Universitat Autònoma de Barcelona

Facultad de Medicina
Departamento de Cirugía

BOSTON KERATOPROSTHESIS TYPE I: INDICATIONS, LONG TERM RESULTS AND COMPLICATIONS

Tesis por compendio de publicaciones para optar al grado de Doctor en Medicina y Cirugía por

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For my husband Juan and my daughter Francesca, my inspiration to bring out the best in me.

For my parents, Johnny and Flor, for teaching me to values of service, humility and faith.

For Professor Joaquín Barraquer, to whom I owe my professional growth.

For my patients, for their trust and friendship.

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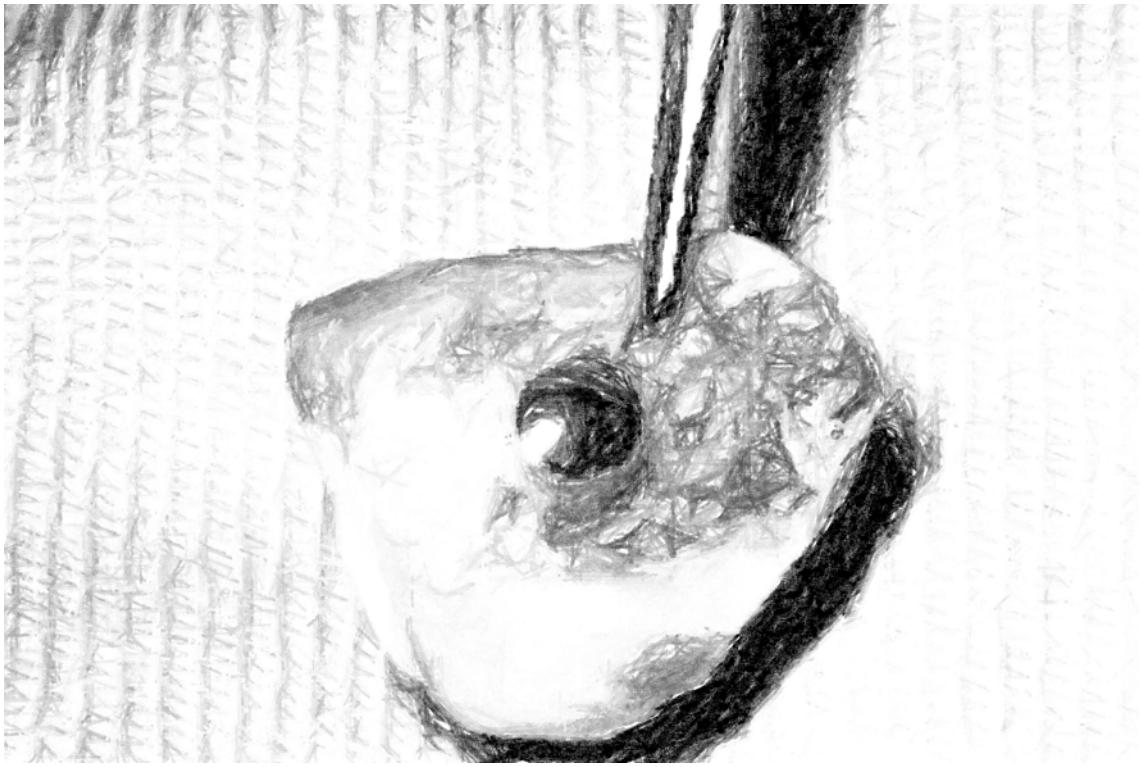
For Professor Claes Dohlman, for his determined efforts in perfecting a modern and practical keratoprosthesis that may be accessible to most, if not all, cornea surgeons around the world.

INDEX



1. INTRODUCTION

1.1 Definition and etymology of "kerato-prosthesis"

Kerato, keras, κεραϛ, from the greek word cornea, "horn or horny substance".

Prosthesis, πρόσθεσις, 1550's, "addition of a letter or syllable to a word," from Late Latin, from Greek *prosthesis* "addition," from *prostithenai* "add to," from *pros* "to" + *tithenai* "to put, place", meaning "artificial body part" is first recorded c.1900, from earlier use to describe the medical art of making artificial limbs (1706), on notion of "that which is added to" the injured body (Real Academia Nacional de Medicina).

Kerato-prosthesis therefore means artificial cornea.

A keratoprosthesis basically has two parts: the clear part in the center for optical purposes, called the **optic** and the supporting material of the optic, called the **haptic**. The haptic must integrate into the surrounding tissue for long-term retention of the artificial cornea.

1.2 Historical background

It was a French ophthalmologist Pellier de Quengsy from Montpellier, France who is traditionally considered to be the first one to describe "artificial cornea" in 1789 (Chirila, 1999). In 1853, Johann N. Nussbaum implanted in his own body small spheres of different material like glass, wood, iron and copper and concluded that glass produced no irritation. After several experiments on rabbits, he implanted the first artificial cornea in a human eye, which was

retained for seven months (Day, 1957) (**Figure 1)**. This marked a milestone in the history of artificial corneal surgery. Afterwards, several other ophthalmologists from around the world experimented with different materials. Heusser from Switzerland described an artificial cornea with quartz that was implanted into a blind eye showing anatomical retention for more than six months (Day, 1957). Fritz Salzer from Germany designed a quartz disc with a surrounding platinum ring with prongs in 1895. These were implanted in human eyes with limited retention and he was the first to suggest that a material lighter than glass should be used (Chirila T, 1999). F. Dimmer used celluloid, the first commercially available thermoplastic, which he molded and implanted in human eyes but with poor anatomic outcomes in 1891. He was the first to use a polymeric material as a bio-functional prosthetic device (Chirila T, 1999).

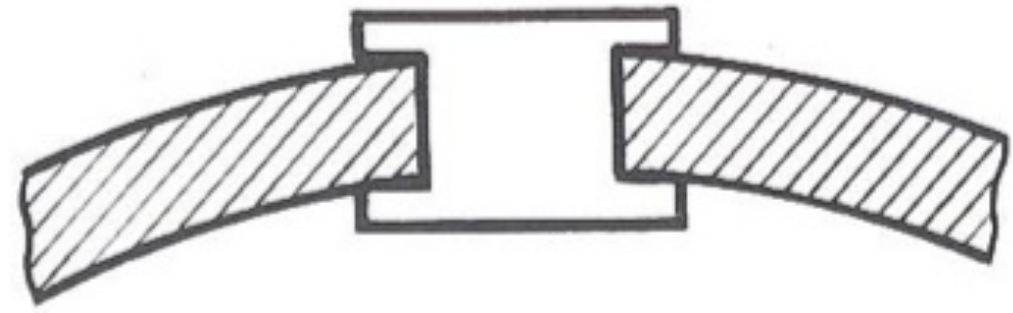


Figure 1. 1853, Nussbaum´s idea of an artificial cornea placed in the center of the cornea (courtesy of Fyodorov et al´s book on Keratoprosthesis).

At the turn of the century, there was a decline in the interest in artificial corneas due to the first successful full thickness corneal transplant by Eduard Konrad Zirm in 1906 using a cadaveric donor (Armitage J, 2006). With the improvement of surgical techniques and material, and increasing success in cadaveric corneal transplantation, the first half of the twentieth century saw less

interest in artificial corneas. Years later, corneal surgeons realized that human corneal transplantation was not successful in all cases of corneal blindness thereby reviving the interest in searching for the ideal material for artificial corneas (Gomaa. 2010).

During World War II, a breakthrough discovery occurred when Sir Harold Ridley noticed that acrylic plastic material of shattered canopy was inert in the eyes of Royal Air Force pilots. On November 29, 1949 the first artificial acrylic lenticule was inserted in a human eye to replace the lens after extracapsular cataract surgery at the St. Thomas´ Hospital in London, United Kingdom (Williams HP, 2001). From there, Wunsche reported the use of polymethylmetacrylate (PMMA) as a lighter alternative material to glass for artificial corneas (Chirila T, 1999; Temprano, 1991).

Gyorffy conceptualized the idea of a two-piece keratoprosthesis in 1951 (Figure 2). However, mono-block keratoprosthesis were used afterwards. In 1956 Binder and Binder designed another model whose circular haptic of 8 mm in diameter was made of poly-ethylene (Figure 3). Other designs during this era were those with partially perforated haptic by Barraquer (1956), and by Barraquer-Cardona (1958). Later on, in the 1960´s Stone and Herbert, as well as MacPherson and Anderson, designed poly-methyl metacrylate (PMMA) mono-block keratoprosthesis models for intralamellar fixation (Figure 4). In 1953, Stone and Herbert designed a keratoprosthesis with a central optical cylinder and a round haptic with peripheral holes. Their idea was for corneal scar tissue to grow within the nutritional holes and help anchor the prosthesis within the corneal stroma (Temprano, 1991; Chirila T, 1999) (Figure 5).

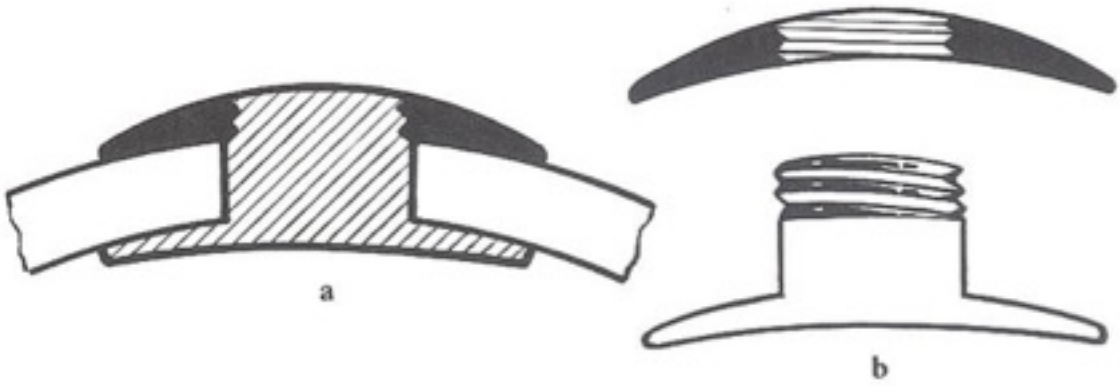


Figure 2. 1951; Gyorffy´s keratoprosthesis. a: placed in the center of the cornea b: prior to fixation (courtesy of Fvodorov et al´s book on Keratoprosthesis).

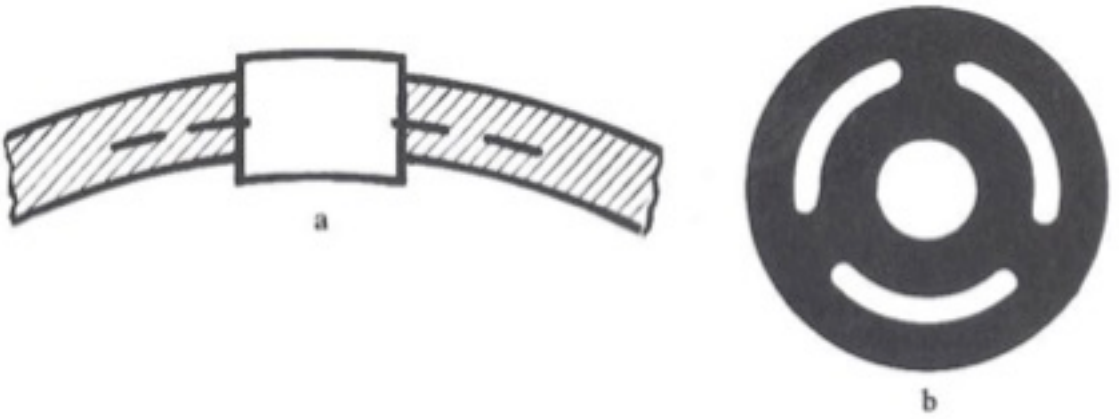


Figure 3. 1956; Binder and Binder´s keratoprosthesis. a: placed within in the corneal lamella and b: view from the top (courtesy of Fvodorov et al´s book on Keratoprosthesis).

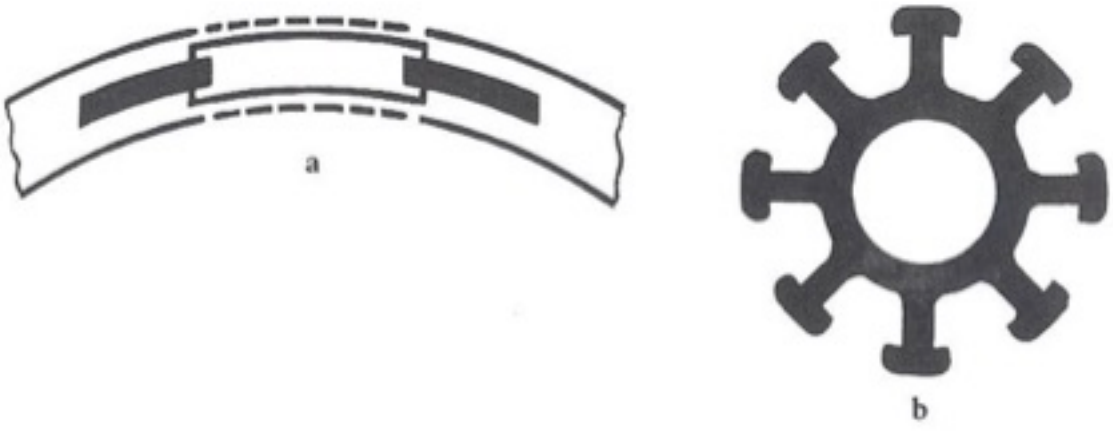


Figure 4. 1953, MacPherson and Anderson´s keratoprosthesis. a: placed within the corneal lamella and b: view from the top (courtesy of Fvodorov et al´s book on Keratoprosthesis).

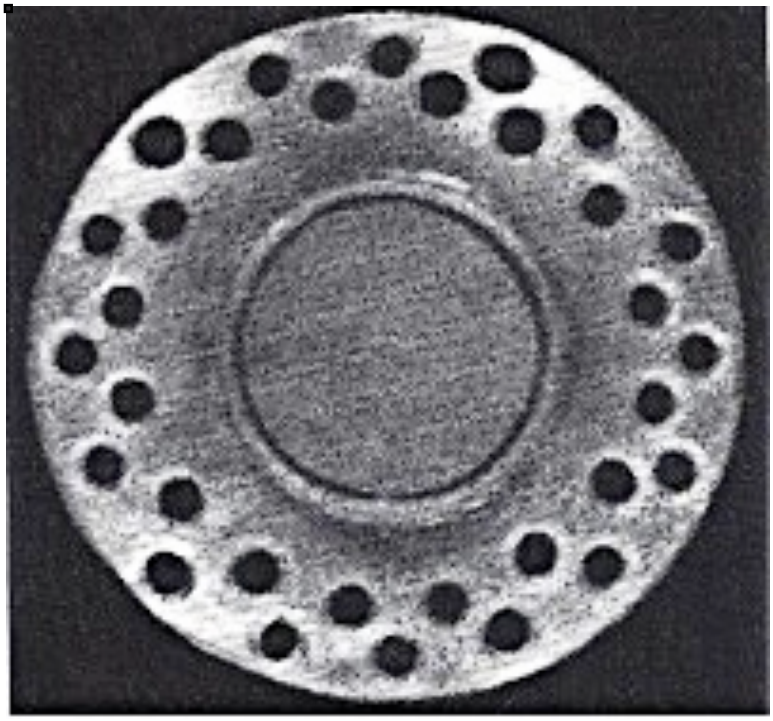


Figure 5. 1953; Stone and Herbert´s keratoprosthesis (courtesy of Fvodorov et al´s book on Keratoprosthesis).

