Expanding indications for the Boston keratoprosthesis

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Purpose of review

To review emerging indications for the Boston keratoprosthesis (KPro) and to discuss current research underway to improve clinical outcomes.

Recent findings

In addition to multiple failed corneal grafts, other ocular conditions for which the Boston KPro has been used include herpetic keratitis, aniridia, autoimmune ocular disorders, and pediatric corneal opacities. In the recent years, the KPro has been implanted for various other conditions and has also been explored as a cost-effective treatment for severe corneal diseases internationally. Cicatricial and inflammatory ocular conditions remain the most difficult cases for KPro use but studies investigating various immunomodulators and biologic materials for improved retention are ongoing. Postoperative management of glaucoma is critical for preserving the visual gains achieved with the Boston KPro. Current studies are evaluating novel devices for intraocular pressure measurement.

Summary

Accrued experience with the Boston KPro has demonstrated its versatility but also the difficulties that remain in postoperative management. With many studies underway to improve cost–effectiveness, intra-operative and postoperative management, keratoprostheses will be made increasingly available to those countries most in need.

Keywords

artificial cornea, Boston keratoprosthesis, corneal blindness, corneal transplant

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Introduction

The Boston keratoprosthesis (KPro), once considered as the last treatment option for patients with multiple failed corneal transplants, is increasingly being used worldwide as a promising option for many other indications. In recent years, numerous publications have reviewed various indications, outcomes, and complications of the Boston KPro [1,2•,3–6]. A retrospective single-surgeon case series by Aldave *et al.* [1] reviewed 57 KPro procedures in 50 eyes of 49 patients with various diagnoses and reported encouraging results for the use of the Boston KPro. Similarly, a retrospective study of patients with various pre-operative diagnoses who underwent the Boston KPro procedure at the Wills Eye Institute between August 2005 and October 2007 reported largely positive results with improvements in best corrected visual acuity (BCVA) of two lines or better in 92% of the patients at last follow-up [3]. Surgeons from University of California Davis, USA also reported encouraging results of the Boston KPro performed between 2004 and 2008 with a retention rate of 83.3% at a mean follow-up period of 19 months [6]. These studies reflect the growing diversity of patients undergoing the Boston KPro procedure and improvements in outcomes as a result of advancements in the Boston KPro design and postoperative management.

This article will further discuss the results of investigations published in the last year exploring emerging indications for the Boston KPro.

Boston keratoprosthesis for herpetic keratitis

Penetrating keratoplasty (PKP) in the setting of herpes zoster has a poor prognosis due to frequent graft rejection episodes, corneal vascularization, and epithelial defects requiring vigilant postoperative monitoring and care [7]. Many patients who undergo PKP following herpes zoster may eventually need an artificial cornea transplant due to graft failure. These patients may benefit from the Boston KPro as the initial treatment.

Todani *et al.* [8] reported the results of a 'KPro Triple' (Boston KPro, cataract removal, and intraocular lens placement) in a 74-year-old white female with a mature cataract and severe corneal scarring and complete corneal anesthesia secondary to herpes zoster ophthalmicus. Preoperative visual acuity was counting fingers. The patient

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underwent primary KPro placement without prior PKP. Uncorrected visual acuity postoperatively was 20/25 at 1 month and was maintained at 7 months of follow-up.

Pavan-Langston and Dohlman also reported remarkable improvement in visual acuity in a 95-year-old male with a severely diseased cornea following an episode of herpes zoster in the right eye 10 months prior to presentation. The course of the disease was complicated by a fungal ulcer and subsequent descemetocele with impending perforation. After undergoing the Boston KPro procedure with extracapsular cataract extraction, his pre-operative visual acuity of light perception improved to 20/60 over the course of 4 months [9].

Khan *et al.* [10] reported success of the Boston KPro in a study of 17 eyes in 14 patients who had repeatedly failed traditional corneal grafts. All 14 patients had undergone 2–5 keratoplasties prior to the Boston KPro. Of 14 patients, 12 had a history of either herpes zoster or herpes simplex as the initial diagnosis necessitating a corneal transplant. The other two patients had keratoconus and later developed herpetic keratitis in their corneal graft. Pre-operative visual acuity ranged from light perception to 20/200 with most patients in the lower range of this spectrum. BCVA following KPro placement ranged from 20/25 to 20/70 in 15 of 17 eyes, and 11 of 15 eyes maintained visual acuity at the end of the study. No complications were reported in 10 of 14 patients over the course of their follow-up that ranged from 7 to 39 months. The remaining patients experienced complications from progression of pre-existing glaucoma or new-onset sterile vitritis [10].

