The International Use of the Boston Type I Keratoprosthesis

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Introduction

According to the World Health Organization, there are an estimated 289 million visually impaired individuals worldwide, 39 million of which are considered blind.[1] The burden rests predominantly in developing countries, where an estimated 90% of these visually impaired individuals reside.[1] The incidence of corneal disease, the second most significant cause of blindness worldwide after cataracts,[2] is disproportionately high in developing countries. Corneal transplantation has long been the standard treatment option for patients suffering from corneal disease, but limitations in the supply of donor corneal tissue in the developing world have resulted in tissue availability for only a fraction of those in need.[3] In addition, poor prognostic indicators for keratoplasty, such as prior graft failure, significant corneal vascularization, limbal stem cell deficiency, autoimmune diseases, and severe chemical injury, have precluded a subset of patients from being considered for corneal transplantation.[4–7]

The Boston type I keratoprosthesis (Massachusetts Eye and Ear Infirmary, Boston, MA) has filled the need for an alternative therapeutic option in these patients. Introduced into clinical practice in the United States in 1992, it has rapidly gained popularity over the last decade.[8] Consisting of an optical cylinder made of polymethylmethacrylate (PMMA) with an attached anterior plate and a separate PMMA posterior plate that secures the keratoprosthesis to a donor corneal graft, the keratoprosthesis has undergone several design modifications that have significantly improved postoperative outcomes and made it a viable treatment for corneal opacification not amenable to traditional corneal transplantation.[9–11] The outcomes of Boston type I keratoprosthesis

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implantation in the United States have been encouraging, and its use outside of North America has increased rapidly in recent years (Fig. 1).[12,13] However, only about 1200 keratoprosthesis implantations are performed per year worldwide, as compared with about 100,000 corneal transplants utilizing cadaveric donor corneal tissue.[3] Although it is anticipated that an increasing number of Boston type I keratoprosthesis procedures will be performed internationally each year, multiple barriers exist that limit the availability of the Boston keratoprosthesis outside of North America. In this chapter, we will discuss the outcomes of Boston keratoprosthesis implantation outside of the United States, the barriers to its use outside of the United States, and strategies to overcome these barriers to make the Boston keratoprosthesis available to appropriate candidates throughout the world.

■ Review of International Keratoprosthesis Results

The majority of reports concerning the international results of Boston keratoprosthesis implantation are single reports or small case series that concern a specific indication or complication. Only 3 reports include more than a dozen patients, and only 1 includes results from more than a single center (Table 1).[12–17] Although the outcomes of

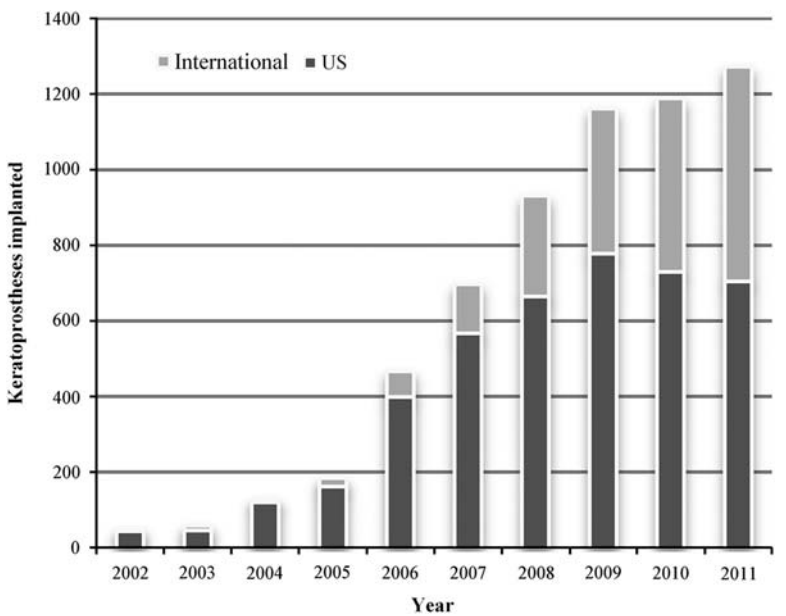

Figure 1. *Number of Boston type I keratoprostheses implanted in the United States and worldwide since 2002. Courtesy of James Chodosh, MD, MPH and Claes Dohlman, MD, PhD.*

Boston keratoprosthesis surgery outside of North America are similar to those reported by North American surgeons, direct comparisons should be made with caution given differences in patient selection, surgical technique, postoperative management, length of follow-up, etc. In addition, reporting of results in terms of final visual acuity and percentages of eyes affected with various postoperative complications instead of interval visual acuities and rates of complication development limit the ability to compare outcomes between centers. A recently published study reporting the indications for and outcomes of 223 Boston keratoprosthesis procedures performed in 8 different countries, half of which were performed by the lead author at the Jules Stein Eye Institute at the University of California in Los Angeles (UCLA), provides the most comprehensive comparison of the outcomes of Boston keratoprosthesis implantation within and outside of North America.[13] The same patient selection strategy, surgical technique, and postoperative management were used at both UCLA and the international centers, thus allowing for a more accurate comparison of outcomes of Boston keratoprosthesis surgery within and outside of North America.