In the 70´s, Stone designed a prosthesis whose optical cylinder could be changed in order to modify the patient´s refraction. Later on, Cardona

designed the "nut and bolt" prosthesis whose optical cylinder penetrates into the anterior chamber and also supports the internal face of the cornea (Chirila, 1999; Temprano, 1991) **(Figure 6)**. In 1972, Fyodorov y Zuev designed a two-piece prosthesis whose haptic is made of titanium (Temprano, 1991) **(Figure 7)**. Moroz and Zuev later on modified this model. The central optical cylinder in both models is made of PMMA **(Figure 8)**.

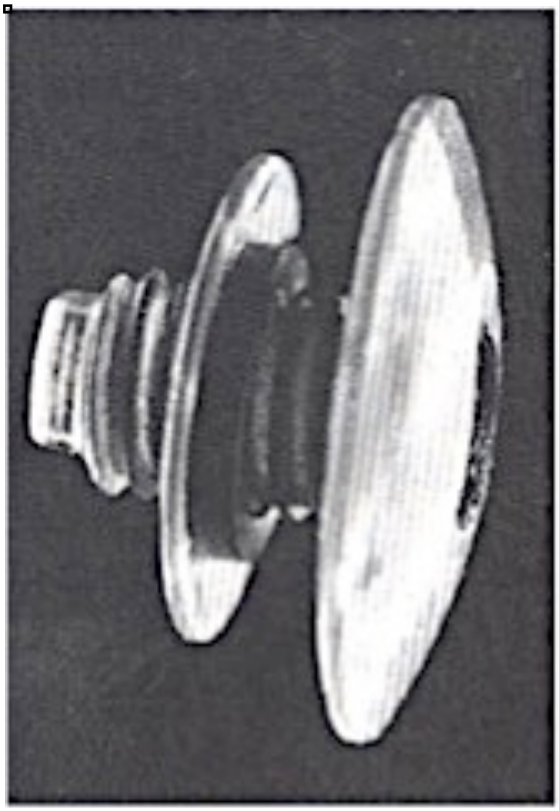


Figure 6. 1969; Cardona's "nut and bolt" type keratoprosthesis (courtesy of Fvodorov et al´s book on Keratoprosthesis).

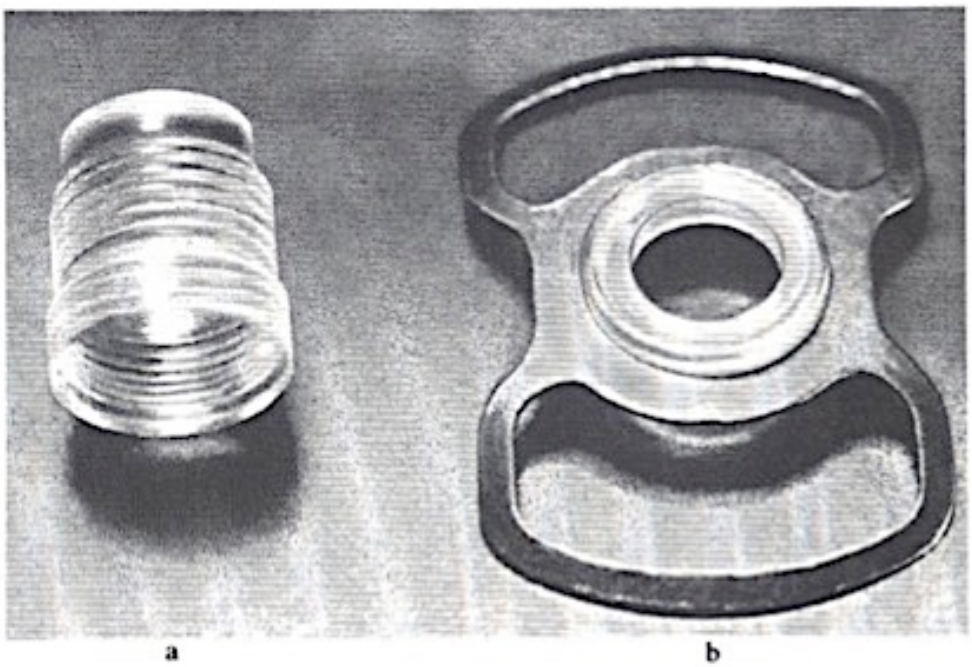


Figure 7. 1972, Fyodorv's keratoprosthesis with a:PMMA optical cylinder and b: titanium haptic (courtesy of Fvodorov et al´s book on Keratoprosthesis).

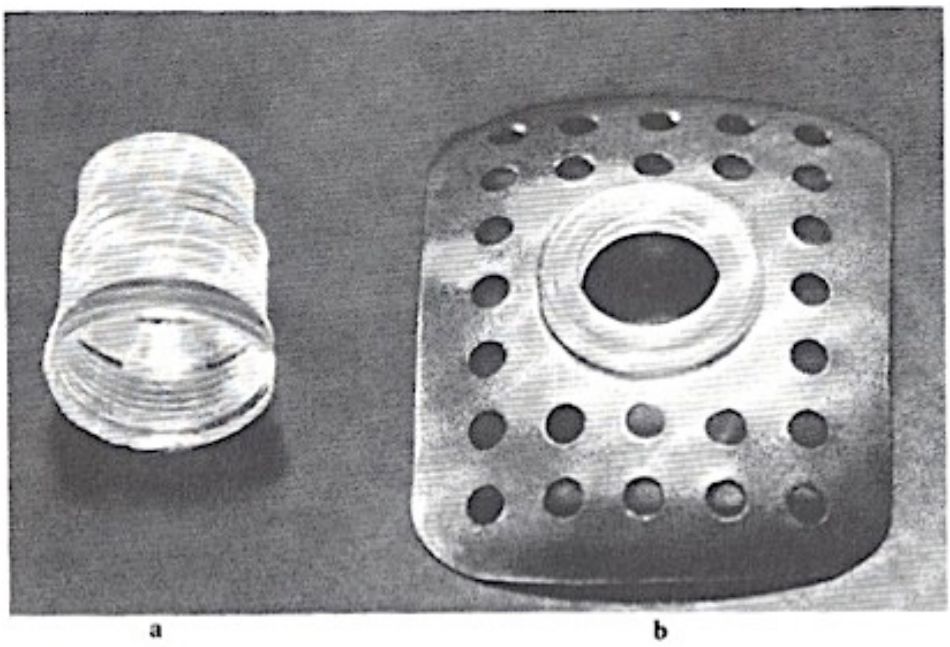


Figure 8. 1972, Moroz and Zuev's modification of the above keratoprosthesis using the same materials (courtesy of Fvodorov et al´s book on Keratoprosthesis).

1.3 Evolution of haptic material

The key factor to the success or failure of any artificial cornea lies hugely in the haptic material. In the 19th century gold was used, followed by platinum and tantalium.

Cardona, Castroviejo, Barraquer, Dorzee, Legrand and Baron designed mono-block acrylic keratoprostheses for intra-lamellar fixation with different kinds of haptics in the 1950's. The use of titanium as haptic material is credited to the group of Fyodorov (Temprano J, 1999).

In 1962, Strampelli from Italy, used autologous heterotopic material using the root of a tooth, and in edentulous patients, Casey proposed the use of cartilage (Temprano, 1991; Gomaa 2010), while Temprano tried tibial bone (Temprano, 1991). Nylon, dacron, teflon, silastic, silicone or proplast, have also been tried as synthetic alternatives to autologous tissue. Parallel to the development of autologous tissue as haptic material in the 1960's, Dohlman and Doane started their studies using PMMA. Details of this prosthesis are discussed in the section on "Non-biological Haptics".

1.4 Keratoprosthesis in Spain

In 1955 Joaquin Barraquer performed the first documented keratoprosthesis ever implanted in Spain. It was a case of severe chemical burn on both eyes of a young lady. He used a Dorzee acrylic keratoprosthesis. **(Figure 9).** The patient had good functional and anatomical results until 5 years later when she had extrusion of the prosthesis and superior retinal detachment. The Dorzee-Barraquer-Cardona acrylic prosthesis implanted in

1958 on a patient with end-stage glaucoma was also tried **(Figure 10).** The patient had good anatomical retention until his death in 1970. The third type of acrylic keratoprosthesis implanted was on a case of chronic graft failure after 2 corneal transplants, where Joaquin Barraquer implanted the Cardona keratoprosthesis in 1960 **(Figure 11).** The patient had good anatomical and functional results for 8 years until suffering from an acute endophthalmitis. The fourth type that he tried was a Teflon-supported keratoprosthesis designed by Girard; it was retained for several months until eventual extrusion **(Figure 12).** The first documented implantation of the presently used prosthesis for end-stage corneal cicatricial disease, osteo-odontokeratoprosthesis designed by Strampelli, was actually performed by Joaquin Barraquer on a blast injury showing good anatomical and functional results for 10 years **(Figure 13).** The case in figure 13 was with the first technique of Strampelli, which was a lamellar insertion of the osteo-dental lamina.

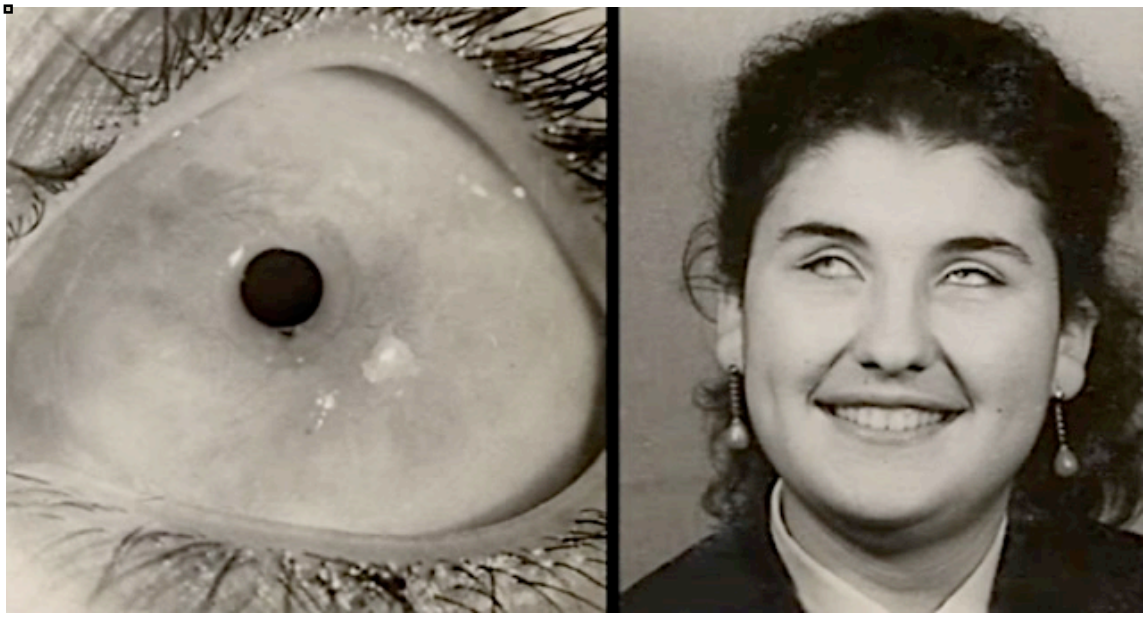


Figure 9. 1955, Dorzee keratoprosthesis implanted by Joaquín Barraquer on a bilaterally blind patient due to chemical burn.

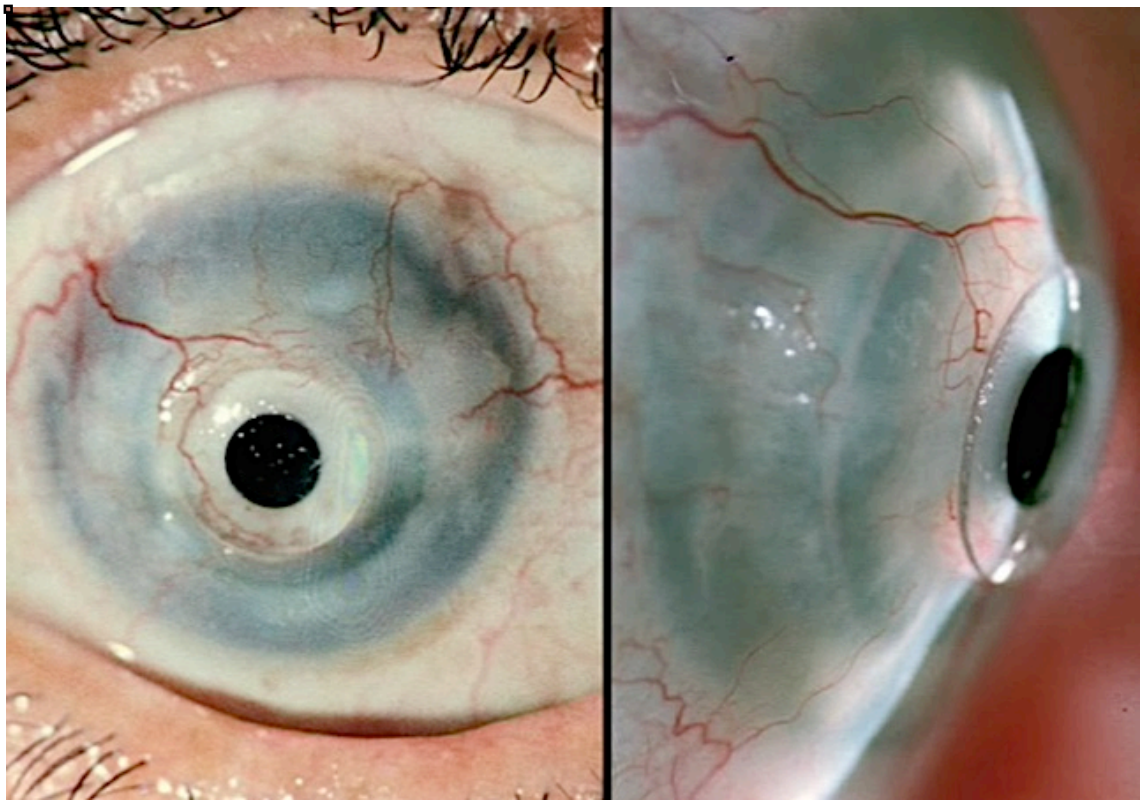


Figure 10. 1958; Dorzee-Barraquer-Cardona keratoprosthesis on a patient with advanced glaucoma.

