theoretical reference for clinical selection of FS laser assisted corneal transplantation. Compared with manual-DALK, there was no improvement in visual acuity in FS-DALK, but seemed to be more stable throughout the follow-up period. Limitation in this study was the small sample which needs further large sample studies. The benefits of FS-DALK were limited, demonstrating a need for optimization in terms of surgical indication, design, and continuous improvement of FS laser equipment. With respect to surgical indication, we can use the FS laser in the treatment of corneoscleral lamellar keratoplasty for peripheral corneal disease to achieve a smooth optical zone interface. Moreover, if the FS laser can achieve different depths of cutting or OCT-guided accurate ablation location, its application in corneal pathology will be more promising.

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collection and analysis, writing the manuscript, Chen M: critical revision of the manuscript, Dong YL: critical revision of the manuscript, Zhang J: data analysis and revision of the manuscript, Du XL: critical revision of the manuscript, Cheng J: critical revision of the manuscript, Gao H: critical revision of the manuscript, Xie LX: conception and design, critical revision of the manuscript, surgeon of this study.

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