AMERICAN ACADEMY™ OF OPHTHALMOLOGY

Boston Keratoprosthesis Type 1

A Randomized Controlled Trial of Fresh versus Frozen Corneal Donor Carriers with Long-Term Follow-up

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Purpose: To compare the long-term clinical outcomes of fresh versus frozen corneal graft carriers for the Boston Keratoprosthesis type 1 (B-KPro).

Design: Prospective, single-center, nonblinded, randomized controlled trial. All participants were followed through the initial study protocol of 24 months and were approached to enter an extension phase, with continuing follow-up visits to 60 months.

Participants: All patients undergoing B-KPro surgery between October 2008 and December 2009 by a single experienced surgeon at the Centre Hospitalier de l'Université de Montréal using an allograft carrier were considered. Patients were excluded if they had previously undergone B-KPro implantation.

Methods: Participants were randomized individually to receive a B-KPro using a frozen or a fresh corneal graft carrier on the basis of tissue availability on the day of surgery, as determined by the local eye bank.

Main Outcome Measures: The primary outcome measure was device retention at 24 and 60 months. Secondary outcome measures included surgical feasibility, visual acuity (VA), and complications.

Results: Thirty-seven eyes of 37 patients were enrolled in the initial study protocol, with 19 eyes randomized to fresh and 18 to frozen carrier grafts. Thirty-six eyes were followed through to 24 months, with 1 lost to follow-up. Of these, 26 were enrolled in the extension (11 eyes with a frozen and 15 eyes with a fresh carrier graft). There were no differences in the baseline characteristics of patients enrolled in the extension phase versus those who were not. At 60 months, median corrected distance VA) in the fresh group had improved to 20/150 from a baseline of counting fingers, whereas the frozen group improved to 20/400 from a baseline of hand motions. Device retention was 100% at 24 months and 96% at 60 months. There were no significant differences in the rate of complications between groups.

Conclusions: Fresh and frozen corneal donors offer similar clinical outcomes when used as carriers for the B-KPro, with no significant differences in device retention, visual rehabilitation, or rates of complications at 24 or 60 months. *Ophthalmology 2017;124:20-26 © 2016 by the American Academy of Ophthalmology.*

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Throughout the 20th century, advances in standard penetrating keratoplasty techniques have contributed to dramatically improved outcomes in the treatment of corneal blindness. However, a subset of patients are known to have a poor prognosis when using these conventional techniques.[1,2] The implantation of artificial materials and devices to restore corneal clarity in severe corneal disease has been attempted for more than 2 centuries.[3] The Boston Keratoprosthesis type 1 (B-KPro), approved by the Food and Drug Administration in 1992, has garnered widespread use over the past 2 decades, with more than 11 000 devices implanted in patients worldwide.[4,5]

In selected cases, successful B-KPro implantation can be achieved using the patient's own trephined corneal tissue as a carrier graft; however, the majority of cases are performed using an allogeneic corneal button. The donor tissue in the B-KPro acts as a peripheral carrier and interface to facilitate suturing of the device to the host, rendering the otherwise highly desirable optical clarity of fresh tissue unnecessary. In some countries, the use of fresh tissue places further stress on eye banks already struggling with shortages and waitlists for other keratoplasty procedures, in addition to the significant cost associated with fresh tissue procurement, storage, and transportation.[6,7]

The relative scarcity of fresh donor tissue in Canada led us to compare the use of frozen corneal donor tissue with standard fresh corneal allografts as carriers for the B-KPro.[8] Although the mean follow-up in this original report was 9.65 months, primary outcomes were assessed after only 3 months of postoperative follow-up. It is now recognized that the risk of certain complications may increase with longer follow-up.[9,10] Therefore, it was imperative to extend the follow-up duration to identify any late-onset complications associated with the use of frozen carrier grafts. The purpose of this study is to compare the clinical outcomes of fresh versus frozen carrier grafts, including visual rehabilitation

http://dx.doi.org/10.1016/j.ophtha.2016.07.019
ISSN 0161-6420/16

and rates of complications, up to the 24 months of the initial study protocol. Further, we compare the long-term outcomes in a subset of these patients over a total of 60 months of follow-up.

Methods

This prospective, single-center, nonblinded, randomized controlled trial comparing B-KPro type 1 surgery with fresh or frozen carrier graft extends the follow-up of the patient cohort first published by Robert et al.[8] The study protocol adhered to the tenets of the Declaration of Helsinki and received approval of the Ethics Committee of the Centre Hospitalier de l'Université de Montréal – Notre Dame before patient enrollment. The study was registered under the clinicaltrials.gov identifier NCT01950598. Patients were informed of the surgical procedure and study design, and written informed consent was obtained. A modification to the initial study protocol was approved by the Ethics Committee to extend follow-up visits from 24 months to 60 months, but this required renewal of the patients' signed informed consent. Thus, informed consent was sought from all patients included in the original study protocol for inclusion in the extension phase.

All patients undergoing B-KPro implantation between October 2008 and December 2009 using an allograft carrier were included in the original study. Patients were excluded from the study if they had undergone previous keratoprosthesis implantation or elected to use a corneal autograft where appropriate.