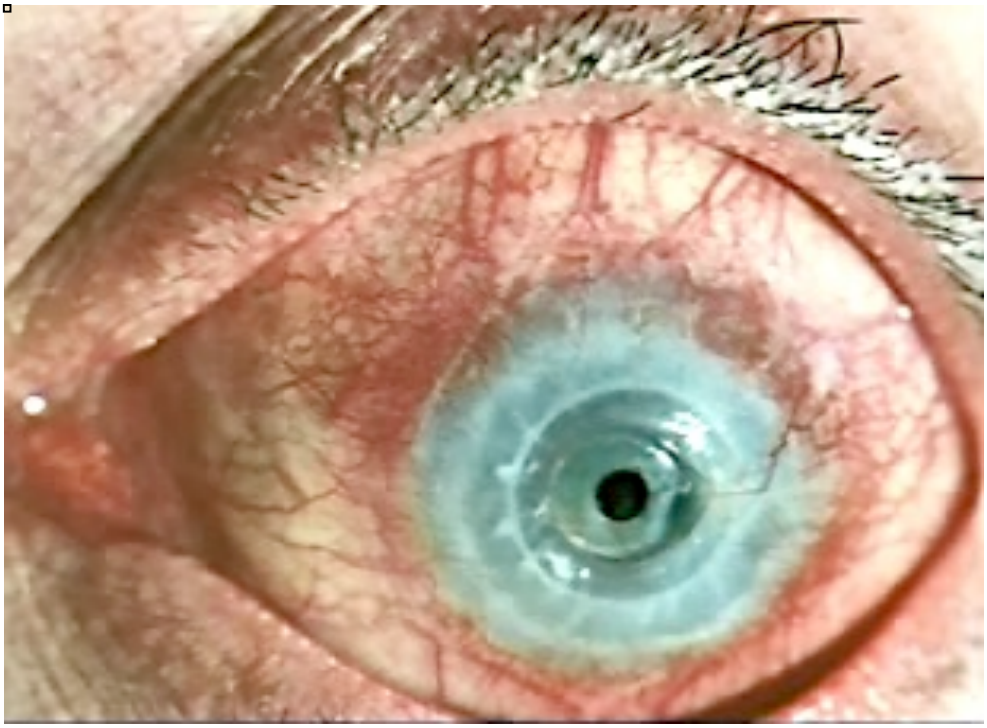


Figure 11. 1960; the Cardona keratoprosthesis implanted on a patient with 2 previously failed grafts.

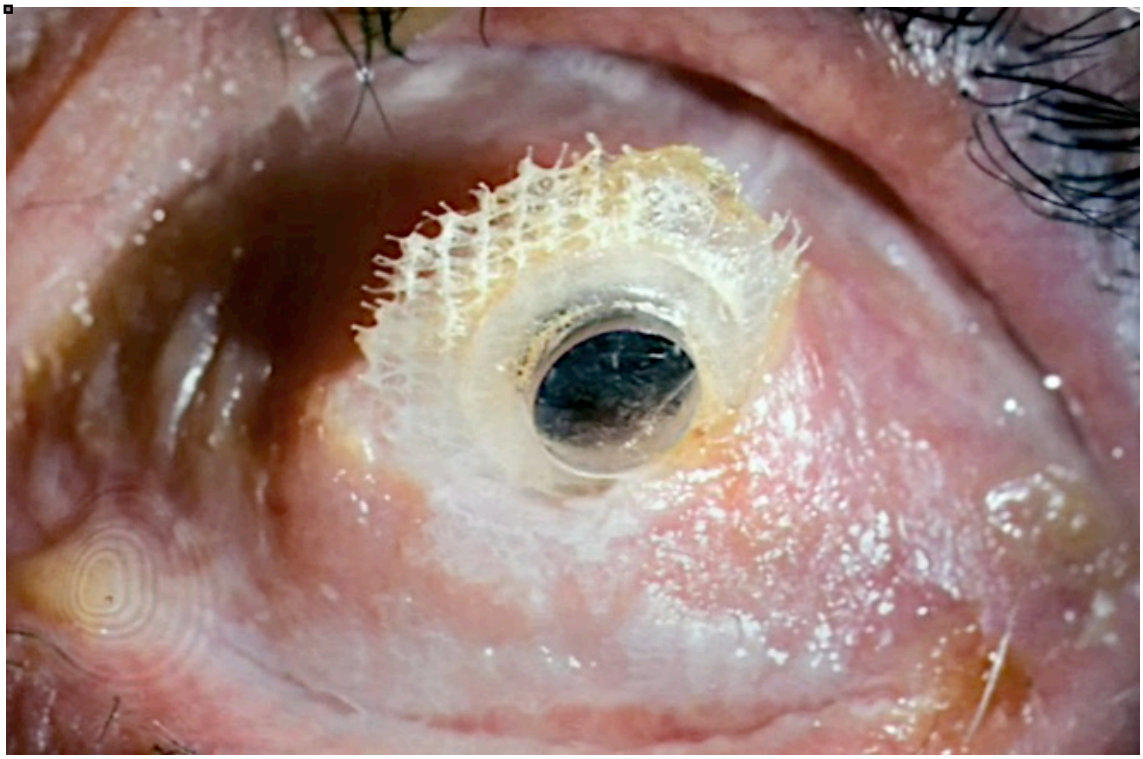


Figure 12. Girard´s Teflon-supported keratoprosthesis with extrusion.

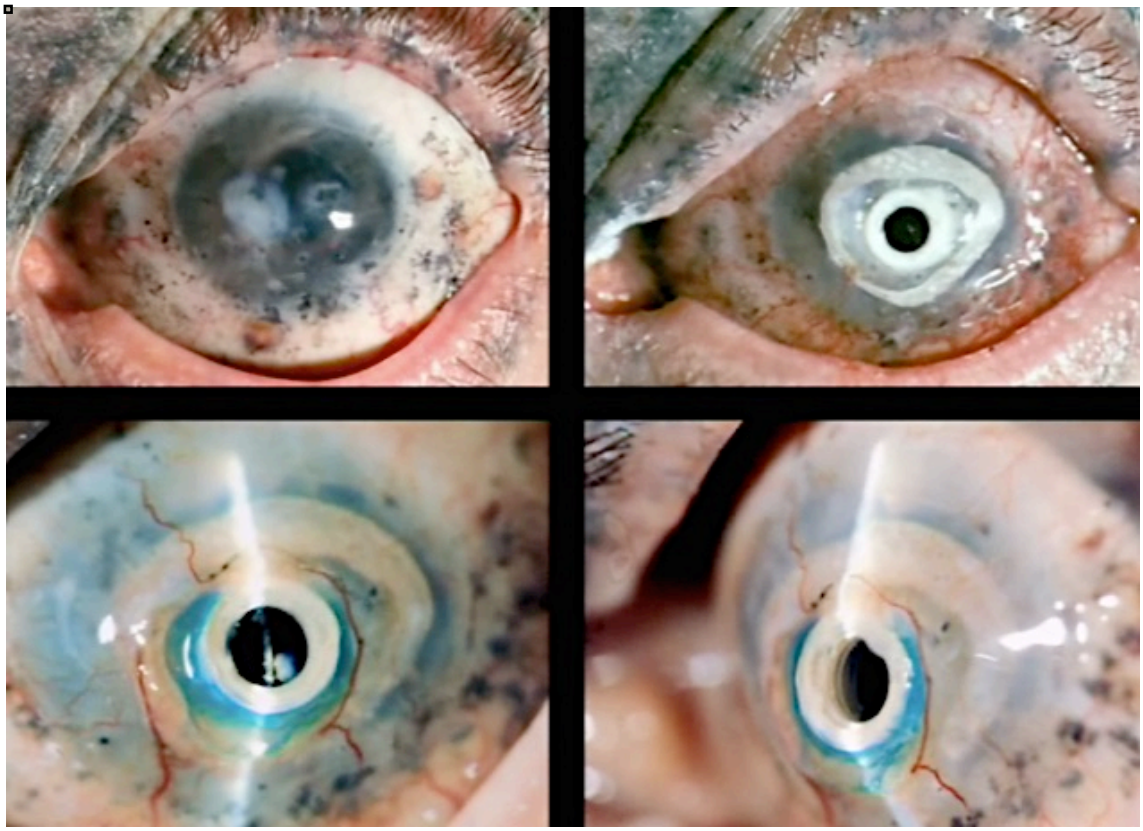


Figure 13. 1965, first documented case of osteo-odonto keratoprosthesis in Spain on a blast injury patient (first technique of Strampelli).

1.5 Types of keratoprosthesis

Any breach in living human tissue tends to be protected and reconstructed by growth of healthy epithelium. An ideal implant for any part of the body is one that would integrate with surrounding tissue. Since keratoprostheses are made of plastic material and there is no fusion between the implant and ocular tissue, the epithelium then tends to engulf the prosthesis, transforming it into an **endo-prosthesis**. Or the opposite may occur wherein the epithelium tends to grow beneath the prosthesis and expel it, transforming it into an **exo-prosthesis**. An ideal keratoprosthesis is therefore one that would integrate with surrounding ocular tissue, or a **meso-prosthesis**, with total integration from above and beneath the implant (Temprano, 1992).

1.5.1 Depending on the material

Acrylic is the present material of choice for the optical part of most keratoprosthesis because of several characteristics. In its colorless state, it is as optically clear as glass but is lighter in weight therefore can be supported by different kinds of haptics. It also has high breakage resistance and can be fabricated into different shapes. In this section we will discuss basically about the haptic material since all present optical cylinders are made of acrylic or its derivatives. Only the ones that have been more popularly used worldwide will be mentioned.

1.5.1.1 Biological haptic

In 1962 Strampelli thought of using the patient´s own tooth root and surrounding alveolar bone to support a central optical cylinder. His idea was that since any foreign material in the eye was either engulfed from above or expulsed from underneath by fibrovascular tissue causing poor retention and poor optical results, autologous tissue will achieve total integration into the patient´s eye (Temprano, 1991) (**Figure 14)**. It is known worldwide as the osteo-odonto keratoprosthesis or OOKP for short. Falcinelli has modified Strampelli´s technique and present day surgeons follow this technique called Modified OOKP or M-OOKP (Chodosh, 2010).

In patients without viable teeth for the above technique Casey proposed the use of cartilage (Gomaa, 2010). Temprano has also tried using donor teeth from matched donor relatives for edentulous patients, or from adult relatives for pediatric patients with deciduous teeth to prevent amblyopia. However, there was a 50% extrusion rate. He then decided to use the tibial bone as a substitute for canine tooth, presently referred to as tibial bone keratoprosthesis or Tibia KPro (Temprano, 1991) (**Figure 15)**.

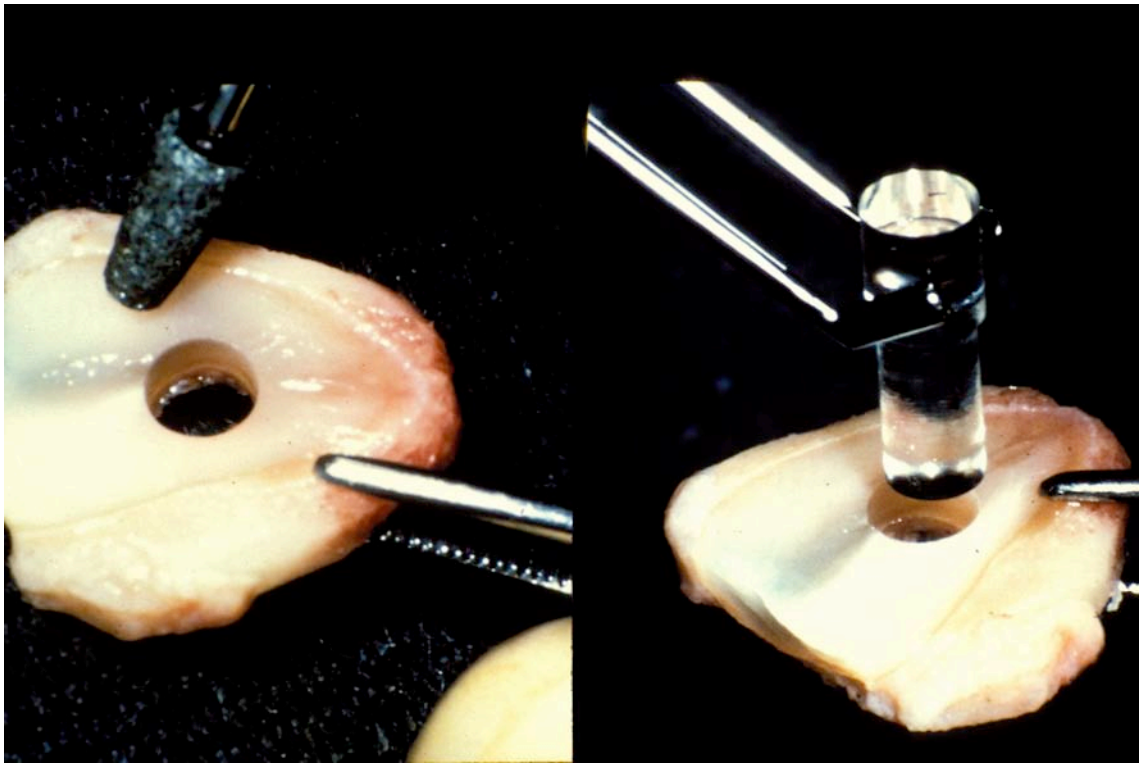


Figure 14. Strampelli´s osteo-odonto keratoprosthesis using canine tooth (OOKP).

Figure 15. Temprano's osteo keratoprosthesis using tibial bone (Tibia KPro).

1.5.1.2 Non-biological haptic

Dohlman and Doane started developing the Boston keratoprosthesis (Boston KPro) since the late 1960´s, but it was not until 1992 that the American Food and Drug Authority (FDA) approved it as a medical device. At present it is the most widely used keratoprosthesis with a synthetic haptic around the world. It is made of a PMMA haptic with several nutritional holes wherein the central optical PMMA cylinder is fit into (**Figure 16).**

Cardona, sometime in 1969 developed a "nut and bolt" type of prosthesis using a cosmetic tinted contact lens (to prevent glare) with a PMMA optical cylinder screwed into its central part. Its haptic is made of a perforated polytetrafluoroethylene plate (Chirila, 1999; Temprano, 1991**) (Figure 17).**

In 1972 Fyodorov and colleagues used titanium as a haptic attached to a central PMMA optical cylinder (Temprano,1991). This is still presently used in eastern Europe and Russia (Zagorski, 2009).

Pintucci in 1979 used Dacron, a material used in angioplasty and cardioprosthesis, weft as a haptic with the optical PMMA cylinder attached thru a central hole (Gomaa, 2010) **(Figure 18).** This has been implanted in Europe, Asia, India and Africa (Pintucci, 1996).

AlphaCor™ was developed from Western Australia and is made of poly-hydroxyethyl metacrylate (poly-HEMA). The FDA approved it in 2003. It has central clear optical zone and an opaque spongy haptic. Both parts are made of poly-HEMA only that they have different water contents making one zone more transparent than the other (Gomaa, 2010) (**Figure 19**).