Indications for Surgery

Overall, corneal transplant failure was the most common indication for keratoprosthesis implantation outside of the United States, accounting for 44% and 57% of procedures in the 2 largest series reported to date (Table 1).[13,15] The second most common indication in these series were chemical injury and aniridia, but the frequency of these disorders was observed to vary significantly between different centers. When comparing indications for surgery within and outside of North America, Aldave et al[13] found that corneal transplant failure was a significantly less common indication in the international series than in the UCLA series ($P = 0.005$) and that chemical injury was significantly more common ($P = 0.0001$).

Visual Outcomes

Although only a small percentage of eyes had preoperative corrected distance visual acuity (CDVA) of 20/200 or better, approximately two thirds of eyes achieved a CDVA of at least 20/200 at their last follow-up visit (Table 1).[13,15–17] The only study in which this was not observed was in the series reported by Verdejo-Gomez et al,[17] in which only 17% of eyes achieved 20/200 CDVA. The authors attributed the limited final CDVA in the majority of patients to a high prevalence of glaucoma or other optic nerve abnormalities in the series (83% of eyes). However, despite the fact that <20% of eyes achieved a CDVA of 20/200 or better in this series, the final postoperative CDVA was improved over the

Table 1. *Summary of the Outcomes of Boston Type I Keratoprosthesis Implantation Outside and Inside the United States*

Author	Country	No. Eyes	Mean FU (mo)	Top Indications	CDVA ≥20/200 (≥20/50)		Retention at Last FU	Complications§
					Preop	At last FU		
Robert and Harissi-Dagher[15]	Canada	47	10	Failed corneal transplant (57%), aniridia (21%), limbal stem cell deficiency (6%)	6% (≤3%)	66% (≥11%)	100%	Elevated IOP (51%), RPM (25%), glaucoma progression (23%), RD (6%)
Verdejo-Gomez et al[17]	Spain	12	23	Failed corneal transplant* (92%), HSV keratitis (8%)	0% (0%)	17% (8%)	100%	Corneal thinning (33%), glaucoma progression (8%)
Al Arfaj and Hantera[14]	Saudi Arabia	4	11	Trachoma (50%), failed corneal transplant (25%), chemical injury (25%)	0% (0%)	100% (25%)	75%	Sterile corneal stromal necrosis (25%), corneal epithelial defect (25%)
Shihadeh and Mohidat[16]	Jordan	20	18	Failed corneal transplant* (95%), mucous membrane pemphigoid (5%)	0% (0%)	65% (25%)	90%	RPM (45%), development or progression of glaucoma (20%), infectious keratitis (10%), endophthalmitis (5%)
Aldave et al[13]	Armenia, India, Indonesia, Nepal, Philippines, Russia, Saudi Arabia	113	14	Failed corneal transplant (44%), chemical injury (27%), Stevens-Johnson syndrome (8%)	2% (0%)	68% (29%)†	81%	RPM (27%), sterile corneal stromal necrosis (18%), elevated IOP (14%), infectious keratitis (12%), PED (10%), endophthalmitis (9%)
Zerbe et al[12]		141	9	Failed corneal transplant (54%),	4% (0%)	57% (26%)	95%	

	United States (17 institutions)			chemical injury (15%), bullous keratopathy (14%)				RPM (25%), elevated IOP (15%), vitritis (5%), RD (4%)
Aldave et al[13]	United States (UCLA)	110	24	Failed corneal transplant (64%), repeat keratoprosthesis (12%), chemical injury (7%)	6% (0%)	60% (34%)‡	80%	RPM (49%), PED (36%), elevated IOP (20%), RD (16%), sterile corneal stromal necrosis (16%)

*Failed corneal transplant was recorded as the indication for surgery when original diagnosis was also given.

†This is not a comprehensive list of all complications reported.

‡CDVA reported at 1 year, which approximates the mean FU time.

§CDVA reported at 2 years, which approximates the mean FU time.

