Single-piece femtosecond-assisted mushroom keratoplasty in children

Amr Elkamshoushy, MD,[a] Reem Gonnah, MD,[a] Silvana Madi, MD,[a] and Jacqueline Beltz, FRANZCO[b]

PURPOSE	To report outcomes of femtosecond-assisted single-piece mushroom keratoplasty for the treatment of full-thickness corneal disease in pediatric patients with healthy endothelium.
METHODS	Femtosecond-assisted mushroom keratoplasty was performed in 8 eyes of 8 patients (age range, 8-17 years) with central full-thickness corneal opacity. The single-piece mushroom-shaped graft consisted of a large anterior portion (9 mm in diameter; 250 μm in thickness) and a small posterior portion (6-6.5 mm). Donor and recipient corneas were prepared using the WaveLight FS200 laser (Alcon Laboratories, Fort Worth, TX). The donor cornea was oversized by 0.2 mm. Outcome measures were best spectacle-corrected visual acuity, spectacle refraction, topographic astigmatism, endothelial cell density, graft rejection, and graft failure at 1, 3, 6, and 12 months.
RESULTS	Mean best spectacle-corrected visual acuity at 1, 3, 6, and 12 months was 0.28, 0.16, 0.13, and 0.10 logMAR; all patients achieved logMAR of at least 0.4 at 1, 3, 6, and 12 months. The mean refractive cylinder was 2.6 D, and mean endothelial cell loss was 13.3% at 12 months postoperatively. Two eyes had immunologic rejection episodes that were reversed with topical steroids. All corneas remained clear at final follow-up.
CONCLUSIONS	Femtosecond-assisted mushroom keratoplasty is a viable surgical option for eyes of older pediatric patients with full-thickness corneal stromal disease and healthy endothelium. Mushroom keratoplasty combines the refractive advantage of a large keratoplasty with the immunologic advantage of a small keratoplasty. Single-piece femtosecond-assisted mushroom keratoplasty may have a mechanical advantage over regular penetrating keratoplasty. (J AAPOS 2019;23:28.e1–5)

Penetrating keratoplasty (PKP) has long been the standard treatment for full-thickness corneal opacities in children. Visual outcomes of PKP in children are guarded due to increased incidence of rejections, failure, and suture-related complications.[1] The risk of immune rejection is high, and suture-related complications leading to corneal neovascularization often further increases that risk.

Large-diameter PKP has the advantage of improved refractive outcome compared to small-diameter PKP, but it carries a greater risk of immunologic rejection.[2-4] Small-diameter PKPs are less likely to experience immunologic events but carry an increased risk of poor visual outcome due to high-degree postoperative astigmatism.[5-7]

In 2003 Busin and colleagues[8] described a two-piece microkeratome-assisted mushroom keratoplasty technique in which a two-piece donor tissue consisting of a 9 mm top hat and a 6 mm posterior stem was placed in a manually dissected recipient cornea. This technique compared favorably to conventional PKP with regard to visual and refractive results in both adults[9,10] and children[11] with full-thickness corneal opacity and healthy endothelium. Single-piece femtosecond-assisted mushroom keratoplasty, described here, involves the use of a femtosecond laser to cut the donor and recipient tissue. The donor tissue is transplanted as a single piece, avoiding the presence of an interface between the anterior and posterior lamellae. This allows for accurate apposition of graft and host and simplifies the procedure.[12,13] In this case series, we present the one-year results of single-piece femtosecond-assisted mushroom keratoplasty for the treatment of full-thickness corneal disease in older children with healthy endothelium.

Subjects and Methods

Pediatric patients (<18 years of age) requiring keratoplasty for full-thickness corneal opacities in the presence of healthy

endothelium were included prospectively. All surgeries were performed by the same surgeon (SM) at Alexandria University from December 2015 to July 2016. Informed consent was obtained from the legally responsible parent or guardian in each case. The study followed the tenets of the 1964 Declaration of Helsinki and was approved by the Alexandria University Institutional Review Board.