In patients with severe corneal disease following complicated herpes zoster or herpes simplex, traditional corneal transplants are known to have a poor prognosis with a high rate of graft failure; the Boston KPro may be a reasonable first-line approach to treatment for these patients.

Boston keratoprosthesis for children

As in cases of pediatric lens opacities, appropriate treatment of corneal disease in young children is crucial in preventing stimulus deprivation amblyopia [11]. To date, PKP remains the primary treatment for children with visually significant corneal disease undergoing their first corneal surgery, although the visual results following PKP can be limited by surgically induced astigmatism. Additionally, the robust immune response in children often complicates the postoperative course after a traditional PKP with prolonged time to recovery and risk of neovascularization extending into the visual axis over time [12]. Huang *et al.* [13] reported that in a study of 60 primary grafts, approximately 42% of the grafts required a repeat transplantation with little improvement in visual acuity. Progression to phthisis bulbi following PKP was reported in nine cases. Pre-operative or postoperative glaucoma was reported as a significant risk factor for decreased graft survival.

Key points

- The Boston keratoprosthesis (KPro), once considered a last option following multiple unsuccessful penetrating keratoplasties, may be a reasonable first-line treatment for certain conditions deemed likely to fail a traditional corneal graft.
- Studies investigating immunomodulators and further exploring inflammatory pathways are underway but Boston KPros remain challenging in children and in inflammatory ocular conditions including autoimmune and cicatricial diseases.
- With international interest in the KPro as a potential treatment for debilitating corneal diseases in developing countries, there is a great push to improve and simplify postoperative management, to broaden indications, and to discover more ways to increase cost–effectiveness.

Nallasamy and Colby [12] recently illustrated the potential benefits and difficulties of using the Boston KPro in children in a case report of a baby girl who underwent the Boston KPro for a large progressive congenital lacrimal gland choristoma that extended into the visual axis. An aphakic Boston KPro was placed in the child's left eye at 6.5 months of age with a clear visual axis immediately following surgery. Elevated intraocular pressure and retroprosthetic membrane (RPM) formation complicated the postoperative course. Following RPM removal, intracameral bevacizumab injection, and pars plana vitrectomy with Ahmed valve placement, the patient's eye was quiet and had a clear red reflex by 11.5 months of age.

The Boston KPro allows more rapid visual recovery compared to a standard PKP, and this can facilitate amblyopia management in children in whom prolonged visual deprivation can be very harmful to the normal development of vision. Dunlap *et al.* [14] reported that approximately 25% of their study's 122 patients (126 eyes) achieved BCVA within the first postoperative week. Of note, the youngest patient in this study was 5 years of age.

In a study of 22 eyes of patients 1.5–136 months of age, Aquavella *et al.* [15] demonstrated that the visual axis can remain clear for a significant period following KPro surgery (mean of 9.7 months) with good device retention. Of the 22 eyes, 21 had Boston KPros implanted, and no extrusion was reported in these cases. An extruded

AlphaCor KPro initially implanted in one eye was replaced with a Boston KPro.

The risk of developing RPMs or glaucoma and the necessity of lifelong management must be considered in the placement of a Boston KPro in a child. With advances in management of postoperative complications and further experience with pediatric keratoprostheses, the Boston KPro may become increasingly valuable in the management of pediatric corneal opacification, although these cases remain challenging at present.

Boston keratoprosthesis for autoimmune disease

Patients with ocular disorders of autoimmune causes are often poor candidates for a traditional PKP given the common association with corneal limbal stem cell deficiency and ongoing ocular surface inflammation. Autoimmune diseases such as Stevens–Johnson syndrome and mucous membrane pemphigoid (MMP) are well established to have the least favorable prognosis for long-term Boston KPro success [16]. The high incidence of donor tissue melt and retraction surrounding the central stem of the prosthesis makes the use of the Boston KPro in autoimmune eye diseases very challenging [17]. Corneal melting in autoimmune eye disease is thought to be due to the heightened inflammatory response intrinsic to the pathogenesis of autoimmune diseases. The poly-(methylmethacrylate) (PMMA) backplate of the KPro has been suggested as a possible instigator of inflammation and subsequent corneal necrosis [17]. The scant tear film observed in autoimmune ocular disorders allowing increased microbial activity and proliferation may also contribute to ongoing inflammation and subsequent corneal melt [17].