As previously described, subjects received a fresh or frozen cornea during implantation of the B-KPro. The allocation to either group was determined by the availability of fresh corneal tissue from the local eye bank on the day of surgery. The surgeon was not informed of the graft tissue characteristics before the morning of the surgery, and, as such, tissue allocation could not have an impact on patient scheduling. Tissues deemed unsuitable for standard penetrating keratoplasty were placed as whole globes in a solution of Optimyxin, gramicidin 0.025 mg/ml, and polymixin B sulfate 10 000 U/ml ophthalmic solution (Sandoz Canada, Inc., Quebec, Canada) and were cryopreserved at −80°C. Frozen globes were transferred to the operating room on the morning of surgery and thawed inside their sterile containers under running water. Once opened and placed onto the sterile operating room table, Westcott scissors were used to fashion a corneoscleral button, which was then cut using a standard trephination technique into a corneal graft carrier button.

Surgeries were performed at the Centre Hospitalier de l'Université de Montréal – Notre Dame by one experienced surgeon (M.H.-D.) between October 2008 and December 2009 using the Boston KPro type 1 threadless design with an 8.5-mm, 16-hole polymethylmethacrylate back plate. With the exception of the use of a fresh versus frozen carrier graft, the surgery was performed using the same standard technique in all patients, as described previously.[11,12] A soft contact lens (Kontur Kontact Lens, Hercules, CA) was placed at the end of surgery in all patients and was maintained or replaced at all follow-up visits as necessary. Patients were prescribed topical prednisolone acetate 1% (Sandoz, Boucherville, Canada) and topical moxifloxacin (Vigamox; Alcon Canada, Mississauga, Canada) ophthalmic drops 4 times daily, which were both subsequently tapered to be used once daily indefinitely.

Patients were evaluated at postoperative day 1, weeks 1 and 2, months 1, 3, and 6, and typically every 1 to 6 months thereafter, gradually extending the time between visits at the discretion of the treating physician. A complete ophthalmological examination including corrected distance Snellen visual acuity (VA) and slit-lamp examination for leaks, melts, tissue necrosis, extrusion, inflammation, retroprosthetic membrane and infectious endophthalmitis was performed at each assessment. Given the considerable distance some participants traveled for the purposes of the study, study visits were accepted if they were within 4 months of their expected date. If more than one visit satisfying this criteria existed, the closest one to the exact date was considered. For the final 24- and 60-month visits, if no visits fell within 4 months of the expected date, the next visit within 12 months was used for assessment of VA and complications. Otherwise, the patient was considered to be lost to follow-up.

The primary outcome measure of this study is device retention at 24 and 60 months of follow-up. Secondary outcome measures include surgical feasibility, postoperative VA, and complications. These included potentially graft-related complications such as retroprosthetic membrane, intraocular inflammation, and corneal melt, as well as glaucoma and posterior segment complications. Intraocular inflammation (uveitis) was defined as any inflammation greater than 1+ cell in the anterior chamber. Corneal melts were defined as any noticeable corneal thinning in the carrier graft on slit-lamp examination. New or worsening glaucoma was defined as increased intraocular pressure (IOP) (IOP >25 mmHg as measured by digital palpation or IOP high enough to warrant additional topical or systemic medication), increased cup-to-disc ratio, or visual field loss.[13]

Every patient received the corneal graft carrier they were assigned by the Eye Bank on the day of surgery (i.e., received their intended treatment), and all were analyzed within their assigned group for all outcome measures. No patients were excluded after randomization.

Fresh and frozen cornea groups were compared using the Fisher exact test for prognostic category (autoimmune, chemical injury, and other diagnoses) and gender composition. A 2-sided Student *t* test was performed to compare patient age and follow-up duration for the 2 groups. The number of prior penetrating keratoplasty procedures among patients in each group was compared using the Mann–Whitney *U* test. To ensure that enrollment for the extension phase of the study did not select a biased group of patients, baseline characteristics and outcomes at 24 months were compared for those patients who were enrolled versus those who were not. Furthermore, the cumulative incidence of complications at 24 and 60 months and 95% confidence intervals were calculated for the group as a whole, and then for the fresh and frozen graft carrier subgroups. Kaplan–Meier survival analyses for VA better than or equal to 20/200 and B-KPro extrusion/exchange were performed. In cases where a VA measurement was worse than 20/200 before returning to ≥20/200 (i.e., fluctuation), the eye was considered to have retained 20/200 or better until the first measurement worse than 20/200 that did not recover. The Mantel-Cox log-rank test was performed to compare the survival curves of the fresh and frozen carrier graft groups. Statistical analyses were performed using SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY), using an alpha level of 0.05 for all measures.

Results

Baseline Characteristics

Thirty-seven eyes of 37 patients were enrolled in the initial study protocol, which involved regular follow-up assessments up to and including 24 months postoperatively. The baseline characteristics of the 37 patients in the initial study have been described.[8] All patients enrolled in the initial study protocol reached 24 months of follow-up with the exception of 1 patient in the frozen carrier graft group who was lost to follow-up after the 12-month follow-up visit, representing 97% retention. Ten patients who completed the initial study were not enrolled in the extension. Of these, 9 patients declined consent to extend follow-up visits within the parameters