Before surgery all patients underwent complete ophthalmologic examination, including slit-lamp examination, uncorrected and best spectacle-corrected visual acuity, applanation tonometry, fundus examination, and, when required, B-scan ultrasound. Data were analyzed using a standard spreadsheet program. Visual acuity was measured using a Snellen chart in all cases. Corneal vascularization was evaluated using slit-lamp biomicroscopy and rated according to the number of clock hours involved as well as the depth of the blood vessels within the stroma. Corneal topography (Allegro Topolyzer topography system, Alcon Research, Ltd, Fort Worth, TX) and specular microscopy (EM-3000; Tomey Gmbh, Erlangen, Germany) were performed at 1, 3, 6, and 12 months postoperatively when possible. Postoperative endothelial cell density was evaluated centrally and compared to the density obtained from data provided by the Midwest Eye-Banks (Michigan, USA), regarding the donor tissue. Postoperative examinations occurred at regular intervals, including, but not limited to, day 1, day 7, month 1, month 3, month 6, and annually thereafter.

The femtosecond laser (WaveLight FS200; Alcon Laboratories Inc, Fort Worth, TX) was first used to prepare the donor cornea, which was mounted on an artificial chamber (Katena Inc, Denville, NJ). The mushroom-shaped cut was made upon complete cone applanation. The donor diameter of the anterior top hat portion was 9 mm, with a height of 250 μm. The posterior portion, or stem, was 6.5 mm in diameter cut at 90°.

Subsequently, under general anesthesia the recipient's eye was stabilized with a disposable suction cone positioned at the corneoscleral limbus. After docking, the recipient cornea was cut at the same energy settings as those of the donor (top and bottom sides, 2.4 μJ; side spot, 4 μm; line spot, 1 μm). The diameter was 200 μm smaller than that of the donor cornea. An 85 μm superficial corneal bridge was left uncut by the laser in order to preserve globe integrity until the patient was transferred to the operating room.

After the laser trephination, patients were transferred, under general anesthesia, from the femtosecond laser suite room to an adjacent operating room with an eye shield in place and carefully monitored. Dissection of the superficial bridge was completed with a blunt spatula, and the donor cornea was placed. The number and configuration of the sutures varied according to the pathology. In older patients and cases of keratoconus we used 8 interrupted sutures, with a single running continuous suture, as shown in Figure 1. In younger patients and cases of vascularized corneas, 16 interrupted sutures were used. Postoperative treatment included topical moxifloxacin 6 times daily for 1 month and topical prednisolone acetate 1% hourly for the first 3 days, tapered down gradually to once daily over 6 months. Sutures were removed as required starting from 3 months after surgery. All sutures were removed within 6 months.

Results

A total of 8 eyes of 8 patients (4 males), 8-17 years of age, were included. The mean age of the patients at the time of surgery was 13 years (range, 8-17 years).

Of the 8 eyes, 5 had a history of herpetic keratitis, 2 had keratoconus, and 1 had a history of bacterial keratitis. One of the eyes with keratoconus had a preexisting deep anterior lamellar keratoplasty with a poor visual outcome due to the presence of an interface opacity. Six eyes had corneal neovascularization of at least one quadrant at the time of surgery. All eyes were phakic. Demographic data and preoperative characteristics of patients are presented in Table 1.

Four patients with significant corneal neovascularization underwent concurrent corneal intrastromal injection of bevacizumab, with the aim of minimizing corneal neovascularization. Additional bevacizumab injections have not been performed. Two patients required manual refinement of the trephination because the femtosecond laser could not penetrate the corneal opacities in the host corneas. There were no cases of corneal perforation at the time of host-tissue preparation. All procedures were otherwise uneventful.

Two patients required resuturing because of early loosening of sutures. One patient developed postoperative glaucoma that responded to medical management. One eye had an episode of immunologic rejection (at month 6) and one had 2 episodes of rejection (in months 3 and 9). All rejection episodes responded to medical management with intensive topical steroids. One eye had a preexisting cataract that had not been detected because of significant corneal opacification. In that case, phacoemulsification and insertion of an intraocular lens were performed 6 months after the transplant procedure, following removal of all sutures.