An in-vitro study comparing cell proliferation and cell death of human corneal–limbal epithelial (HCLE) cells exposed to either PMMA or titanium demonstrated superiority of titanium as measured by HCLE survival and proliferation [18]. Early clinical work suggests that the titanium backplate is associated with reduced RPM formation [19], although no data exist at the moment regarding whether the titanium backplates will reduce tissue melt in patients with autoimmune diseases.

Several recent reports have been published on KPro in autoimmune diseases including toxic epidermal necrolysis (TENS), MMP, and autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) [17,20,21]. One series reported two complicated cases in a patient with TENS and one with MMP who required repeated Boston KPro procedures over 2–7 years [17]. The patient with TENS required four Boston KPro procedures due to repetitive corneal melts over the course of 3 years. BCVA after the first Boston KPro was 20/40 in the left eye improved from counting fingers in both eyes. The final implanted Boston KPro remained stable at the 7 months follow-up visit and BCVA of 20/70. The patient with MMP who presented with visual acuity of hand motions in both eyes underwent two type II Boston KPro procedures in the right eye and one in the left eye due to extrusions. Eventually, the patient underwent a total tarsorrhaphy in the right eye, and the type II Boston KPro that was subsequently implanted in the left eye was stable and provided the patient with uncorrected visual acuity of 20/30 at 6 months [17]. Other publications have been more encouraging with reports of successful KPro retention and significant improvement in visual acuity during a 2-year postoperative period. In these reports, the patients (two cases of APECED and one case of TENS) had exhibited severe corneal involvement on pre-operative examination and deemed likely to fail a traditional PKP procedure [20,21]. The two patients with APECED had an initial BCVA of 20/400 and 20/100, respectively, which improved to 20/40 with the Boston KPro in both cases. Their visual acuity remained stable over the 2-year follow-up period with no postoperative complications [21].

In comparing cases of KPros in autoimmune disease, differences in severity of the corneal disease including the extent of limbal stem cell loss at initial presentation, the type of KPro backplate utilized in each case (titanium or PMMA), and postoperative management must be considered when evaluating outcomes. At the current time, these cases remain the most problematic for the KPro surgeon. Further understanding of the pathogenesis of the associated complications and advancements in use of systemic immunologic modulators are necessary to surmount the challenges of KPro use in autoimmune diseases.

Boston keratoprosthesis for aniridia

Congenital aniridia is a bilateral disease attributed to mutations on chromosome 11 in PAX6 [22]. This disease affects multiple structures within the eye including the cornea, iris, lens, retina, macula, and optic nerve. Aniridia-associated keratopathy (AAK) results from invasion by conjunctival stem cells, and the poor prognosis of traditional corneal grafts in these patients is due to the lack of limbal stem cells [22]. Stem cell replenishment from a living-related or cadaveric donor is one treatment approach for AAK. However, systemic immunosuppression is necessary, and benefits gained from the treatment can be short-lived. The Boston KPro with its optic surrounded by donor tissue avoids the problem of conjunctival growth into the visual axis and also has an added aesthetic benefit of the titanium backplate emulating an iris.

A retrospective multicenter study from 2007 showed that, in a group of 15 patients (16 eyes) predicted to fail a traditional corneal graft, all but one patient experienced improved visual acuity from a median of counting fingers to 20/200 after undergoing a Boston KPro procedure [23]. No extrusions were reported throughout the follow-up period which ranged from 2 to 85 months. Additional procedures including tube shunts and pars plana vitrectomy were necessary in some patients. Further investigation of the Boston KPro as a standard treatment approach to AAK is warranted and underway, but results thus far are promising.

Boston keratoprosthesis for other indications

Other pre-operative diagnoses for which the Boston KPro has been used include atopic keratoconjunctivitis, medication toxicity, keratoconus, and other corneal dystrophies [1,3]. Chew *et al.* [3] reported diverse original diagnoses in 37 patients who underwent the Boston KPro including pseudophakic bullous keratopathy, aniridia, iridocorneal endothelial syndrome, keratoconus, various other corneal dystrophies, trauma, and tumor. Many of these patients (29) had undergone previous PKP. Overall success rate in this group was high with good retention rates and improvement in BCVA ($\geq$20/50 in 16 patients at last follow-up and in 25 patients at some point over the follow-up period). Those patients that did not demonstrate much improvement in BCVA had pre-existing ocular comorbidities.