Emerging keratoprosthesis are the KeraClear™, a soft and foldable keratoprosthesis designed for intra-lamellar fixation using femto-second laser,

from the United States of America (Alió, 2015) **(Figure 20),** and the Miro® Cornea from Germany, made of hydrophobic acrylic polymer coated with fibronectin for epicorneal fixation as an alternative to the OOKP (Duncker, 2014; Schrage, 2014) **(Figure 21)**.

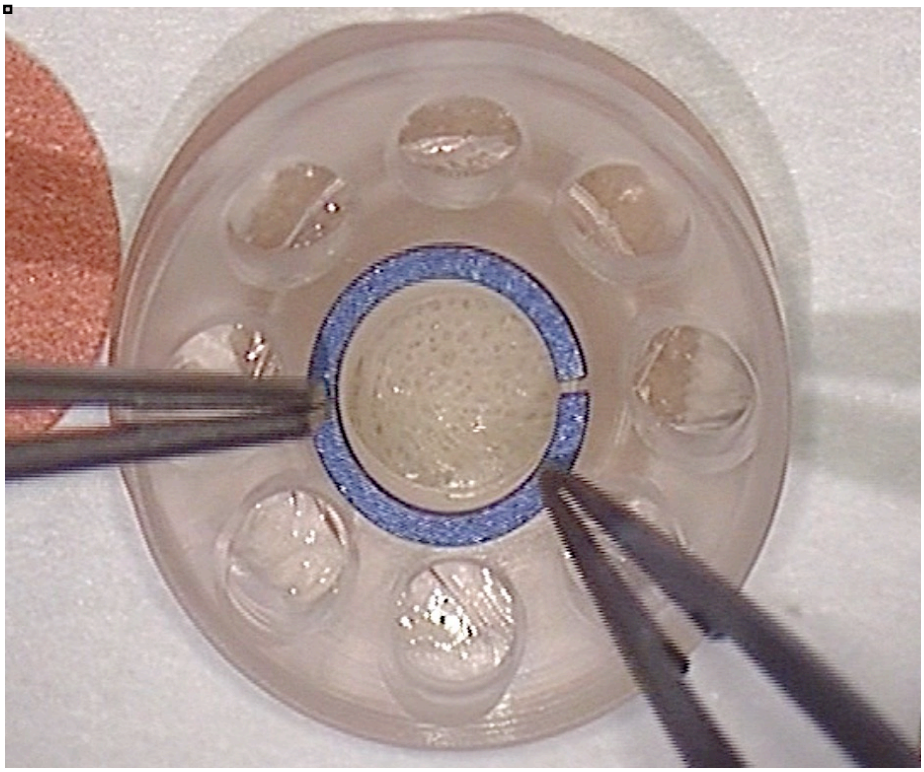


Figure 16. 1992 FDA Approved Boston Type 1 Keratoprosthesis.

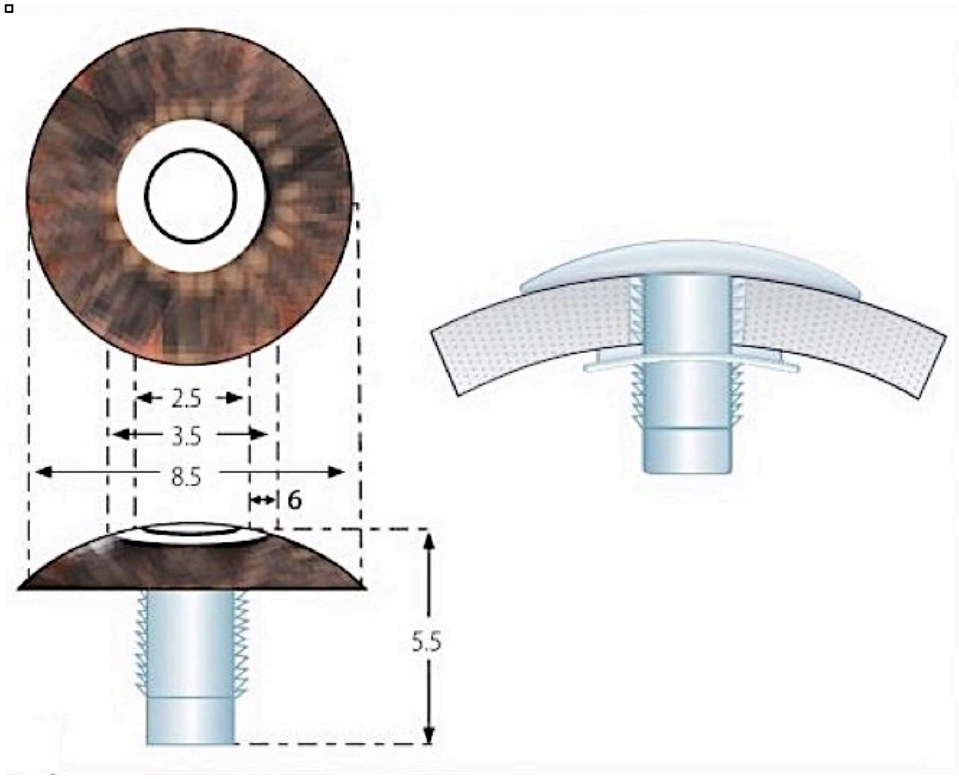


Figure 17. Cardona´s keratoprosthesis with tinted lens to reduce glare (courtesy of Salvador B in Ocular Surface Disorders, Benitez del Castillo y Lemp ed. 2013).

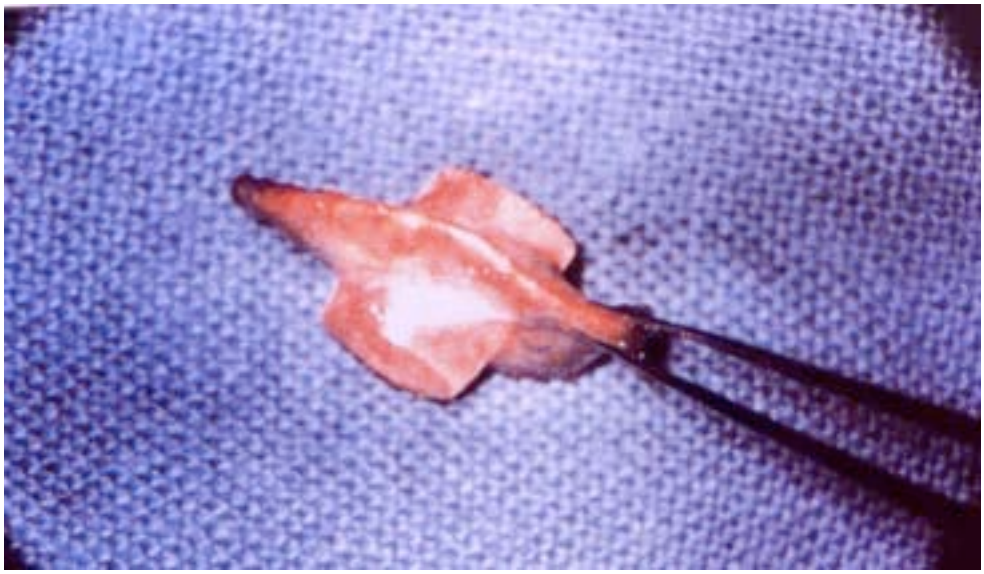


Figure 18. Pintucci's dacron mesh kerato-prosthesis (courtesy of Anales del Instituto Barraquer).

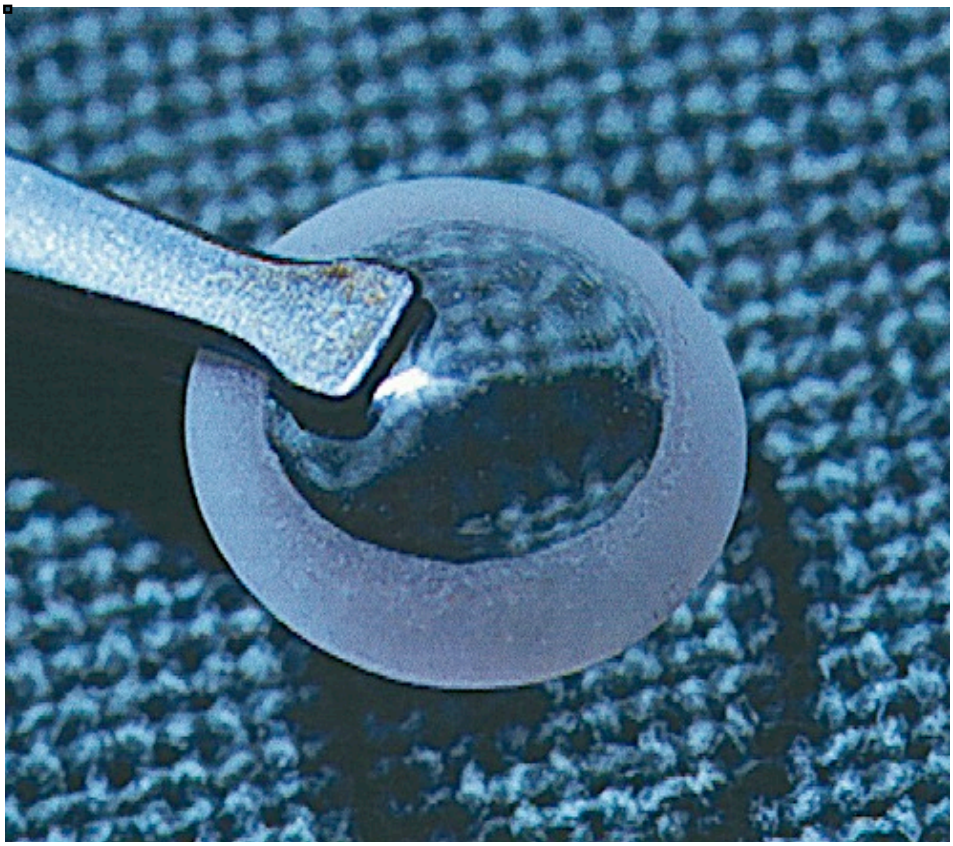


Figure 19. AlphaCor™ keratoprosthesis (courtesy of Salvador B in Ocular Surface Disorders, Benitez del Castillo y Lemp ed. 2013).

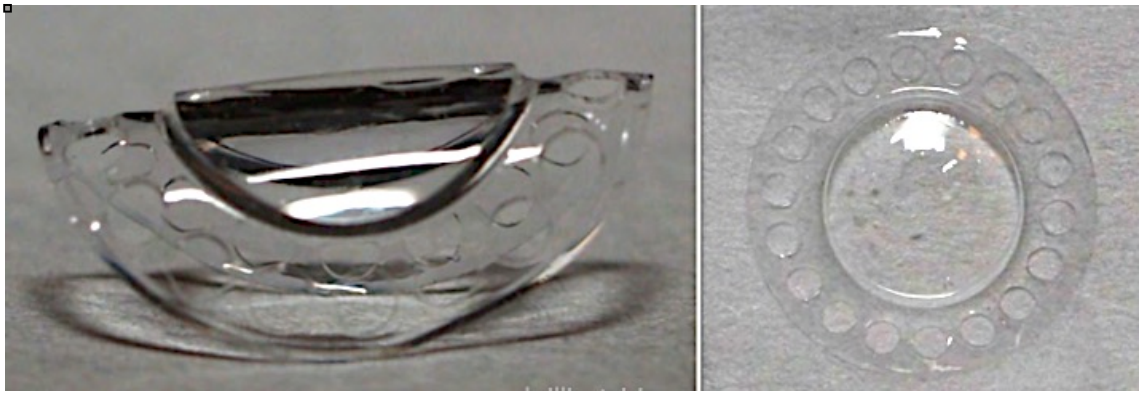


Figure 20. KeraClear™ foldable keratoprosthesis (courtesy of Ocular Surgery News).

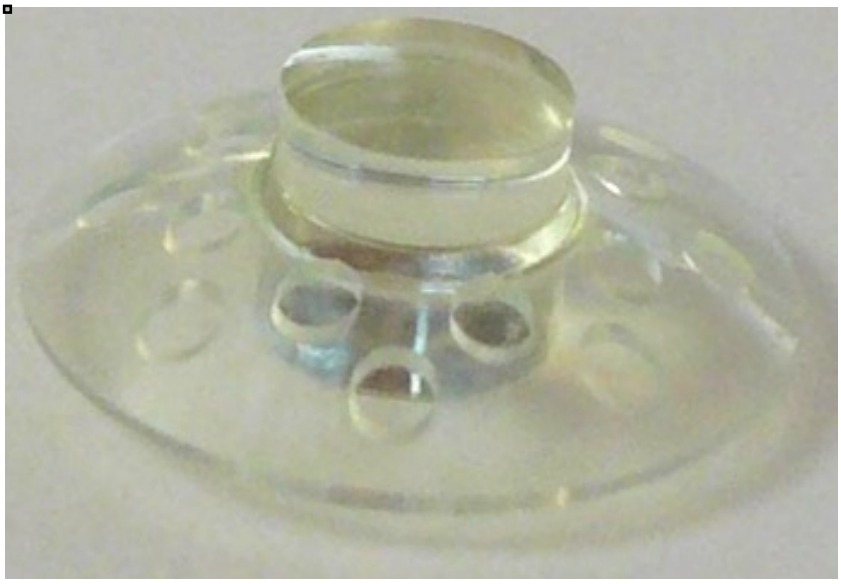


Figure 21. Miro® Cornea (courtesy of Spektrum der Augenheilkunde 2014).

1.5.2 Depending on mode of fixation

1.5.2.1 Trans-corneal fixation

Trans-corneal fixation means that the cornea tissue is sandwiched by the artificial corneal implant, whether the patient´s own cornea or a donor one **(Figure 22)**. The Cardona keratoprosthesis and the Boston keratoprosthesis (Types 1 and 2) are of this type.

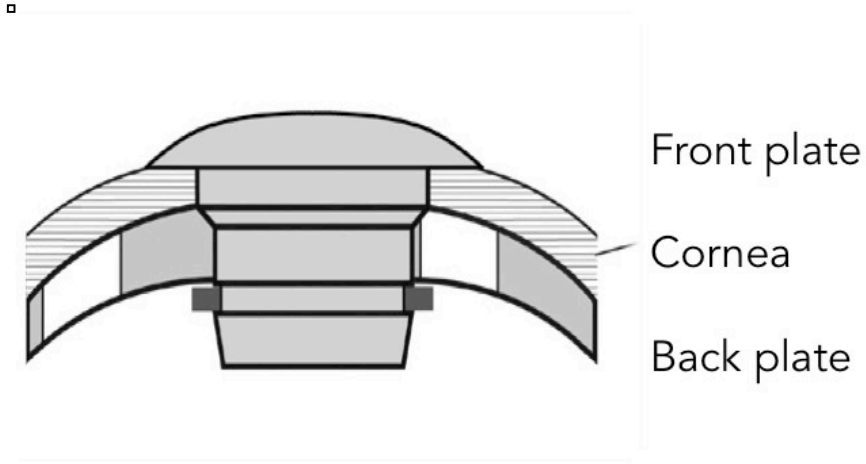


Figure 22. Schematic diagram of a trans-corneal device (courtesy of Digital Journal of Ophthalmology 2007).