All patients completed 12 months of follow-up. There have been no cases of corneal graft failure to date. The mean best spectacle-corrected visual acuity in logarithm of the minimum angle of resolution units (logMAR) was at 0.28 at 1 month, 0.16 at 3 months, 0.13 at 6 months, and 0.10 at 12 months; all patients achieved at least 0.4 logMAR at 1, 3, 6, and 12 months. The percentages of patients with at least 0.1 logMAR were 25%, 50%, 75%, and 75% at 1, 3, 6, and 12 months, respectively.

The mean refractive cylinder was 1.9 D (range, 0-3 D) at 1 month and 2.6 D (range, 1-6 D) at 12 months. The mean endothelial cell loss (ECL) at final follow-up, compared to eye bank data, was 11.8% (range, 0%-36.8%). Operative characteristics and postoperative ECL, as well as postoperative visual and refractive data, are provided in Table 1.

Discussion

An ideal keratoplasty for a pediatric patient should result in early and fast visual recovery and excellent final visual outcomes. It should also induce minimal refractive error and allow long-term graft survival.[5,6] Unfortunately, PKP in
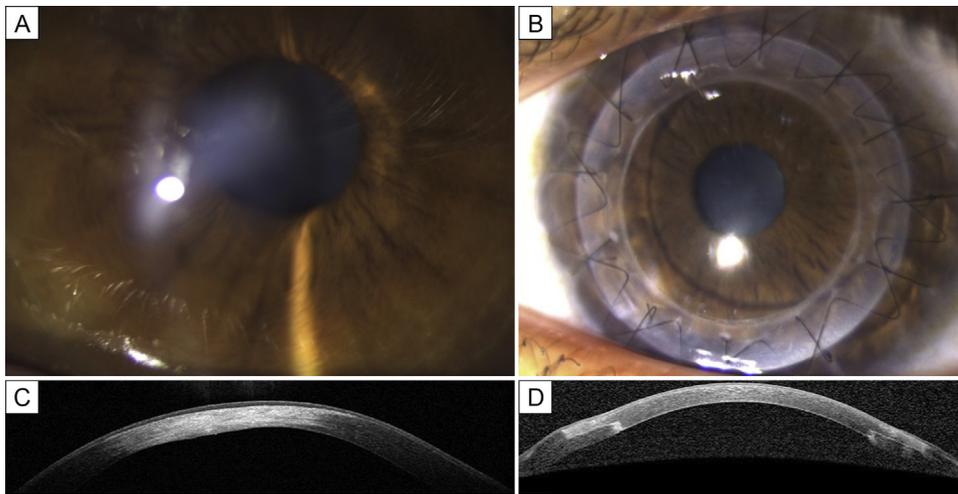
FIG 1. Slit-lamp image (A) and corresponding anterior segment optical coherence tomography image (B) of keratoconus with full-thickness cornea opacity and corresponding images (C-D) of 1 month after femtosecond-assisted mushroom keratoplasty.

children often does not meet these criteria. Irreversible immune rejection, suture-related complications, and wound dehiscence due to trauma can limit success. Early visual rehabilitation and minimal final refractive error are crucial in children to allow early treatment of amblyopia and/or correction of vision with spectacles rather than rigid gas-permeable contact lenses.[14,15] This would be of special advantage if the technique is used in younger children.

Femtosecond laser was used to perform single-piece mushroom keratoplasty with a 9 mm top hat and a posterior 6.5 mm stem with the aim of minimizing an astigmatic outcome and reducing the risk of immunologic rejection. Pirouzian reported the use of femtosecond-assisted deep anterior lamellar keratoplasty (DALK) in a child[16]; although a different technique was used, there was early visual recovery and low-degree astigmatism. Buzzonetti and colleagues[17] reported a case series where femtosecond laser was used to facilitate big-bubble DALK in children; their technique was hampered by the presence of dense corneal opacities with posterior corneal adhesions, which made it difficult to achieve a big bubble and necessitated reverting to PKP.[17] During femtosecond-assisted mushroom keratoplasty, manual refinement is possible if the laser fails to penetrate the opacities, and adhesions between Descemet's membrane and posterior stroma are less significant.