The Boston KPro has also been successfully used in cases of ocular trauma including chemical (21 eyes), mechanical (six eyes), and thermal injury (three eyes) [24]. In 30 patients (30 eyes), pre-operative visual acuity ranging from counting fingers to light perception improved to postoperative visual acuity ranging from 20/20 to no light perception. Postoperative complications including glaucoma continue to be a challenge especially following chemical injury.

Binocular vision restoration has recently been posed as another possible advantage of the Boston KPro. Pineles *et al.* reported 20 patients with relatively preserved (>20/50) BCVA in the contralateral eye who underwent Boston KPro placement. Of the 17 patients who underwent binocular testing, 16 showed binocular function following surgery [25]. The possibility of binocular vision may be a benefit that patients and ophthalmologists may want to discuss in select cases with relatively intact visual acuity in the contralateral eye.

The use of the Boston KPro in conjunction with pars plana vitrectomy and silicone oil injection to treat chronic hypotony and corneal opacification has also been recently reported [26]. Three monocular patients with chronic hypotony in their functional eye were treated with permanent keratoprostheses. Improvement in visual acuity from pre-operative to postoperative examination for the three patients were counting fingers at 1 foot to 2/200, light perception to hand motion, and light perception to 20/800 with functional vision achieved in two out of three patients. The follow-up ranged from 11 to 13 months, and at the last visit, all three of the KPros were still in place with no RPM or epithelial defects and with a quiet anterior chamber. Eyes which otherwise may have failed another corneal graft and eventually progressed to phthisis bulbi were salvaged with some improvement in visual function.

International use of the Boston keratoprosthesis

A recent study by Ono *et al.* [27] showed that corneal blindness secondary to trachoma is unevenly distributed in the world with lower income countries shouldering the heaviest burden of this disease. Unfortunately, corneal transplants and appropriate postoperative follow-up and management are challenging to execute in these countries that have inadequate funding and resources. The Boston KPro may be a promising option for these countries that have limited access to medications and high-quality corneal donor tissue.

A recent publication by Ament *et al.* [28••] explored the challenges that developing countries such as China, India, and Ethiopia face in treating blinding corneal diseases. Public sanitation, climate, and limited resources including financial support and trained medical personnel are only a few of the obstacles that must be overcome. In these countries, medical treatments that are both effective and affordable are crucial. The Boston KPro has demonstrated both of these qualities in the USA. In the multicenter Boston Type I Keratoprosthesis study, the KPro had a retention rate of 95% at an average follow-up of 8.5 months and no incidence of bacterial complications [29]. A retrospective cohort study in the USA showed that the Boston KPro is highly cost-effective and comparable with the cost utility of a traditional PKP [30••]. India is developing a more affordable version of the Boston KPro, and countries like China continue to show interest in participating in an international KPro program [28••].

The possibility of using ipsilateral autologous corneal tissue instead of allograft donor tissue has been explored in Africa as another cost-effective approach to the KPro procedure [31]. The study consisted of four eyes of three patients who were bilaterally blind according to the WHO criteria. Aphakic Boston KPros were used, and all patients experienced improvements in daily activities and in uncorrected visual acuity [31]. Although it was a

small study, its promising results warrant further investigations to uncover more ways of providing appropriate and affordable treatment to these countries with limited resources.

Conclusion

The Boston KPro has preserved, and in many cases, improved the vision of patients with no other remaining treatment options. Despite advancements in design and increasing success of the Boston KPros for novel indications, significant hurdles remain for the use of the Boston KPro in highly inflammatory, cicatricial, or autoimmune ocular disorders. Given the lower retention rate of KPro in these conditions, there is continuing interest in the use of various biologic coatings and scaffolds for improved KPro integration [32]. Systemic immunomodulators including monoclonal antibodies to pro-inflammatory cytokines are currently being explored as another strategy for improving KPro integration and retention [33,34]. Infliximab, a monoclonal antibody to tumor necrosis factor-α shown to relieve systemic inflammatory conditions, has successfully been used in the postoperative management of the Boston KPro. A case report of a woman with Stevens–Johnson syndrome and two failed type II Boston KPros received monthly infusions of infliximab after the third implant and subsequently retained the KPro without necrosis or leakage for more than a year postoperatively [33]. Unfortunately, systemic immunomodulators such as infliximab have adverse effects that warrant regular laboratory testing and close clinical follow-up. Cost and the necessity of frequent infusions must also be considered. Further investigation and understanding of inflammatory pathways and the mechanism of systemic immunomodulators in the eye are necessary to improve the clinical outcome of the Boston KPro in inflammatory ocular conditions.