CDVA indicates corrected distance visual acuity; FU, follow-up; HSV, herpes simplex virus; IOP, intraocular pressure; PED, persistent epithelial defect; Preop, preoperative; RD, retinal detachment; RPM, retroprosthetic membrane; UCLA, University of California, Los Angeles.

preoperative CDVA in >80% of eyes. In the single study in which interval visual acuities were reported, Aldave et al[13] found a similar proportion of eyes with a CDVA ≥20/200 in the International and UCLA series at 6 (70% vs. 69%), 12 (68% vs. 63%), and 24 months (59% vs. 60%).

Complications

The most common postoperative complication was retroprosthetic membrane formation, which occurred in 25% to 45% of eyes in the 3 largest published international series (Table 1).[13,15,16] Other complications include but are not limited to intraocular pressure elevation and/or glaucoma progression (14% to 23%), sterile corneal stromal necrosis or corneal thinning (18%), infectious keratitis (0% to 12%), persistent epithelial defect (10%), and endophthalmitis (0% to 9%). Retroprosthetic membrane formation, the development of a persistent epithelial defect, and retinal detachment were reported significantly more frequently in the UCLA series ($P = 0.002$, <0.0001, and 0.017, respectively) than in the International series, although the authors acknowledged that these differences may be due to differences in reporting and the availability of diagnostic imaging devices.[13] The only complication that was found to occur more commonly in the International series was endophthalmitis (8.9% vs. 1.1%; $P = 0.0019$).[13]

Retention

As interval retention rates were provided only in a single publication on international results with the Boston keratoprosthesis, comparisons of retention rates between international centers and with previous reports from the United States are limited. However, between 81% and 100% of keratoprostheses were reported as retained at the last follow-up in the 3 largest international series (Table 1).[13,15,16] The percentage of keratoprostheses implanted that were retained at 1 year was lower in the International series as compared with the UCLA series (79% vs. 92%), but was comparable at 2 years (75% vs. 78%). No significant difference was indentified in the retention failure rates in the International and UCLA series at 1 and 2 years after surgery, even when the retention failure rates were compared for the primary indications for surgery, corneal transplant failure, and chemical injury.[13]

■ Barriers to Use Outside of the United States

Despite the recent publications indicating that the results of Boston type I keratoprosthesis implantation outside of the United States are similar to those reported by American surgeons, a number of

socioeconomic, legal, cultural, geographical, and technological barriers must first be overcome before keratoprosthesis implantation will be a viable option for the visual rehabilitation of appropriate candidates worldwide.

Physician Training and Accessibility

The paucity of surgeons trained to perform corneal transplantation in many parts of the developing world necessitates that many patients must travel long distances to obtain care with these providers. This is a formidable challenge in countries with poorly developed infrastructure and where these patients may have limited financial means and access to transportation.[18] Regular follow-up care after keratoprosthesis implantation is important because of the potential development of complications even years after surgery. In addition, as many of the postoperative complications that may develop require evaluation and management by another specialist provider, such as a retina, glaucoma, or oculoplastics specialist, access to these providers is required as well. Thus, the successful implementation of a keratoprosthesis program requires not only a trained corneal surgeon to perform the surgery and manage postoperative complications, but also a multidisciplinary team consisting of other specialists to diagnose, prevent, and manage comorbid ocular disorders that present in the majority of patients undergoing keratoprosthesis implantation.

Financial

The insufficient number of donor corneas available for use with the Boston keratoprosthesis, even those that are not deemed suitable for use for optical keratoplasty, is a significant impediment to keratoprosthesis implantation in both the developing and developed world. Reasons behind an insufficient supply of donor corneal tissue to meet the local demand may include absent or inadequate local tissue recovery and/or inability to purchase the donor corneal tissue from other sources. Inability to purchase the Boston keratoprosthesis, which currently costs $5000 in the United States, or to pay for the facility and surgeon's fees, are obviously other significant financial barriers for many patients.[3] Although the cost-effectiveness of the Boston type I keratoprosthesis has been demonstrated in the United States,[19] it is questionable whether this will be sufficiently compelling for health care policy makers in other countries to make the Boston keratoprosthesis available to all who may benefit. In addition, a patient's ability to pay for the costs associated with the postoperative care, including contact lenses, life-long antibiotic therapy, and additional surgical procedures, must be considered when determining candidacy for surgery.

Regulatory

In both developing and developed countries, legislative and regulatory restrictions apply to the use of biomedical devices such as the Boston keratoprosthesis, and approval must be obtained before the keratoprosthesis can implanted, regardless of the patient's ability to pay for the keratoprosthesis, the surgery, and the postoperative care. Obtaining such approval may prove to be a significant challenge, despite the fact that the Boston keratoprosthesis has been implanted in the United States for 2 decades.[18]

■ Future of the International Use of the Boston Keratoprosthesis

Although daunting challenges exist in trying to make the Boston keratoprosthesis available to all who would benefit, the significant increase in the number of keratoprosthesis procedures performed over the last decade is evidence of the fact that these challenges are not insurmountable. As the reported outcomes after Boston keratoprosthesis implantation have improved, the interest among corneal surgeons worldwide has increased, and the desire to offer this procedure to their patients will continue to grow. Therefore, several initiatives have been undertaken to meet this growing demand.