Our case series demonstrated early and fast visual recovery with minimal refractive astigmatism (Table 1). All eyes had a best spectacle-corrected visual acuity of at least 0.4 at 1 month, with further improvement over the follow-up period. Astigmatism was limited to a mean of 2.6 D at 12 months, and all patients had refractive errors corrected with spectacles rather than contact lenses. The early and fast visual recovery with this technique may be attributable to the ability of the femtosecond laser to create precise and reproducible laser cuts of donor and recipient corneal tissue, leading to accurate matching of host and recipient cornea

tissue.[13,18-20] The large 9 mm anterior lamella used in this technique also provides a refractive advantage by reducing the chance of inducing significantly high-degree astigmatism.[2] Our case series included patients from 8 to 17 years of age, and none of the cases required amblyopia treatment. The fast visual recovery and spectacle-correctable postoperative astigmatism could potentially also be an advantage for younger children, and the advantage might include an earlier possibility to treat amblyopia. However, this would require further investigation.

Busin and colleagues[10,11] obtained excellent visual and refractive results with microkeratome-assisted two-piece mushroom keratoplasty. The femtosecond modification of Busin's technique that we present here allows for the creation of a single-piece donor tissue. The absence of an optical interface in this single-piece tissue may provide an optical advantage and reduce recovery time. In addition, this technique avoids the possibility of detachment or folds of the posterior lamella that might occur with a two-piece donor. Detachment of a posterior lamella could be more likely in children who do not comply with postoperative instructions, particularly with regard to eye rubbing. Return to the operating theater for rebubbling procedures is more significant in children than in adults because they require general anesthesia.[10]

The femtosecond laser simplifies and improves donor graft preparation. A single-piece donor may provide good mechanical stability.[21] This is particularly important in children, who may be more likely to experience trauma than adults due to their active nature and reduced compliance. Moreover, increased surgical wound surface area attributable to the mushroom shape of donor and recipient tissues allows for fast healing and improved wound integrity.[10,11] Bahar and colleagues[21] confirmed that femtosecond-assisted mushroom-shaped wound configuration of a much smaller degree than we report here was mechanically more stable than traditional PKP.

Table 1. Demographic data of 8 cases undergoing single-piece femtosecond-assisted mushroom keratoplasty, with pre- and postoperative findings

		Demographics and preoperative data							Postoperative data							
									BSCVA and refraction							
									1 mo		3 mo		6 mo		12 mo	
	Diagnosis	Age, years (sex)	NV	BSCVA	Concurrent intrastromal BV	Post-op complications	ECL (%) 12 mos		BSCVA	Refraction	BSCVA	Refraction	BSCVA	Refraction	BSCVA	Refraction
1	Post-herpetic keratitis	8 (F)	Y	1.3	Y	Rejection	5.9		0.3	+1.0 +3.0 ×080	0.1	+1.0 +1.0 ×090	0.1	+1.0 +1.0 ×090	0	+3.5 ×45
2	Post-bacterial keratitis	16 (F)	N	1.3	N	Rejection×2	13.5		0.1	+4.0	0	−0.75 +2.75 ×160	0.1	−1.0 +3.0 ×150	0	+1.0 ×180
3	Post-herpetic keratitis	8 (F)	Y	1.3	Y	Resuture	4.0		0.2	+2.5 ×150	0.2	+2.5 ×150	0.1	+2 ×150	0.1	−4.0 +2.5 ×170
4	Failed DALK	16 (F)	Y	HM	Y	Malignant glaucoma	3.1		0.4	−4.0 +2.0 ×150	0.1	−8.0 +4.0 ×150	0.1	−6.25 +1.25 ×140	0.1	−5.25 +1.25 ×140
5	Post-herpetic keratitis	12 (M)	N	1.3	N	Nil	29.6		0.4	−4.0 +2.5 ×070	0.2	−3.75 +2.0 ×010	0.1	−3.75 +2.0 ×010	0.1	−3.75 +2.0 ×10
6	Keratoconus	16 (M)	Y	HM	N	Resuture	10.3		0.3	+1.0 +2.0 ×070	0.2	−5.5 +4.5 ×085	0.2	−7.0 +6 ×090	0.2	−7.0 +6.0 ×90
7	Post-herpetic keratitis	13 (M)	Y	HM	N	Nil	36.8		0.1	−2.5	0.1	−5.5 +3.0 ×150	0.1	−5.5 +3.0 ×150	0.1	−5.5 +3.0 ×150
8	Post-herpetic keratitis	16 (M)	Y	HM	Y	Nil	2.9		0.4	+3.0 ×150	0.4	+3.5 ×150	0.2	+3.0 ×005	0.2	−1.0 +1.5 ×175

BSCVA, best spectacle-corrected visual acuity (logMAR); BV, bevacizumab; DALK, deep anterior lamellar keratoplasty; ECL, endothelial cell loss; HM, hand motions; NV, neovascularization of the cornea.

