NICE advice

Boston Keratoprosthesis Type I for corneal blindness

Medtech innovation briefing
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Summary

- The **technology** described in this briefing is the Boston Keratoprosthesis Type I (Boston KPro I). It is an artificial cornea used to provide a transparent optical pathway into the eye of people with corneal blindness, in whom corneal transplant may not be suitable.
- The **innovative aspects** are that compared with other available keratoprostheses, the Boston KPro I is available off the shelf and does not need to be specially made for each patient so it can easily be resupplied after corneal graft failure. When needed, the device can also be customised. It is implanted in a 1-step process. Other than the keratoprosthesis procedure, few treatment options are available for people for whom standard corneal transplant (penetrating keratoplasty) is not suitable.
- The intended **place in therapy** would be after penetrating keratoplasty has failed, or if it is unlikely to succeed, such as in people with severe corneal opacity with wet blinking eyes. The Boston KPro I is assembled around a corneal graft before insertion into the person's eye.

- The **key points from the evidence** summarised in this briefing are from 9 studies (n=1,202 eyes of 1,162 patients in total) published since NICE produced the interventional procedures guidance on implantation of a corneal graft–keratoprosthesis for severe corneal opacity in wet blinking eyes. Two of the studies were prospective and 7 were retrospective. They showed that Boston KPro I improved visual acuity and was more effective than penetrating keratoplasty in patients with severe corneal opacity who have already had a failed corneal graft.
- **Key uncertainties** around the evidence are that the studies do not report which version of the Boston KPro I was used, and that most of the studies are retrospective. None of the studies were done in the UK, so the findings may not be generalisable to wider NHS populations.
- The **cost** of the Boston KPro 1 is about £2,094 per unit (exclusive of VAT). This cost is approximate because the technology is not widely used in the NHS.

The technology

The Boston Keratoprosthesis Type I (Boston KPro I; Massachusetts Eye and Ear Infirmary) is an artificial cornea that can be used in people with severe corneal opacity, a condition caused by scarring or clouding of the cornea that can lead to blindness.

The current model of the Boston KPro I is the 'Snap-on' model of the device (several other versions of the KPro have previously been available). The Boston KPro I consists of 3 sterilised components that have better optical properties than donor corneal grafts, for example, reducing glare from light passing through the device (Sayegh et al. 2010). The 3 components are:

- a front plate, made of clear polymethyl methacrylate (PMMA) plastic, with a central stem
- a titanium back plate which is 8.5 mm in diameter for adult models and 7.0 mm in diameter for paediatric models
- a titanium locking ring.

An assembly tool (used to secure the locking ring onto the stem of the front plate) and an adhesive patch (used as an aid to hold the front plate steady during the assembly process) are included with the device. The Acuderm, a 3 mm disposable skin biopsy

punch, is also supplied with the device.

The Boston KPro I is assembled around a donated corneal graft before insertion into the person's eye. The corneal graft is prepared and a central hole is made in it with the Acuderm punch so that it will fit over the stem. For stability, the front plate of the Boston KPro I can be placed upside down on the adhesive patch. The graft is then placed over the Boston KPro I front plate and the assembly tool is used to gently push it down over the stem. Viscoelastic material is applied to the back surface of the graft and the back plate is placed over the stem without any rotating movement.

The locking ring is pressed onto the stem with a finger and the assembly tool is used to press the locking ring firmly into the groove (usually with an audible snap). The keratoprosthesis should be inspected under the operating microscope for correct assembly.

When fully assembled, the Boston KPro I device has the shape of a collar-button and the front plate acts like a lens. The central portion of the person's opaque cornea is removed, and if the natural lens is in place, it is also removed. The prosthesis is then transferred to the person's corneal opening and secured as in standard transplantation. After the procedure, a soft contact lens is applied to the surface and worn permanently. The person needs to use eye drops throughout their life to prevent endophthalmitis.

The device is available for both pseudophakic eyes (eyes in which the natural lens is replaced with an intraocular lens) and aphakic eyes (absence of the lens due to surgical removal, a perforating wound or ulcer, or congenital anomaly).