1.5.2.2 Intra-corneal fixation

Intra-corneal fixation means that the prosthesis is implanted within the layers of the corneal tissue (**Figure 23**). The Fyodorov, AlphaCor® and KeraClear™ prostheses are of this type.

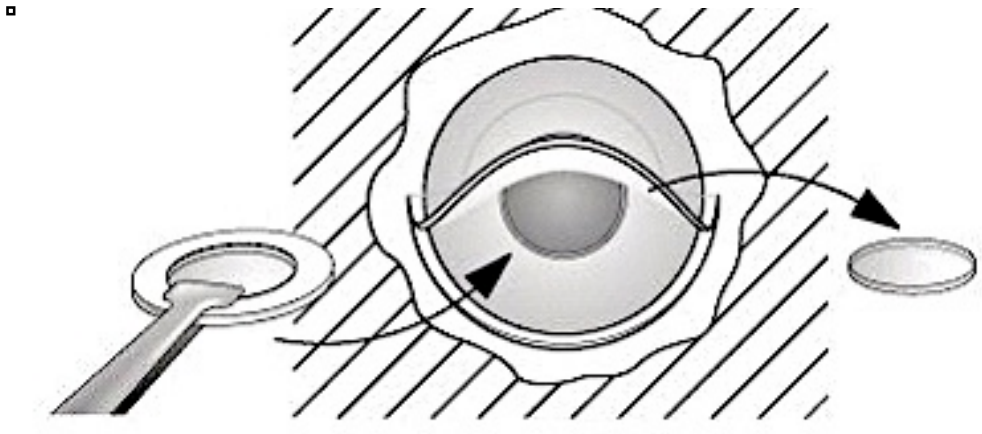


Figure 23. Device to be implanted within the corneal layers after lamellar dissection (courtesy of webeye.ophth.uiowa.edu/eyeforum/ cases-i/case60/AlphaCor).

1.5.2.3 Epi-corneal fixation

Epi-corneal fixation means that the prosthesis is implanted on top of the recipient cornea (**Figure 24**). The OOKP, Pintucci and tibial bone keratoprosthesis are of this type.

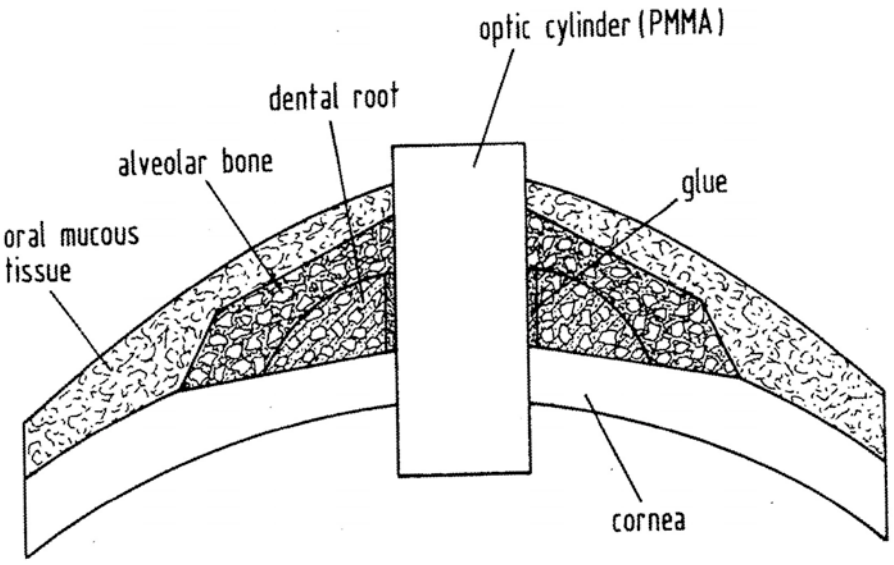


Figure 24. Schematic diagram of an OOKP, an example of an epicorneal device (courtesy of EPA 10/6/2009).

1.6 General Indications for keratoprosthesis

An artificial cornea is indicated when there is a high possibility of a corneal graft failure. Such cases would include limbal stem cell deficiency, whether primary as in the case of congenital aniridia, or acquired, like chemical burns, multiple surgeries, benign intraepithelial hereditary dyskeratosis, multisystemic syndromes affecting the limbus like: KID syndrome (keratopathy, ichthyosis and deafness), EEC syndrome (ectrodactyly, ectodermal dysplasia,

cleft lip and palate), ACL syndrome (acromegaly, cutis verticis gyrate and corneal leukoma), spinocerebellar degeneration with corneal dystrophy (Barraquer, 2004). A corneal graft is also likely to fail in cases of autoimmune limbal stem cell deficiency such as Stevens-Johnson syndrome, mucous membrane pemphigoid, Sjogren´s dry eye syndrome, or in any other condition where there is significant corneal neovascularization (Chodosh, 2011). An emerging indication for keratoprosthesis is repeated graft failure since it has been shown that second and a third graft have a 25% and 0% 5-year survival rate, respectively. Chodosh, 2011). Dohlman and colleagues have simplified the indications for a keratoprosthesis into three main prognostic groups, namely: 1) autoimmune related corneal opacity and ulceration, 2) chemical injury, and 3) corneal allograft failure (non-immune).

However, aside from the aforementioned factors, the characteristics of the ocular surface have to be taken in deep consideration prior to choosing which type of artificial cornea to implant, as certain types of artificial corneas are bound to succeed or fail depending on the hostility of the ocular surface environment.

1.6.1 Wet Blinking Eye

An eye with acceptable tear function and good apposition of eyelids may benefit from ocular surface reconstruction with limbal graft (from varying sources or methods of cultivation), oral mucosal epithelial graft, amniotic membrane transplant, and penetrating keratoplasty for optical purposes or a combination of the above-mentioned procedures (Temprano, 1991; Liu, 2005).

However, when the said alternatives have failed or are unavailable, then artificial corneas like the Boston Type 1, Alphacor® or Keraclear™ keratoprosthesis may be considered.

1.6.2 Dry Non-Blinking Eye

When there is severe cicatrization of the ocular surface, presence of symblepharon, keratinization, severe dry eye and poor lid apposition, reconstruction of the ocular surface with a thick layer of oral mucosa followed by implantation of either an OOKP, Tibia KPro or Pintucci KPro has been shown to last on longer term basis. Surgery is done in three stages over a period of 3 months (Temprano, 1991). Learning curve is steep and the help of a maxillofacial or orthopedic surgeon may be needed for harvesting the biological haptics.

1.7 Common post-operative complications in keratoprosthesis

As with any kind of surgery, complications occur due to several factors. Glaucoma is perhaps the most common complication in artificial cornea surgery. It may occur as "de novo" glaucoma, or worsening of an already pre-existing glaucoma. Most eyes that are candidates for artificial corneal surgery have already undergone multiple previous surgeries and already have the anterior chamber angle altered or non-functional. Most of the eyes have been treated with topical steroids, which may cause drug-induced glaucoma. Another mechanism is the long-standing inflammation, which these eyes have suffered, causing an abnormality in the drainage system of the trabecular

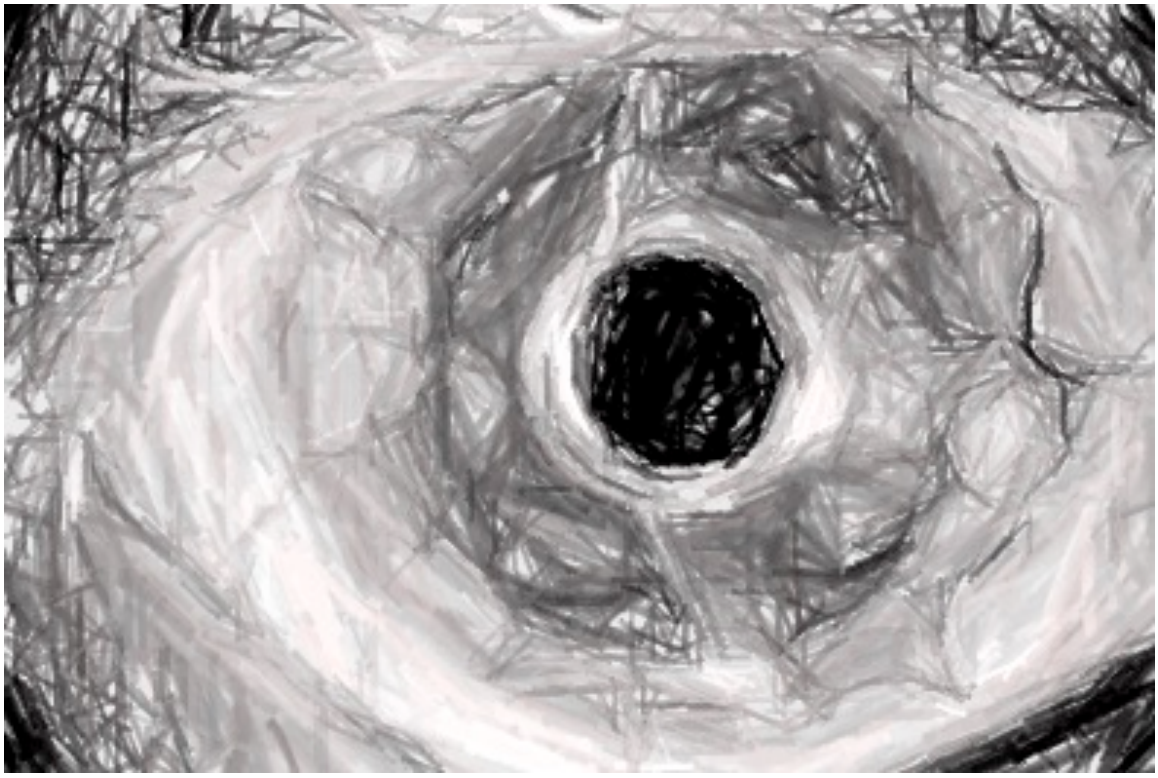
meshwork. In general, all patients who undergo artificial corneal surgery are advised to instill anti-glaucoma medications for life.

Being a foreign body implanted to the eye, inflammation occurs as a natural tendency of the eye to reject something that is not inherent to it. Therefore inflammatory reactions in the anterior segment like retroprosthetic membrane or sterile vitritis are among the frequent complications in artificial corneal surgery. Similar to anti-glaucoma medications, artificial cornea recipients are advised to put anti-inflammatory medications, like steroids, for life.

Infection is probably one of the most dreaded post-operative complications since loss of the eye may occur when not detected and treated early on. Most commonly, infection may be bacterial or fungal. Antibacterial prophylaxis is recommended for life since there is a foreign body in contact with the inside of the eye and/or outside of the ocular surface lids and lashes. Any breach in the integrity of the wound may allow microbial invasion into the anterior segment. Bacterial infection usually occurs when antibiotic post-operative treatment is not followed. Fungal infection may occur due to long-standing antibiotic and steroid use causing an imbalance in the normal flora of the ocular surface favoring the growth of fungus.

Finally, another common complication in corneal artificial surgery is extrusion. As was discussed in the section on historical background, poly-methyl-metacrylate (and derivatives) seems the be the material that is most well tolerated by the eye and is probably the most common material used for implantation in anterior segment ocular surgery. Still, the natural tendency for a living tissue is to reject what is foreign to it, such that in a low percentage, extrusion still occurs. Extrusion may also occur when the carrier tissue, whether

the donor cornea, the patient´s own cornea, tooth, tibia, oral mucosa, etc. undergo desiccation and therefore loss of anatomical stability of the implant.



2. THE BOSTON KERATOPROSTHESIS

(BOSTON KPRO)

2.1 Types and designs of the Boston KPro

The Boston Keratoprosthesis was formerly known as the Dohlman-Doane keratoprosthesis. The said surgeons developed it in the 1960´s at the Massachussetts Eye and Ear Infirmary and the Schepens Eye Institute. The Federal Drug Authority in the United States of America approved it in 1992. Approval has just been given by the European Medicines Agency in 2013.

The Boston KPro has two designs. The Boston Type I KPro is designed for eyes with acceptable tear and lid function while the Boston Type II KPro is intended for end-stage ocular surface cicatricial disease and is designed to be implanted thru the eyelids.

2.1.1 The Boston KPro Type 1

The Boston KPro type 1 has undergone several changes in its design over the last decade. The present threadless "snap-on" design, in use since 2007, has basically three components:

The front part consists of an optical front plate (5.0 mm in diameter) and the stem (3.35 mm in diameter). This is made of medical grade poly-methyl-metacrylate (PMMA).

The back plate (8.5 mm in diameter for adults and 7.0 mm in diameter for pediatric cases) holds the optical cylinder of the front plate thru a central hole, and 16 peripheral holes (1.2 mm each in diameter) designed to help in nutrition and hydration of the carrier cornea. This is also made of poly-methyl-metacrylate (PMMA). The last piece is a titanium-locking ring, which was designed to assure a tight seal between the prosthesis parts and the donor

carrier cornea, thereby decreasing the occurrence of wound leaks, infection and extrusion.

Figure 25 shows a schematic diagram of the different parts in relation to the donor cornea, while Figure 26 shows the device after being mounted without the donor cornea, and also implanted into the eye. The type I device allows a visual field of approximately 50 degrees as can be shown in Figure 27.

Over the last few months, changes have been done in the design of the prosthesis wherein the back plate material has been changed to titanium, and the titanium-locking ring has been fused with the back plate to facilitate preparation of the device. This is referred to as the "click-on" design. Also due to the occurrence of the most common complication, studies using titanium, which is thinner in thickness than its PMMA counterpart, seem to show that the occurrence of retroprosthetic membrane is less, as titanium is a more inert material than plastic. On the other hand, due to its unacceptable cosmetic appearance in the eye, studies are also underway to color titanium using special anodization techniques (Paschalis, 2013) (Figure 28). The "snap-on" titanium back plate design is the one that has the CE mark, approved in 2013.

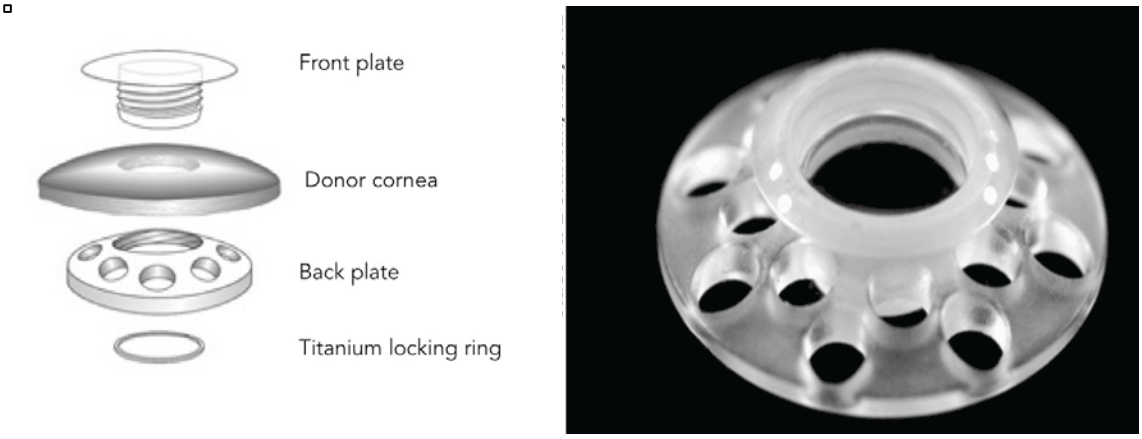


Figure 25. Schematic diagram of the different parts of the Boston KPro Type 1 "snap-on" design (left); mounted Boston KPro Type 1 "snap-on" design, PMMA back plate, without donor cornea (right) (courtesy of Keratoprosthesis and Artificial Corneas, fundamentals and surgical applications).