Physician Training and Accessibility

Although courses on the Boston keratoprosthesis have been offered at international ophthalmology meetings held in the United States for many years, only in the last several years have such courses appeared on the scientific program at national and international meetings held around the world. Formal training programs in Boston keratoprosthesis implantation, led by experienced American surgeons, are offered in various countries including India, Ethiopia, and Sudan. Training is provided in all aspects of keratoprosthesis surgery, in accordance with the International Boston Keratoprosthesis Protocol (http://www.masseyeandear.org). Various nonprofit foundations, such as Visionaries International (http://www.visionaries-international.org) are also involved in training surgeons in the developing world to perform keratoprosthesis surgery, with the goal of these surgeons training other corneal specialists in their respective countries.

Financial: Cost of the Keratoprosthesis

Although the Boston keratoprosthesis is made available at a reduced cost to surgeons in the developing world, the majority of the potential

recipients are still not able to afford the keratoprosthesis and the surgical fees. To address this financial barrier, a revised, less expensive version of the Boston keratoprosthesis, termed the LUCIA, has been developed.[20] Intended only for use in developing countries, the LUCIA is composed of the same 2 plate design and PMMA material as the Boston keratoprosthesis. However, a design modification of the back plate obviates the need for the titanium locking ring, and its production in only an aphakic model for a single axial length allows for efficient, cost-effective production. Additional cost savings are expected from transfer of responsibility for the cleaning and sterilization process to the surgeon. The LUCIA has been implanted in Ethiopia, Sudan, and India, with promising initial results.[20]

Another closely related alternative to the Boston keratoprosthesis available to keratoprosthesis surgeons in India is the AuroKPro (Aurolab, Tamil Nadu, India). Composed of the same material and design as the Boston keratoprosthesis, the AuroKPro has been implanted by surgeons across India since 2010 and is available at a fraction of the cost of the Boston keratoprosthesis. Efforts are currently underway to collect outcomes data for the AuroKPro and compare the results with those obtained in India with the Boston keratoprosthesis.

Financial: Alternatives to Fresh Donor Corneal Tissue

Although fresh cadaveric donor corneal tissue has traditionally been used as the carrier for the Boston keratoprosthesis, given the increasing demand for corneal tissue in industrialized countries and the lack of even poor-quality donor corneal tissue in the developing world, alternative sources of donor corneal tissue are being investigated and utilized. The use of the ipsilateral autologous cornea as the carrier for the Boston keratoprosthesis has been shown to be successful in a series of 4 recipients in Ethiopia and Sudan, with no cases of complications related to the autologous corneal graft during a follow-up period of 5 to 20 months.[21]

The use of long-term preserved corneas in either glycerin or albumin represents another means of reducing costs associated with the donor cornea and maximizing utilization of the donor corneal tissue supply. A recent publication reported the successful use of the VisionGraft Sterile Cornea (Tissue Banks International, Baltimore, MD), a sterile, γ-irradiated corneal tissue stored in albumin, in keratoprosthesis surgery.[22] The demonstration of successful outcomes in a series of 11 patients, with no complications attributable to the donor corneas over an average follow-up length of 16.5 months, indicates that viable keratocytes and endothelial cells are not necessary to maintaining the tectonic function of the cornea.[22] The reduced cost of the VisionGraft Sterile Cornea compared with fresh cadaveric donor tissue, and the ability to

store the corneal tissue at room temperature for up to 1 year, make it especially attractive for use with the Boston keratoprosthesis in locations where the availability and cost of cadaveric donor tissue are a concern.[22] Similarly, keratoprosthesis surgeons have also utilized frozen donor tissue as an alternative to fresh donor tissue to facilitate distribution and availability of corneal tissue for keratoprosthesis surgeons.[23]

Regulatory

Although the US Food and Drug Administration granted 510(k) clearance for the Boston keratoprosthesis in 1992, CE marking has not yet been granted, which is required of all medical devices before use in the 27 Member States of the European Union. As the manufacturer of the Boston keratoprosthesis is optimistic that CE marking will be granted soon,[24] it is hoped that approval will also be granted in other countries with similar regulations governing the sale of medical devices, such as Russia and China.

The authors declare that they have no conflicts of interest to disclose.

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