The innovation

Implantation of an artificial cornea (keratoprosthesis) is one of few treatment options available for people with severe corneal opacity in wet blinking eyes in whom standard corneal grafts have failed or are not suitable. The Boston KPro I is a 1-step procedure unlike Alphacor, the only other CE-marked artificial cornea for wet blinking eyes that has been used on a wide scale, which is implanted in 2 stages separated by a period of 2 to 3 months.

In pseudophakic eyes, the Boston KPro I keratoprosthesis procedure can be easily repeated if the first implant fails, because it is available off the shelf and does not need to be specially made for patients (Avadhanam et al. 2015). In aphakic eyes, the Boston KPro I

needs to be customised for people based on the axial length of the eye.

According to the manufacturer, the double-plated (collar-button) Boston KPro I design has advantages over designs in which the optical stem is anchored by a flexible looping extension placed within or in front of the person's cornea. It is thought that positioning the Boston KPro's back plate entirely behind the corneal tissue may give better long-term retention than other arrangements (Cruzat et al. 2013).

The Boston KPro I can restore sight for several years. The main reason for eventual vision loss after implantation is post-operative glaucoma (Ahmad et al. 2015).

Current NHS pathway

Standard treatment for significant corneal opacity is a full-thickness corneal transplant, known as penetrating keratoplasty (PK). During PK, the opaque cornea is removed using a trephine (hole saw) and replaced with a donor cornea. Some people cannot have PK for reasons including: disease severity; severe involvement of the conjunctiva; a failed previous corneal transplant; or when measures needed to prevent graft rejection are contraindicated. For these patients, PK using an artificial cornea (keratoprosthesis) may be an option.

NICE interventional procedures guidance on implantation of a corneal graft–keratoprosthesis for severe corneal opacity in wet blinking eyes found that the current evidence on the efficacy of this procedure was adequate in the short to medium term. The evidence on safety showed a high incidence of significant adverse effects, but it concluded that there are few options for patients with severe corneal opacity if standard corneal grafts have failed or are not appropriate. The guidance recommended that this procedure may be used with normal arrangements for clinical governance, consent and audit.

NICE is aware of the following CE-marked devices that appear to fulfil a similar function as Boston KPro I:

- AlphaCor KPro (Argus Biomedical).
- KeraKlear Artificial Cornea KPro (KeraMed).
- Legeais BioKPro-III (FCI Ophthalmics).

Population, setting and intended user

Boston KPro I would be used in a tertiary care setting. The implantation procedure would be done in a specialist ophthalmic operating theatre on a patient who has had a general or a local anaesthetic. It is typically a day case procedure.

Boston KPro I should only be used by surgeons specialising in the implantation of corneal grafts or keratoprostheses. Based on the indications for use, the device is likely to be used in people with severe corneal opacity:

- who have had at least 1 failed graft
- in whom standard donor grafting is unlikely to be successful
- who need a repeat PK but cannot have systemic immunosuppression
- who have high-risk features such as total limbal stem cell loss, deep corneal neovascularisation, but whose blink and tear mechanisms are reasonably intact (wet blinking eyes)
- whose vision in the eye being considered for grafting is poorer than 6/60 (metric) and who have reduced vision of 6/12 in the opposite eye.

The Boston KPro I is not suitable for people with retinal detachment or extreme optic nerve cupping.

The instructions for use for Boston KPro I (Massachusetts Eye and Ear Infirmary 2014) describe any additional training needed to use this technology.

Costs

Device costs

The Boston KPro I costs $3,000 (USD) within the EU, about £2,904 (excluding VAT). A shipping fee is charged in addition to this.

Costs of standard care

The NHS tariff for PK is around £1,500 (NHS 2015 [see papers January 2016, 'Letter re PbR

Tarriffs']). However, tariffs can underestimate the full long-term costs of a procedure.

The NICE interventional procedures guidance on implantation of a corneal graft–keratoprosthesis for severe corneal opacity in wet blinking eyes states that antibiotics and steroids can be used in conjunction with PK and keratoprosthesis. The manufacturer recommends that levofloxacin (around £7 for a 5-ml bottle) and vancomycin (£12.50 for a 1-g powder concentrate for solutions) are used post-operatively. Corticosteroids can cost around £30 to £80 for a pack of 30 tablets, which is about £3 to £8 per dose (British national formulary [BNF] 2016). Specialist commentators noted that bandage contact lenses are also used after the operation. One commentator indicated that they cost £9 for a pack of three, and another stated that they cost £12.25 per lens.