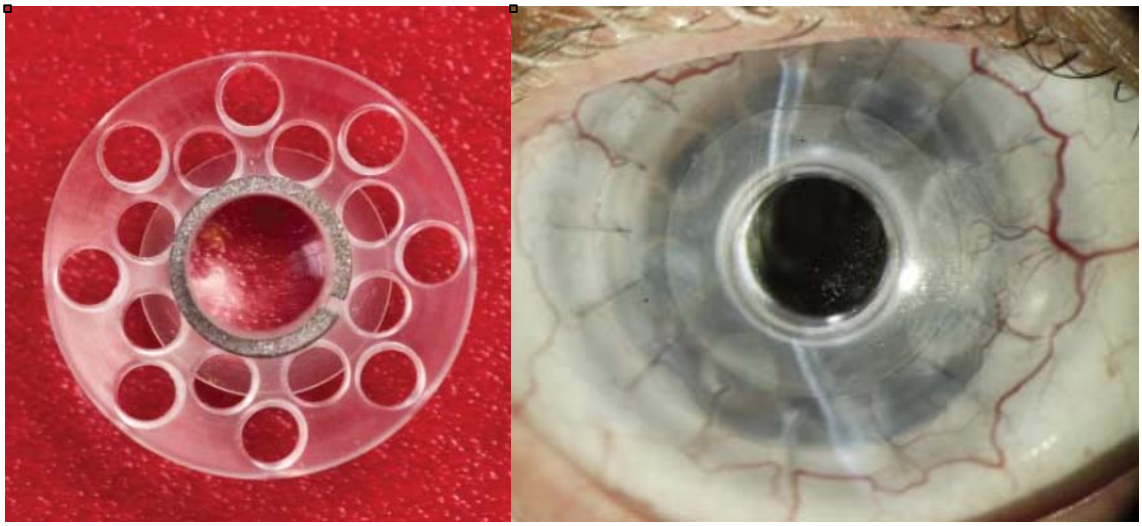


Figure 26. Back view of the Boston KPro Type I "snap on" design with PMMA back plate, mounted without donor cornea (courtesy of Boston KPro Newsletter 2013) (left) ; implanted Boston KPro Type I (right).

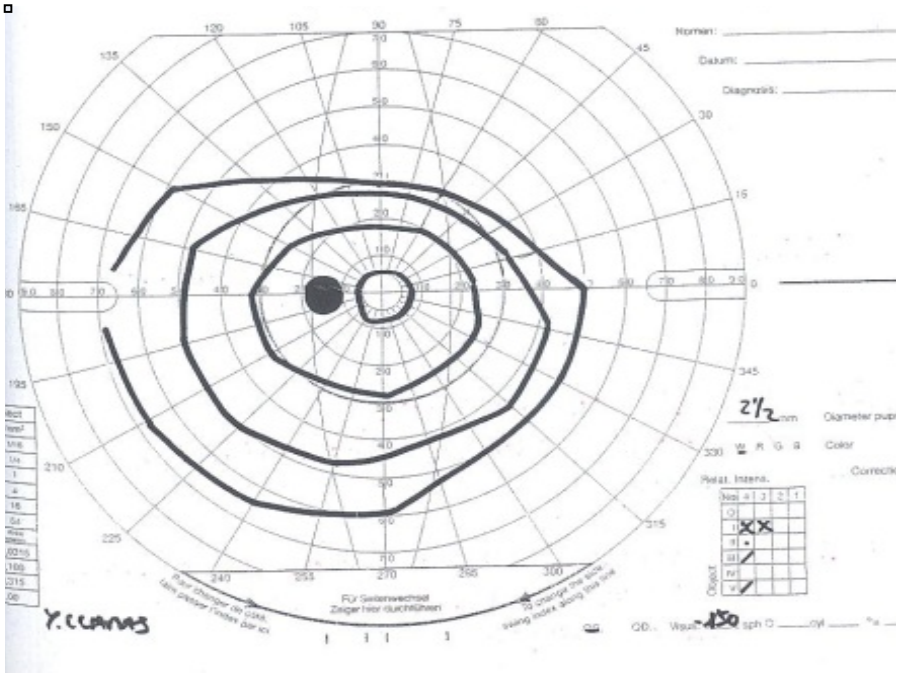


Figure 27. Goldman visual field (approximately 50 degrees) of the only seeing eye of a patient 6 months after Boston Type I Kpro implantation.

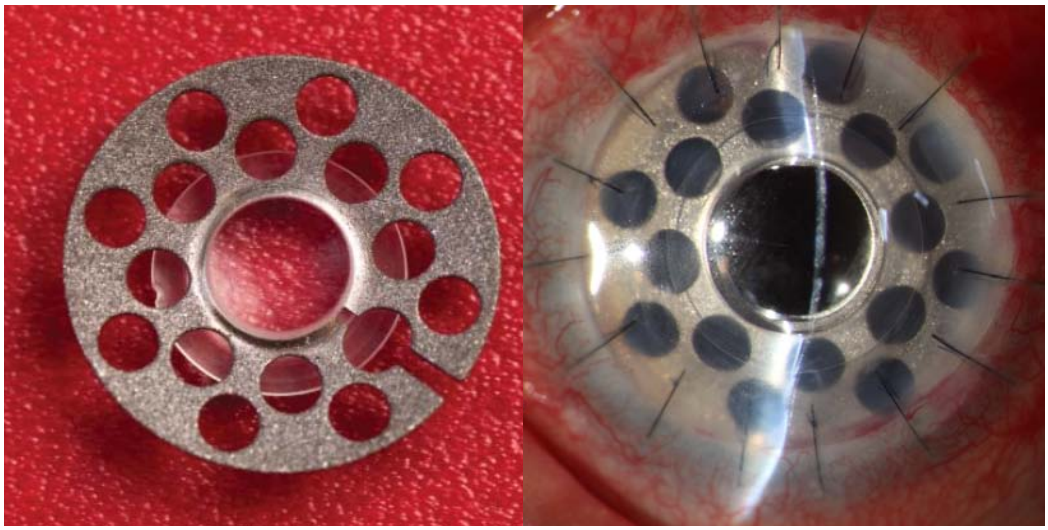


Figure 28. The Boston Type I KPro "click-on" design with titanium back plate, mounted without donor cornea (courtesy of Boston KPro Newsletter 2013) (left): implanted Boston KPro Type I with titanium back plate (right).

2.1.2 Boston KPro Type 2

The Boston KPro Type II device is similar to the Type I device except that it has a 2 millimeter long anterior nub which is designed to protrude thru the lid, such as in cases of severe ocular cicatricial pemphigoid or end stage Stevens Johnson syndrome, where there is keratinization and severe symblepharon (**Figure 29**).

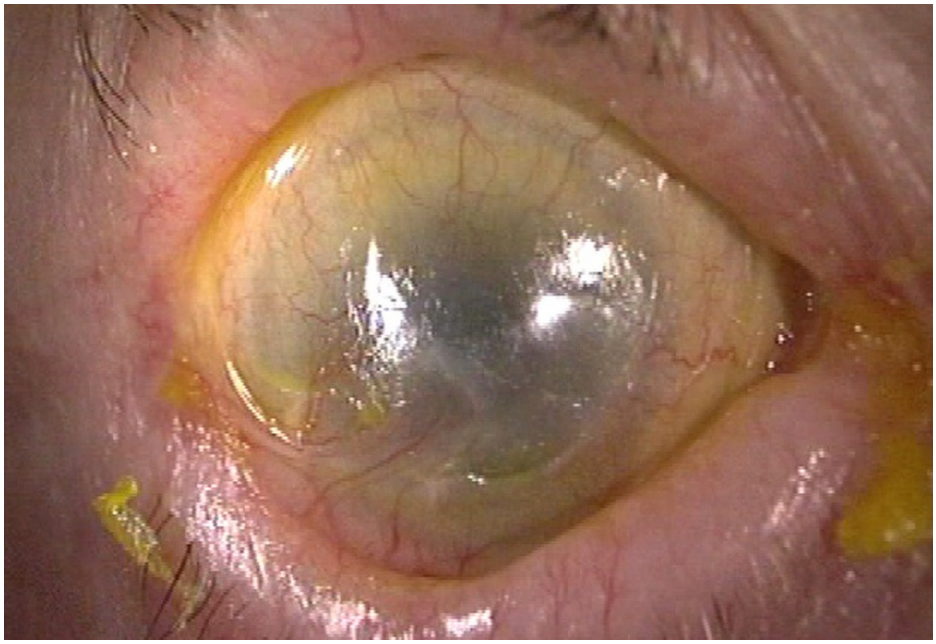


Figure 29. Ocular cicatricial pemphigoid with symblepharon and keratinization of the ocular surface.

This is how the type II device looks like without the donor cornea (**Figure 30**). With this device approximately 40 degrees field of vision may be achieved.

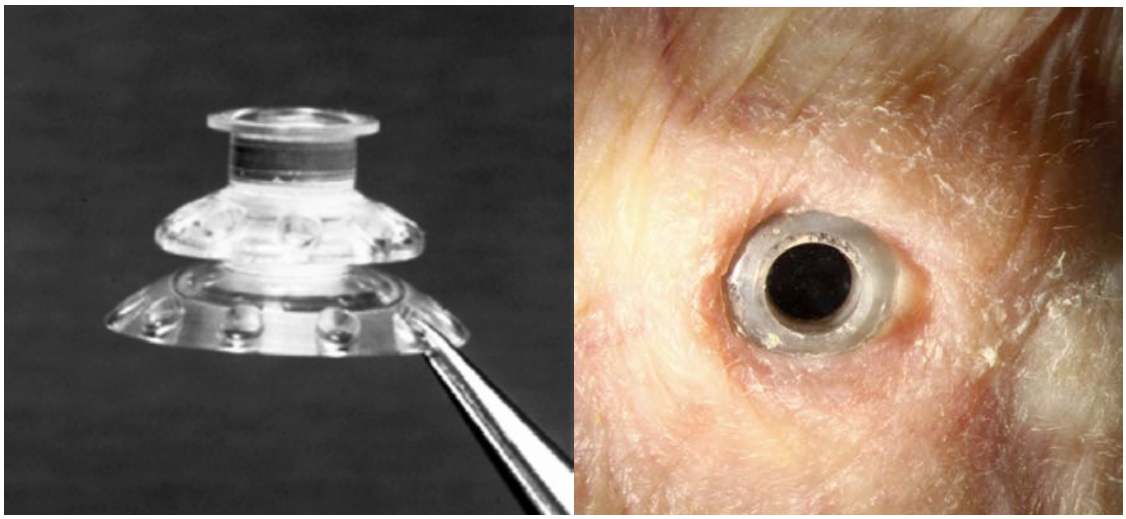


Figure 30. The Boston KPro Type II mounted without donor cornea (left) and its appearance after implantation thru the lid (courtesy of Keratoprostheses and Artificial Corneas, fundamentals and surgical applications) (right).

2.2 Indications of each type of Boston KPro

2.2.1 The Boston KPro Type I

The Boston KPro type I is generally indicated in cases of graft failure. In the user´s manual of the Type I Boston KPro published in 2008, the general indications for keratoprosthesis after failed grafts were outlined as follows:

1. At least one failed graft (plus/minus), with poor prognosis for further grafting
2. Vision less than 20/400 – with suboptimal vision also in the opposite eye
3. No end-stage glaucoma or retinal detachment
4. Contraindications: longstanding severe intraocular inflammation, autoimmune diseases, phthisis.

Good indications would include cases of recurrent corneal dystrophy, keratoconus, aphakic and pseudophakic bullous keratopathy. Thru the years, with accrued experience, the indications for a type I Boston KPro have expanded (Colby, 2011). Nowadays, herpetic keratitis, opacity with limbal stem cell deficiency like congenital aniridia, chemical injury, autoimmune cases like Stevens-Johnson /Lyell syndrome, mucous membrane pemphigoid, uveitis, are also indications for this procedure. Even pediatric corneal opacities are an indication for the type I Boston KPro due to its excellent optics as an alternative procedure to prevent amblyopia (Colby, 2011). Dohlman and colleagues thru years of experience have shown that inflammation has a negative role in the success of the type I Boston KPro, stating that there is a much worse prognosis in severe inflammatory diseases than in non-inflammatory diseases. Success in more likely in cases of dystrophy, bullous keratopathy, trauma, post-infectious leukomas, and prognosis is guarded in cases of Stevens-Johnson, pemphigoid, uveitis, severe chemical burn, etc. In increasing order of success, the indication may therefore be summarized in three categories:

1) auto-immune related corneal opacity and ulceration
2) chemical injury
3) non-autoimmune corneal graft failure

2.2.2 The Boston KPro Type II

The Boston KPro type II is indicated for end-stage dry eyes like pemphigoid, Stevens-Johnson, some chemical burns, where there is poor lid function due to symblepharon or keratinization of the ocular surface (Dohlman,

2005). Experience is limited to the Massachussetts Eye and Ear Infirmary and only around 15 patients have benefited from this procedure according to literature review (Ament, 2011).

2.3 Pre-operative Evaluation of the Boston KPro Type I candidate

- Complete medical history and pre-operative assessment of the patient´s general health status to find out which kind of anesthesia is best for the patient.

- Complete ocular surgical history. Ask for number of previously failed grafts and reasons why the graft failed, whether due to poor compliance of medications, poor follow-up, uncontrolled intraocular pressure. Ask for previous glaucoma surgery as the presence of prominent filtering blebs may impede the central fit of a bandage contact lens. Ask for previous retinal surgery as the status of the retina may affect visual prognosis.

- Visual acuity testing is for prognostication. Best-corrected visual acuity may be measured with hard contact lens when necessary. The accuracy of light projection is important to rule out end-stage glaucoma.

- Slit lamp examination to check the anterior segment, status of the iris, status of the lens.

- Tonometry may be done by finger palpation or pneumotonometry. Applanation tonometry may be inaccurate due to irregular corneal surface.

- Evaluations of blink mechanism and tear secretion. Good and complete lid apposition is mandatory for good contact lens adaptation. Otherwise, previous oculoplastic surgery to correct anatomical integrity must be performed prior to Boston Type I KPro surgery.