The absence of graft failure at the 1 year's follow-up in our series is consistent with the reported incidence in two-piece mushroom keratoplasty cases in adults.[9,11] In contrast, graft failure in children after PKP has been reported to be most common in the first postoperative year.[14,15,22] For patients <5 years of age, Huang and colleagues[23] reported that 48% of graft failures occur within the first year. The same report identified that 51% of graft failures in older children occurred during that time frame. Our results indicate that single-piece mushroom keratoplasty might offer advantages in this regard.

For small PKPs, the larger distance between the deeper graft stroma and the limbus as well as the replacement of only a small area of the patients' healthy endothelium with donor endothelium may result in a lower risk of rejection.[5-7] In addition, endothelial cells are known to migrate from areas of higher endothelial density to areas of lower endothelial density.[24-27] Thus theoretically a patient's healthy endothelium might migrate to the small posterior lamella following an episode of graft rejection in mushroom keratoplasty. This may explain why 2 corneas recovered after they experienced graft rejection in the current series.

ECL in this series was comparable to that published for standard PKP.[28] The use of femtosecond laser and increased donor tissue handling for mushroom keratoplasty could be thought to result in an increased cell loss; however, this was not our experience in this small series. Levinger and colleagues[18] also reported higher endothelial cell counts with the Intralase femtosecond laser PKP incision.

Early loosening of sutures is a common occurrence in children and can potentially lead to graft failure caused by significant inflammation, infection, and/or rejection.[14,15,22] Using a large anterior diameter and a femtosecond single-piece mushroom-shaped donor graft allowed for the removal of all sutures in as early as 3 months in this series.[12] Despite this advantage, two eyes still required resuturing under general anesthesia.

Presence of dense corneal opacities or blood on the ocular surface is known to hinder full penetration of the femtosecond laser, leading to incomplete cuts of the recipient tissue[29-31] and the need for manual refinement. The manual refinement required in 2 of our cases was not technically difficult and did not appear to affect the final visual outcome. We note, however, that our sample size is small, and that the follow-up period of 1 year is relatively short. Further investigation would be required to determine whether manual refinement is important. Manual refinement is performed as a routine procedure of two-piece microkeratome-assisted mushroom keratoplasty, and excellent results have been published, perhaps lending support to the theory that this is not important for the final visual outcome.[10,11]

The expense associated with the use of femtosecond laser is a limitation of this technique. A further limitation is that the laser requires a dedicated suite within a surgical complex, and patients may need to be transported under general

anesthesia. Transporting the patient may increase the risk of penetration. To avoid full penetration, a superficial bridge of 85 μm was left, as has been reported elsewhere.[30] No corneal perforations following the femtosecond laser trephination occurred in our series. It has been reported that bursting pressure is higher in cases with a remaining posterior corneal bridge and/or in shaped keratoplasties (eg, top hat and mushroom-shaped wound profiles) compared to straight wound profiles.[32] The same is presumed to apply with this mushroom technique.

In conclusion, single-piece femtosecond laser-assisted mushroom keratoplasty may be appropriate for older pediatric patients with full-thickness corneal opacity and healthy endothelium. Results of this technique for the younger children (<8 years) is yet to be tested. This technique combines the refractive advantage of a large corneal transplant with the improved survival and endothelial preservation of a small corneal transplant. The femtosecond laser allows for the creation of a single piece graft that may result in a stronger wound profile and avoid the complication of posterior lamellar dehiscence that might be seen in two-piece mushroom keratoplasty, as well as provide an interface-free optical zone. This technique may lead to favorable visual and astigmatic outcomes with a low rate of graft failure.

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