Resource consequences

No other practical difficulties have been identified in using or adopting the technology.

The Boston KPro I is currently used in 2 NHS centres. Limited use in the NHS makes it difficult to estimate the costs associated with using the Boston Pro or to compare them with relevant current practice.

No published evidence on the resource consequences of adopting the Boston KPro 1 were found in the systematic review on cost effectiveness.

Regulatory information

The Boston KPro Type I was CE marked as a class II, category B device in 2014.

A search of the Medicines and Healthcare Products Regulatory Agency website revealed that no manufacturer Field Safety Notices or Medical Device Alerts have been issued for this technology.

Equality considerations

NICE is committed to promoting equality, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. In producing guidance and advice, NICE aims to comply fully with all legal obligations to:

promote race and disability equality and equality of opportunity between men and women, eliminate unlawful discrimination on grounds of race, disability, age, sex, gender reassignment, marriage and civil partnership, pregnancy and maternity (including women post-delivery), sexual orientation, and religion or belief (these are protected characteristics under the Equality Act 2010).

In people aged 50 and over, age-related conditions (such as Fuchs' endothelial dystrophy) or inherited corneal dystrophies may cause severe corneal opacity that can be painful, disfiguring and blinding. Also, in 10% to 20% of younger people with advanced keratoconus (severe and rapidly progressive disease) the cornea will eventually become too scarred or will not tolerate a contact lens and the diseased tissue will need to be replaced with a donor cornea (corneal transplant). Men may be at higher risk for corneal diseases than women. Keratoconus is more common in certain ethnic groups, particularly in people of Asian family origin. People who are registered as blind or sight impaired are deemed to have a disability. Other visually impaired people may be considered to have a disability if their condition significantly affects their ability to carry out daily activities in the long term. Age, sex, race and disability are protected characteristics under the Equality Act 2010.

Clinical and technical evidence

A literature search was carried out for this briefing in accordance with the published process and methods statement. This briefing includes the most relevant or best available published evidence relating to the clinical effectiveness of the technology. Further information about how the evidence for this briefing was selected is available on request by contacting mibs@nice.org.uk.

Published evidence

Evidence published on the efficacy and safety of the device before January 2015 is included in the NICE interventional procedures guidance on implantation of a corneal graft–keratoprosthesis for severe corneal opacity in wet blinking eyes and so has not been included in this briefing. Nine studies (2 prospective and 7 retrospective) including a total of 1,162 patients (1,202 eyes) were selected for inclusion and are summarised in this briefing.

Of the 2 prospective studies, 1 reported visual acuity improvement after implantation with

the Boston KPro Type I (Boston KPro 1; Rudnisky et al. 2016), and the other reported a higher incidence of bacterial microbiota colonising the ocular surface of patients' eyes with Boston KPro I implantation compared with the patients' untreated eyes (Jassim et al. 2015).

Of the 7 retrospective studies, Akpek et al. (2015) and Ahmad et al. (2016) reported greater visual improvement, and greater likelihood of maintaining the visual improvement, with Boston KPro I compared with repeat penetrating keratoplasty (PK). Additionally, Akpek et al. reported less frequent graft failure for the Boston KPro I. Fadous et al. (2015) reported better visual acuity for people who had Boston KPro I as a primary penetrating corneal surgery compared with the Boston KPro I as a secondary procedure (after a failed PK), with similar complication rates. In a non-comparative study, Goins et al. (2016) reported that although Boston KPro I implantation was associated with satisfactory visual acuity outcomes and device retention, serious postoperative complications were common.

Two studies compared visual acuity and complications in patients with and without Stevens–Johnson syndrome (Alexander et al. 2015) and in eyes with and without limbal stem cell deficiency (Aravena et al. 2016). The studies found that Boston KPro I was an effective means to restore vision in individuals in people with these co-morbidities. However, Chan et al. (2016) reported a higher incidence of KPro-corneal melt-related complications in patients with severe ocular surface disease than in those without.