- Evaluation of chronic inflammation. The presence of active conjunctivitis, red eye, symblepharon and keratinization are relative contraindications for implantation of the Boston KPro Type I.

- Find out if the patient is phakic, pseudophakic or aphakic.

- A-scan biometry to find out the axial length for aphakic cases or when we deem that a lens extraction will be performed at the time of KPro surgery.

- B-scan ultrasonography to check the status of the retina, presence of surgical or medical retinal problems to be treated, like proliferative vitreo-retinopathy or macular edema. Check for optic nerve status for visual prognostication especially in cases with previously diagnosed glaucoma.

- External photographs for documentation.

2.4 Surgical procedure of each type of Boston KPro

2.4.1 Boston KPro Type I

The Boston type I keratoprosthesis can be obtained by direct ordering from the Massachusetts Eye and Ear Infirmary in Boston. The package comes with the front plate, the back plate, the titanium locking ring, an adhesive, a 3.0 mm manual punch trephine, and a white plastic rod with a hollow bore to assist in the assembly. A donor cornea is needed for this procedure; it may be from a fresh globe or a preserved cornea. The Boston type II keratoprosthesis, also approved by the FDA may be obtained also thru the same institution however, experience is limited to the said institution to date, and approval for use must be obtained from the Boston KPro team.

- The procedure may be performed under general anesthesia or local regional anesthesia (retrobulbar or peribulbar).

- A donor cornea may come from a fresh whole donor globe or a preserved cornea in storage media. Copious irrigation of the donor cornea with saline solution is done. **(Figure 31)**.

- The donor cornea is prepared for trephination.**(Figure 32)**.

- An 8.5 mm corneal button is trephined from the donor cornea using the surgeon´s preferred technique. **(Figure 33).**

- A concave base is used to mount the previously trephined donor cornea with endothelial side up. A 3.0 hole is punched in the middle of the graft using the manual punch trephine. Centration of the hole is critical **(Figure 34 and 35)**.

- An adhesive patch is used to help in stabilizing the pieces for assembly. The covering tape is peeled off and stuck on to a metal base. One of the round windows is peeled off to bare the adhesive part **(Figure 36)**.

- The KPro front plate is pressed down onto the adhesive with the most anterior part facing down and the stem facing up **(Figure 37)**.

- The 8,5 mm corneal graft with a central hole is slid over the stem using fine instruments like colibri and tying forceps. Care must be taken to damage the endothelium as minimum as possible **(Figure 38)**.

- The back plate is gently pushed against the endothelial side of the graft using fine instruments like colibri or tying forceps **(Figure 39)**.

- The titanium locking ring is placed in position using tying forceps **(Figure 40)**.

- The hollow bore of the white plastic rod is used to firmly push the titanium locking ring until an audible snap is heard signifying that it has been placed correctly in the groove behind the back plate **(Figure 41)**.

- The position of the ring should be inspected by profile view to assure a tight seal between the donor cornea and the KPro pieces **(Figure 42)**.

- The assembled KPro can be placed in visco-elastic or in storage solution while the patient´s eye is being prepared **(Figure 43)**.

- A Flieringa ring is recommended for cases of aphakia or when an IOL is to be explanted, or in cases of high myopia.

- Trephination of the opaque host cornea is performed according to the surgeons preferred technique whether manual or motorized trephine or even with femtosecond laser (**Figure 44)**.

- Hemostasis of bleeder vessels may be achieved with bipolar cautery or with the help of epinephrine in 1:10,000 dilutions.

- The iris should be left intact to prevent glare post-operatively. However in severely inflamed eyes, sphincterotomies may be performed to keep the iris as far away from the back part of the optic as possible as the iris may serve as a scaffold for the formation of retroprosthetic membranes. As for excessively large iridectomies, a pupilloplasty may be performed with prolene 10-0 sutures.

- As for the crystalline lens, removal should be performed with open-sky technique whether cataractous or not, and an aphakic KPro is implanted. However, a plano IOL may be implanted to keep the vitreous base as far back as possible. We try to preserve the posterior capsule if no IOL is to be

implanted for the same reason. If the patient is already aphakic, an aphakic KPro is implanted, a core vitrectomy may be necessary. As for pseudophakic eyes, the IOL may be left in place and a pseudophakic Boston KPro is implanted. An anterior vitrectomy may be performed as needed, especially when a glaucoma drainage device is implanted to assure proper functioning of the device.

- The assembled KPro is sutured in place in similar fashion to a standard penetrating keratoplasty. We use 10-0 nylon sutures and the knots are buried onto the stroma (Figure 45).

- Anterior chamber is deepened with saline solution and or viscoelastic to keep the iris as far back as possible from the optical cylinder.

- During the surgery, protection of the macula from the microscope light is recommended by using a wet sponge.

- A temporal mini-tarsorraphy is recommended in cases where contact lens loss is expected as in cases of mild lagophthalmos or cases of neurotrophic ulcers. A bandage contact lens may be applied immediately at the end of the procedure according to surgeon´s preference (Figure 46).

- Antibiotic drops, steroids and anti glaucoma medications are instilled at the end of the procedure prior to pressure patching with protective shield.

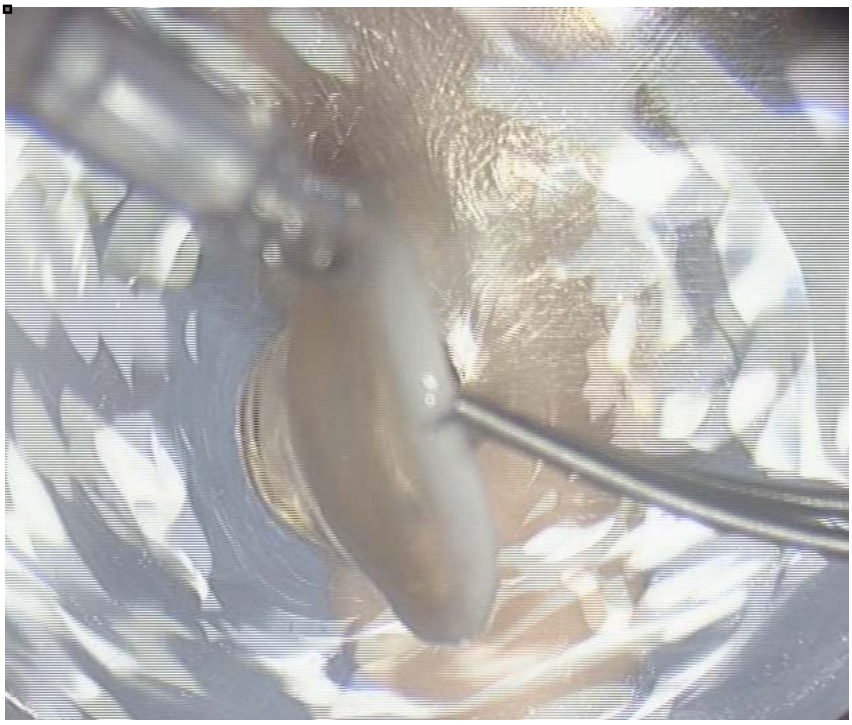


Figure 31. Copious washing of the donor cornea.

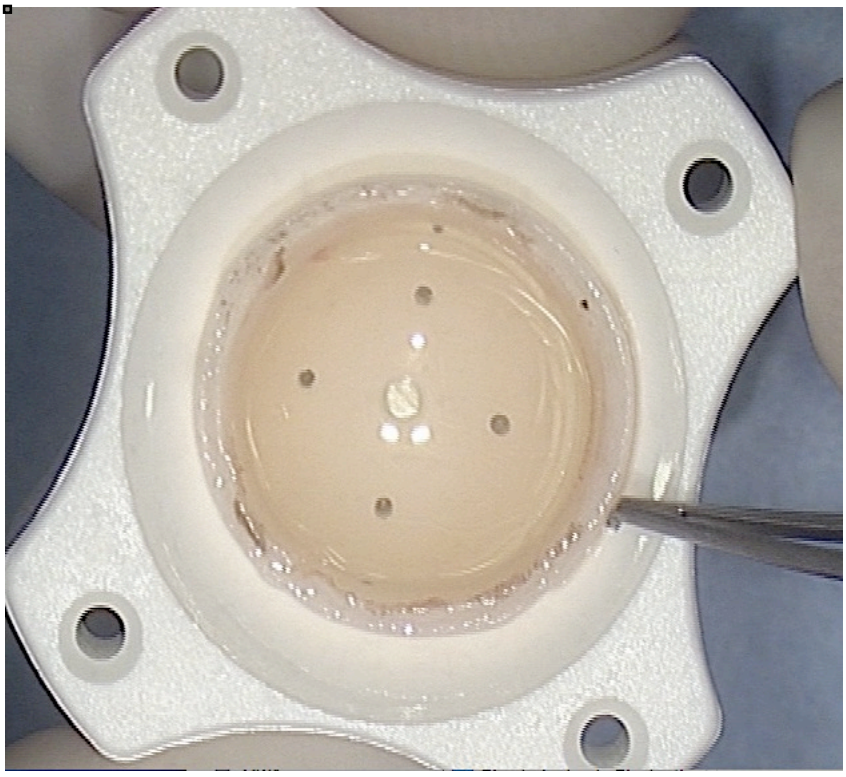


Figure 32. Mounting of the donor cornea for trephination.

Figure 33. 8.5 mm trephination of donor cornea using a punch trephine.

Figure 34. Mounting the 8.5 mm donor cornea on a Teflon block with a metal base.

Figure 35. Central 3 mm trephination using a manual punch trephine.

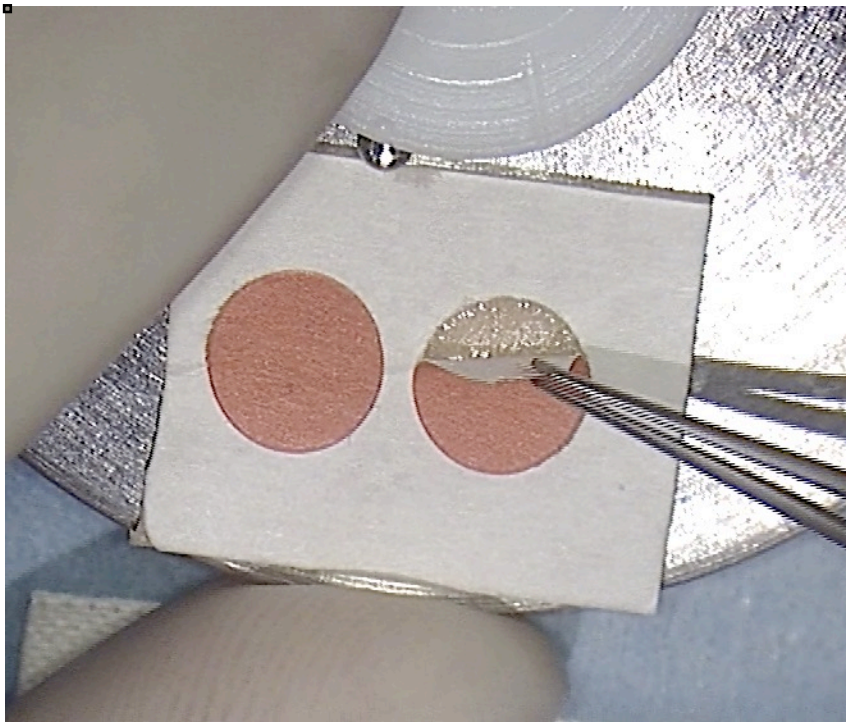


Figure 36. Adhesive helps in stabilizing the parts. Peeling off the adhesive cover.

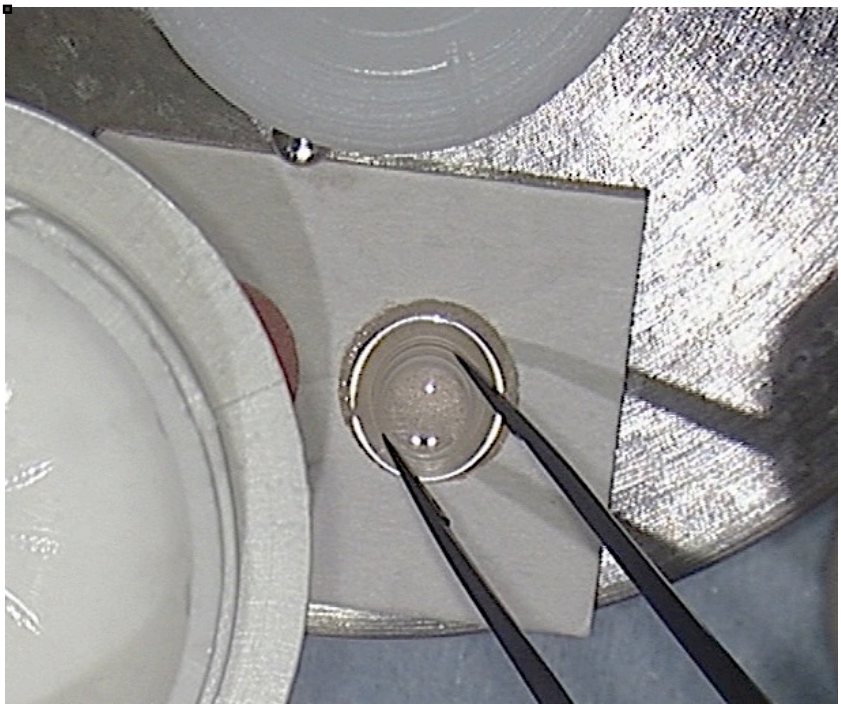


Figure 37. Mounting of the anterior front plate on the adhesive with the stud facing the surgeon.

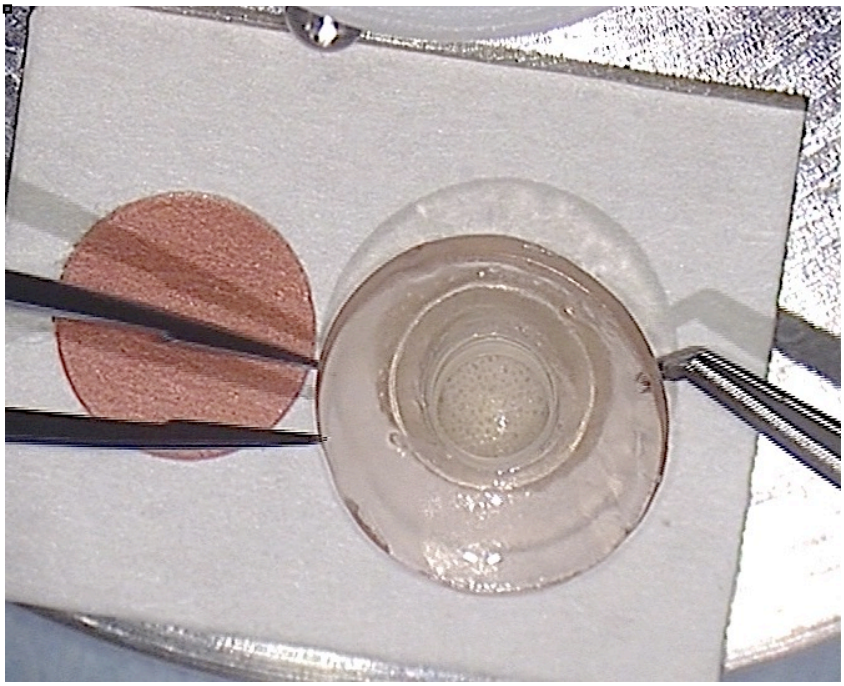


Figure 38. Mounting of the donor cornea over the anterior plate with the endothelial side facing the surgeon.