RPM formation remains the most common postoperative complication following Boston KPro placement, occurring in up to two-thirds of patients. While frustrating for the patient and the surgeon, RPMs usually can be readily managed by YAG membranotomy, although occasional dense or vascularized membranes may require surgical removal or replacement of the KPro. Improvements in technique of YAG laser removal of RPM would be ideal as it is an outpatient and relatively time and cost-effective treatment option compared with surgery. However, effectively treating RPMs using YAG laser without damaging the optic can be challenging given the close proximity of the membrane to the optic. Chak and Aquavella [35] recently described a 'can opener' method of dissolving RPMs in 26 eyes with only two requiring surgical removal. Thicker RPMs require more laser energy and, hence, are less likely to be resolved with YAG treatment. More research in managing one of the most common complications of the Boston KPro and a clearer understanding of the mechanism of RPM formation is necessary in further improving clinical outcomes. A recent study by Stacy *et al.* [36] described the histopathology of RPM in four cases requiring KPro replacement. These results demonstrate that the RPM is formed by migration of host keratocytes through gaps in the posterior aspect of the graft–host junction, suggesting that a larger backplate that 'clamps' the posterior wound may help reduce the incidence of RPM formation. Studies evaluating this hypothesis are currently underway.

Postoperative infection has been virtually eliminated by the addition of prophylactic antibiotics following KPro surgery but this situation requires patient compliance. Recent work suggests that it may be possible to maintain sustained release of antibiotics with drug-eluting contact lenses, which may facilitate postoperative management [37]. The risk of corneal melting has been greatly reduced in nonautoimmune patients by the use of a bandage contact lens but use of amniotic membrane for melts that do occur has recently been reported [38].

Glaucoma remains the single largest threat to long-term preservation of vision following Boston KPro surgery. Several recent reports have been published on new approaches to treating these conditions utilizing various shunts and surgical techniques, as well as adjunctive cyclophotocoagulation to decrease intraocular pressure and divert fluid [38,39•,40,41]. Concerns with techniques involving shunts draining to epithelialized compartments include the risk of endophthalmitis, although a recent clinical case series of 34 patients with modified Ahmed valves connected to tubes draining to various sinuses (lacrimal, ethmoid, or maxillary) or lower lid fornix demonstrated a low incidence of endophthalmitis (0.7% per shunt year) [39•]. Of the 34 patients, 31 had a Boston KPro implanted, and 33 had end-stage glaucoma pre-operatively. Mean follow-up period was 4 years and 3 months. Four eyes developed hypotony, and three exposed valves were removed. A study published in 2004 of 19 patients with keratoprostheses and modified Ahmed valves draining to sinuses also reported no shunt related endophthalmitis [41]. Cyclophotocoagulation, which involves the use of laser to reduce the amount of fluid generated by the ciliary body, has also been explored as an adjunct to valves for treatment of refractory glaucoma. Diode laser transscleral cyclophotocoagulation (DLTSC) was used in a study of 18 patients (18 eyes) with refractory glaucoma and KPro implanted before, during or after DLTSC [40]. The mean follow-up period was 26.6 ± 19.6 months (mean $\pm$ SD). Complications including fungal endophthalmitis and conjunctival dehiscence occurred in two patients. Intraocular pressure was normalized in 67% of eyes with six eyes requiring repeat DLTSC. These results are promising

but also illustrate the difficulties that remain to be resolved in maintaining appropriate intraocular pressure in KPro patients.

Monitoring intraocular pressure also remains a challenge in the postoperative management of the Boston KPro. An animal study in rabbits explored the possibility of an implantable intraocular pressure (IOP) transducer [42]. The device is a donut-shaped single microchip placed in the ciliary sulcus. It was well tolerated with little irritation and demonstrated measurements of IOP correlating well with those obtained by a Tonopen. Long-term studies are underway to further the successful application of intraocular IOP transducers in humans.

Much progress has been made in the use of the Boston KPro over the past decade. The current device is safe and effective in a wide variety of conditions and provides for rapid return of vision. However, continued research to improve outcomes and broaden indications for the Boston KPro is necessary to address the more global need for an effective, affordable, and feasible treatment option in those developing countries most affected by debilitating corneal diseases.

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Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 306).

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