Strengths and limitations of the evidence

Seven of the studies were weakened because they were retrospective in design. All but 3 (Akpek et al. 2015; Fadous et al. 2015; Ahmed et al. 2016) were non-comparative studies that evaluated the Boston KPro I without a control group. The rest of the studies compared outcomes on the same eye before and after the implantation of the Boston KPro I. Although the lack of a control is a limitation of the evidence base, the intended use of Boston KPro I is as a secondary treatment option after PK has failed, and this reduces the opportunity for comparative studies in this field. Instead, the patient becomes their own historical control.

Two studies, Alexander et al. (2015) and Aravena et al. (2016), were done in the same centre, so there could be some overlap in the populations. In their analysis, Aravena et al. included 10 patients with limbal stem cell deficiency who also had Stevens–Johnson syndrome, but because of different recruitment periods it is unclear whether the same patients were also included in the study by Alexander et al.

None of the 9 studies were done in the UK, which may affect their generalisability to the NHS because standard care may differ. It is unclear which version of the Boston KPro I has been used in any of the studies other than in Fadous et al. (2015). The description of the procedure was also generally poor. The studies had long recruitment periods, covering different versions of the technology with most being done before 2014. Most of the studies reported visual acuity or graft survival outcomes with up to 2 years of follow-up for all patients. Longer follow-up periods would have been more informative on the long-term outcomes of this procedure.

The study by Akpek et al. (2015) was a comparative study but participants were not randomised. People having Boston KPro I implantation tended to have a more complicated ocular history. Also, the study was done in a single tertiary care practice, which could lead to selection bias towards including patients with more complex eye conditions and possibly lower visual potential and higher chances of failure with successive donor PK than in previously reported series. However, it is noted that patients with more complex eye conditions may be the most appropriate population to have the Boston KPro I. Post-operative care was not standardised in either group but was instead designed to suit each patient, leading to potential performance bias.

Although the Aravena et al. (2016) study compared the outcomes of Boston KPro I implantation in eyes with limbal stem cell deficiency with those without the condition, it would have been more relevant to compare it with other procedures for managing limbal stem cell deficiency.

The study by Rudnisky et al. (2016) was sponsored (but not funded) by the manufacturer, which could be a source of bias.

Table 1 summarises the clinical evidence for the device as well as its strengths and limitations.

Table 1 Summary of selected studies

Study size, design and location	Intervention and comparators	Outcomes	Strengths and limitations

Ahmad et al. (2016) 174 eyes of 165 patients Retrospective case series Multicentre US	Boston KPro I initial implantation (n=112). Boston KPro I (n=36) repeat implantation. Follow-up period: 2 years.	Visual acuity improved in two-thirds of eyes after the repeat KPro 1 implantation. The probability of maintaining visual acuity was significantly better for the first implantation compared with repeat implantation. Better vision before explantation and immediately after repeat KPro 1 implantation were significant predictors of the ability to maintain vision of 20/200 or more.	Small sample size for repeat KPro 1 implantation. Follow-up periods to assess maintenance of visual acuity differed between the 2 comparisons. Unclear which version or model of Boston KPro I was used.
Aravena et al. (2016) 149 eyes of 149 patients Retrospective cohort study Single-centre US	Boston KPro I (n=149). No comparator intervention. Treated eyes were compared with non-treated eyes. Follow-up period: 5 years.	A significantly greater percentage of eyes with corneal LSCD had improved visual acuity at each of the first 5 years after surgery. Persistent corneal epithelial defect was the only postoperative complication more common in eyes with LSCD compared with eyes without LSCD. Retention failure rates in eyes with and without LSCD were similar.	Unclear which version or model of Boston KPro I was used. The study was carried out at the same location as the Alexander et al. (2015) study and there may be some overlap in the populations.

Chan et al. (2016) 128 eyes of 110 patients Retrospective cohort study Single-centre US	Boston KPro I (n=128). No comparator intervention. Mean follow-up period: 29 months.	Patients in the cohort with severe ocular surface disease who had Boston KPro I implantation experienced more corneal melts, leaks, and extrusions than those without severe ocular surface disease.	This was a large cohort with a long follow-up (29 months on average). Unclear which version or model of Boston KPro I was used.
Goins et al. (2016) 75 eyes of 75 patients Retrospective cohort study Single-centre US	Boston KPro I (n=75). No comparator. Mean follow-up period: 41.4 months.	Improved vision was recorded in more eyes than full functional vision. The first device was retained in most eyes with Kaplan–Meier retention probability decreasing between 6 months and 5 years. One or more sight-threatening complications occurred in more than half of the eyes.	Unclear which version or model of Boston KPro I was used.
Rudnisky et al. (2016) 300 eyes of 300 patients Prospective cohort study Multicentre US	Boston KPro I (n=300). No comparator. Mean follow-up period: 8.5 months.	After Boston KPro I implantation: • visual acuity improved significantly • significantly fewer eyes had light perception, but a small percentage progressed to no light perception • visual prognosis was best in eyes with chemical injuries, and worst in eyes with aniridia.	This was a prospective but non-comparative cohort study. Unclear which version or model of the Boston KPro I was used.

Akpek et al. (2015) 80 eyes of 80 patients Retrospective, non-randomised case series Single-centre US	Boston KPro I (n=27). Repeat PK (n=53). Mean follow up: 19.5 months in the PK group and 16.5 months in the KPro group.	In the post-operative period, a greater percentage of eyes with the Boston KPro I attained visual acuity than eyes having PK, but a greater percentage of eyes with PK kept this visual acuity for longer. The 2-year cumulative rate of graft failure was higher for eyes with PK. Post-operative complications were similar for both groups.	Non-randomised case series, with a short follow-up period. Unclear which version of the technology was used.
Alexander et al. (2015) 209 eyes of 209 patients Retrospective comparative case series Multicentre (US, India, Philippines)	Boston KPro I (n=209). No comparator intervention. Follow-up period: patients with SJS (17.6±16.2 months), patients without SJS (29.3±22.8 months.	A significantly greater percentage of patients with SJS had a corrected distance visual acuity 12 months after surgery compared with those without SJS. Postoperative complications were more common in patients with SJS, which led to a higher retention failure rate and secondary surgical procedures. But, after repeat implantation, eyes in patients with SJS were no less likely to retain a keratoprosthesis than those of patients without SJS.	Unclear which version of the technology was used.

Fadous et al. (2015) 70 eyes of 70 patients Retrospective comparative study Single-centre Canada	Boston KPro I as a primary penetrating corneal surgery (n=30). Boston KPro I as a secondary penetrating corneal surgery (n=40). Follow-up period: 12 months.	Throughout the follow-up period, visual acuity was significantly better in patients who had KPro I as a primary procedure. At 12 months, more eyes had a best-corrected visual acuity in this group than in the group having the device as secondary treatment. The complication and retention rates were similar in the 2 groups.	The threadless 'Snap-on' KPro I with a PMMA backplate and 16 holes was used for all patients.
Jassim et al. (2015) 43 eyes of 26 patients Prospective cohort study Single-centre US	Boston KPro I (n=27). Untreated eyes as the control group (n=16). Follow-up period: over 6 months.	There were more cultures with bacterial microbiota from eyes with the KPro I than from control eyes (healthy eyes from the same patients).	This was a prospective study with a small sample size. Unclear which version or model of the Boston KPro I was used.
Abbreviations: Boston KPro I, Boston Keratoprosthesis Type I; LSCD, limbal stem cell deficiency; PK, penetrating keratoplasty; SJS, Stevens–Johnson syndrome.			

Recent and ongoing studies

One ongoing trial using Boston KPro I was identified.

NCT01950598: a prospective, single-blind, randomised controlled trial to determine the safety and efficacy of using frozen corneas as carriers with the Boston KPro I compared with fresh corneas over long-term follow-up. The estimated completion date is January 2020.

Specialist commentator comments

Comments on this technology were invited from clinical experts working in the field and relevant patient organisations. The comments received are individual opinions and do not represent NICE's view.

All 3 specialist commentators were familiar with the Boston KPro Type I (Boston KPro 1) and 1 has used it, at a rate of 1 to 2 patients per year for 9 years.

Level of innovation

Two specialists felt that the Boston KPro I has a novel concept and design. One commentator noted that it has a niche in the temporary restoration of vision (for several years) in people for whom conventional corneal transplantation is unsuitable because of the high risk of failure.

Potential patient impact

One specialist noted that corneal allograft transplantation is the standard of care for corneal blindness, but if the first graft fails, further grafts are less likely to be successful in the long term. The likelihood of success is particularly poor in people who have high-risk factors, such as deep neovascularisation, certain co-morbidities (for example, bullous keratopathy), and limbal stem cell failure because of chemical injury, aniridia and ocular surface dysplasias. The commentator felt that the Boston KPro provides a valid alternative to repeat corneal allografts in these people. Also, people for whom systemic immunosuppression is unsuitable will also benefit from the Boston KPro I because it is synthetic and so immunosuppression is not needed.

Although the Boston KPro I may benefit some people, the commentator reflected that the keratoprosthesis procedure is as invasive as PK and people having it need the same follow-up as those having PK because of the lifelong risk of glaucoma and infections such as endophthalmitis.

Potential system impact

Two specialists noted that specialist training would be needed to use Boston KPro I. They agreed that Boston KPro I should only be used in specialist centres with cornea and

glaucoma specialist services and would involve long term follow-up by corneal consultants specialising in its implantation and managing of associated complications.

One specialist felt that the Boston KPro I should only be used by experienced corneal surgeons. When the Boston KPro I has to be combined with a glaucoma draining device, surgeons must either have the expertise to implant such a device themselves or should be assisted by a glaucomologist. Another commentator highlighted that using the Boston KPro I might lead to cost savings because although it uses an allograft carrier, it is not of clinical grade and so it costs less than other procedures which need optical grade tissue. Another noted that although it might not lead to cost savings in the NHS, there may be cost savings associated with preventing blindness. One specialist felt that there may be increased costs associated with treating complications after Boston KPro I keratoprosthesis procedures.

General comments

One specialist commentator stated that people of African or Caribbean family origin may be at higher risk for corneal transplant failure and so they may benefit from the Boston KPro I.

One specialist explained that there is no set process for deciding whether to recommend keratoprosthesis with the Boston KPro I or a repeat PK. The clinical decision would be based on the likelihood of success for PK in each person, and the reason behind the poor prognosis. The commentator noted that if the patient's eye is in a poor prognostic group for PK, for example, having a repeat PK (second or more), vascularisation or stem cell failure, the treatment options would be to offer PK with immunosuppression, or the Boston KPro I. If the person is not well enough to have immunosuppression therapy, the Boston KPro I should be offered.

Patient organisation comments

The Royal National Institute of Blind People said that the Boston KPro technology provides a next step for people with a complicated corneal history. Repeated penetrating keratoplasty (PK) is currently the only option for people whose PK graft to treat severe corneal opacity has been rejected. They suggested that using the Boston KPro Type I may mean that people who would otherwise face severe sight loss because of long-term corneal problems or severe corneal damage may able to keep some useful vision.

However, they did highlight that visual acuity seems to vary after having the KPro graft, and there is some uncertainty about the long-term benefits. Maintaining or having a modest increase in visual acuity can be important for people with loss of vision to manage their lives independently. They noted that people can find it difficult to care for their corneal grafts appropriately, and it is not yet clear whether eye care after keratoprosthesis with Boston KPro Type I would be any easier.

Specialist commentators

The following clinicians contributed to this briefing:

- Dr Oliver Baylis, Consultant Ophthalmologist, Sunderland Eye Infirmary, Sunderland, no conflicts of interest declared.
- Professor David O'Brart, Consultant Ophthalmic Surgeon and Professor of Corneal Science, Guy's and St Thomas' NHS Foundation Trust, no conflicts of interest declared.
- Dr Damian Lake, Consultant Ophthalmic Surgeon, Queen Victoria Hospital NHS Foundation Trust, no conflicts of interest declared.

Representatives from the following patient organisations contributed to this briefing:

- Royal National Institute of Blind People.

Development of this briefing

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