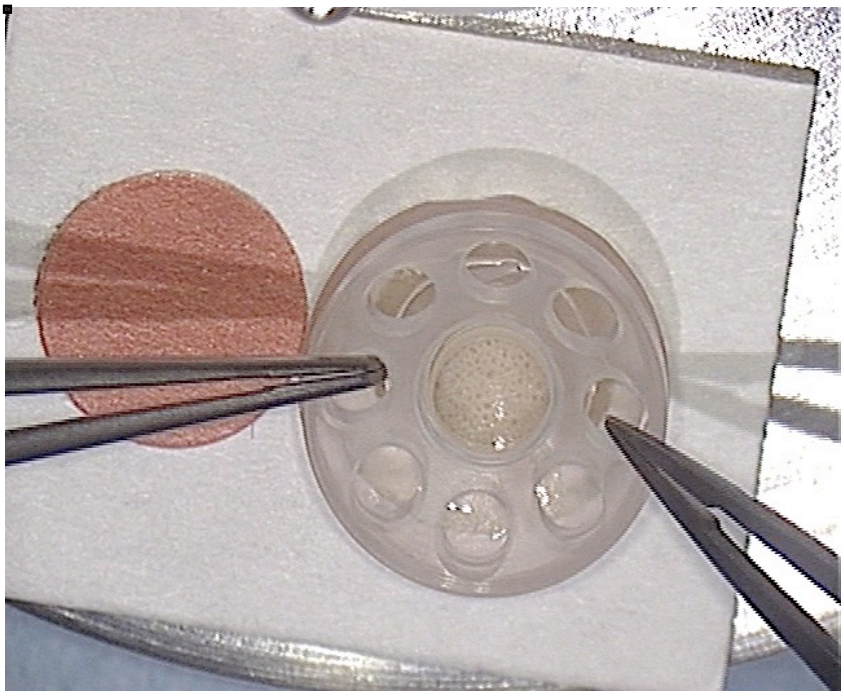


Figure 39. Mounting of the back plate over the donor cornea.

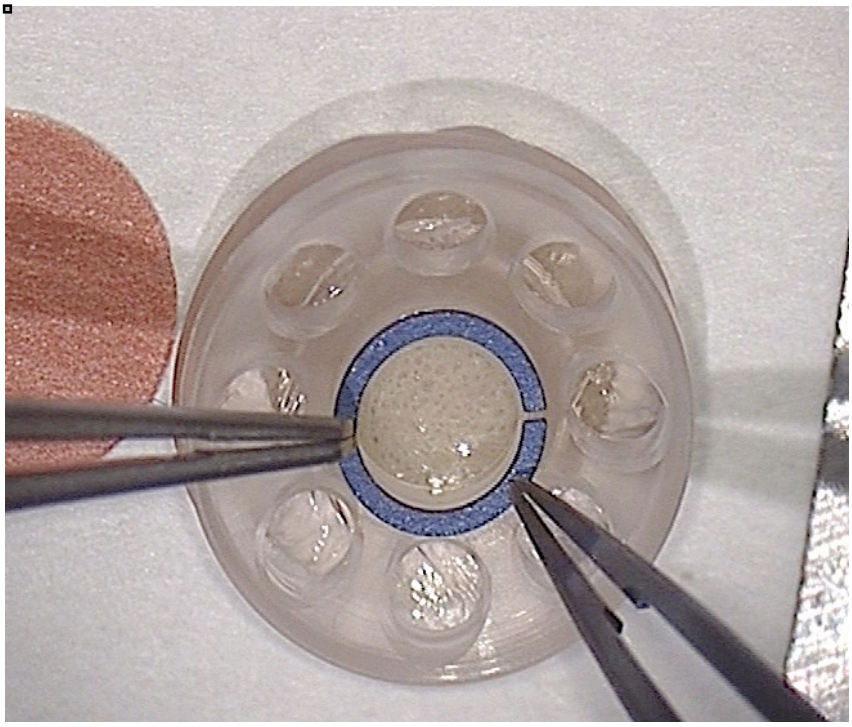


Figure 40. The titanium locking ring is placed over the back plate.

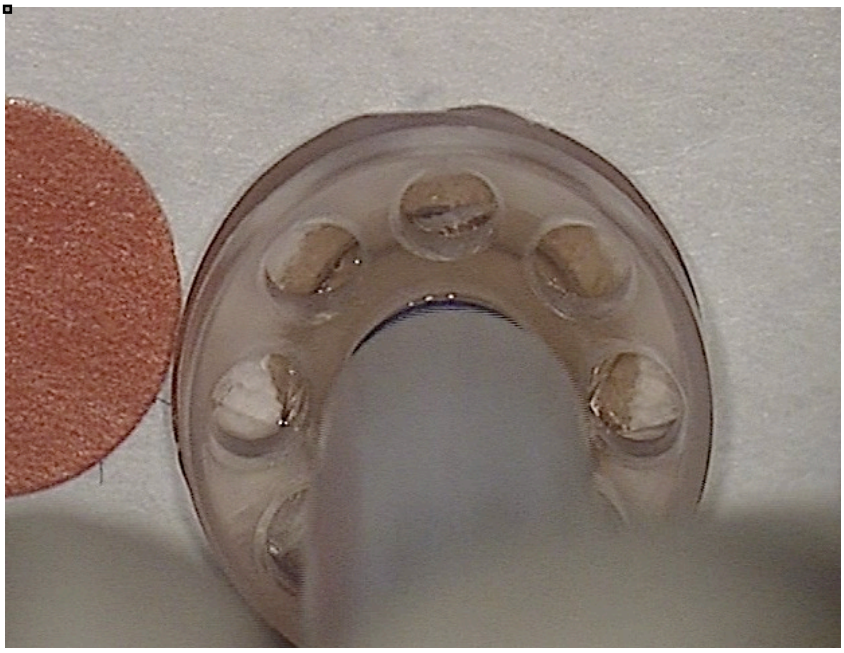


Figure 41. A hollow plastic rod is used to push the locking ring firmly against the back plate.

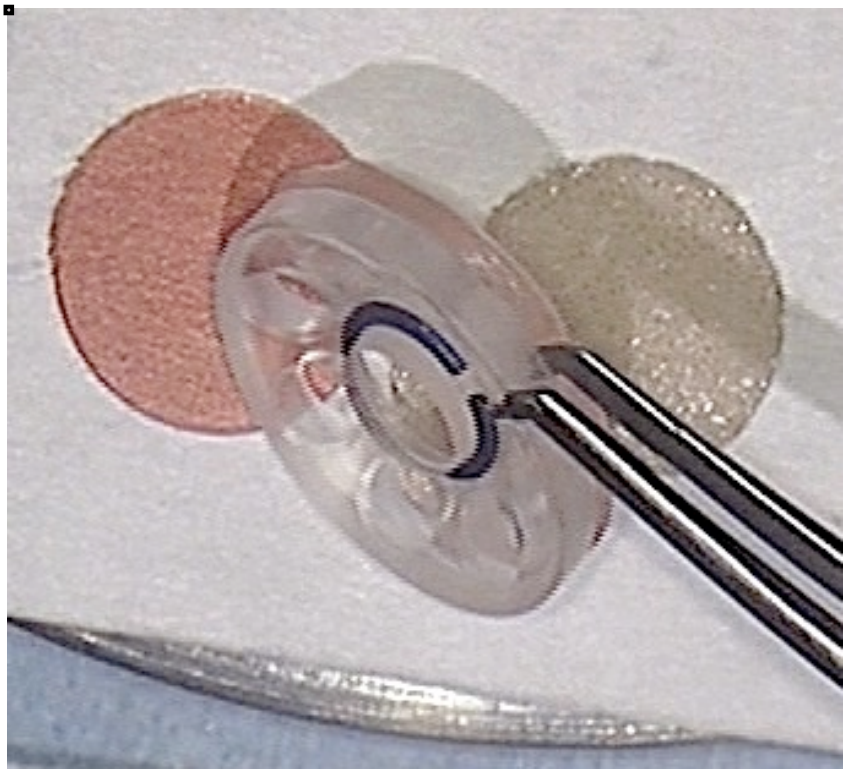


Figure 42. A lateral view of the mounted Boston Type I keratoprosthesis showing correct position of all parts.

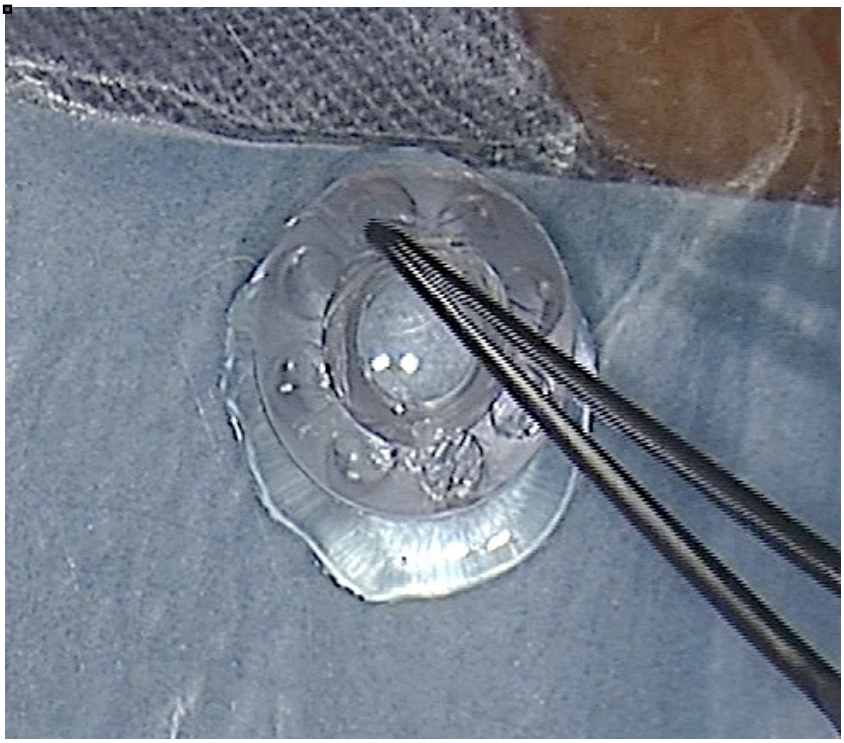


Figure 43. The mounted prosthesis is placed in viscoelastic in a petri dish while surgery is performed on the eye.

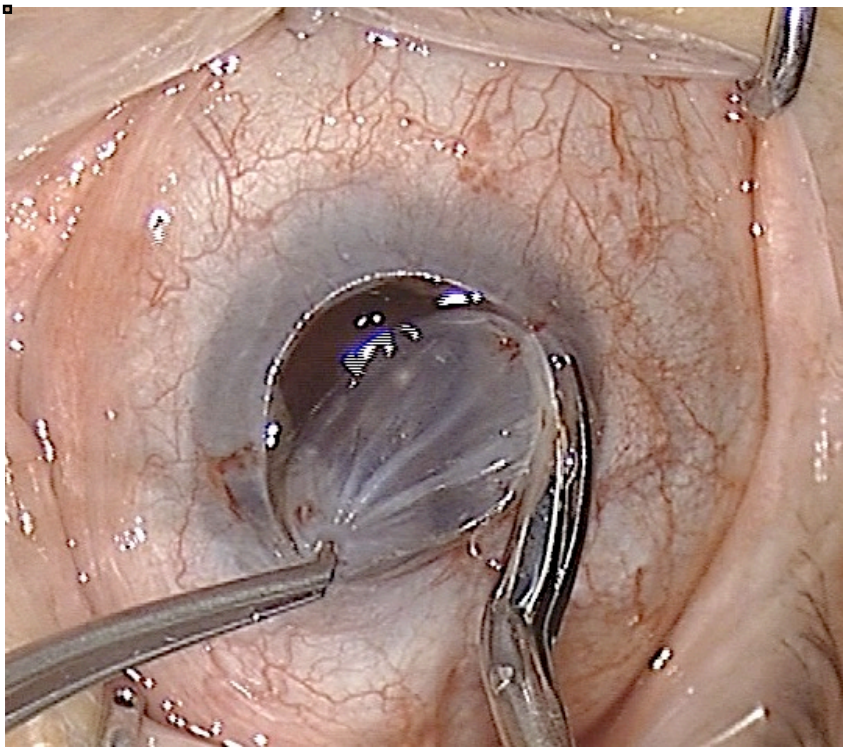


Figure 44. Host cornea trephination is completed with corneal scissors.

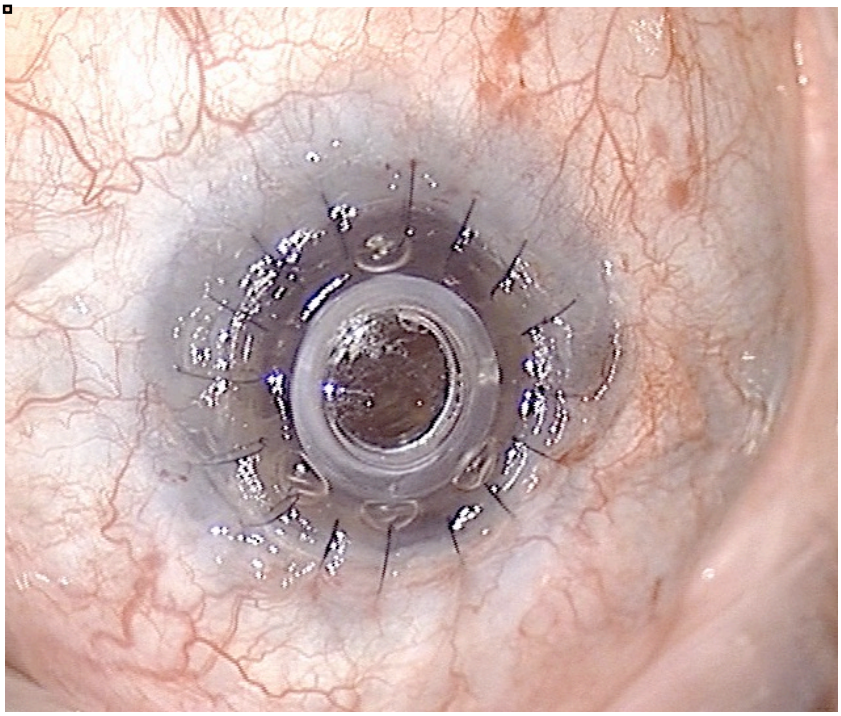


Figure 45. The prosthesis now in place in the host cornea with 16 interrupted 10-0 nylon sutures whose knots are buried into the stroma.

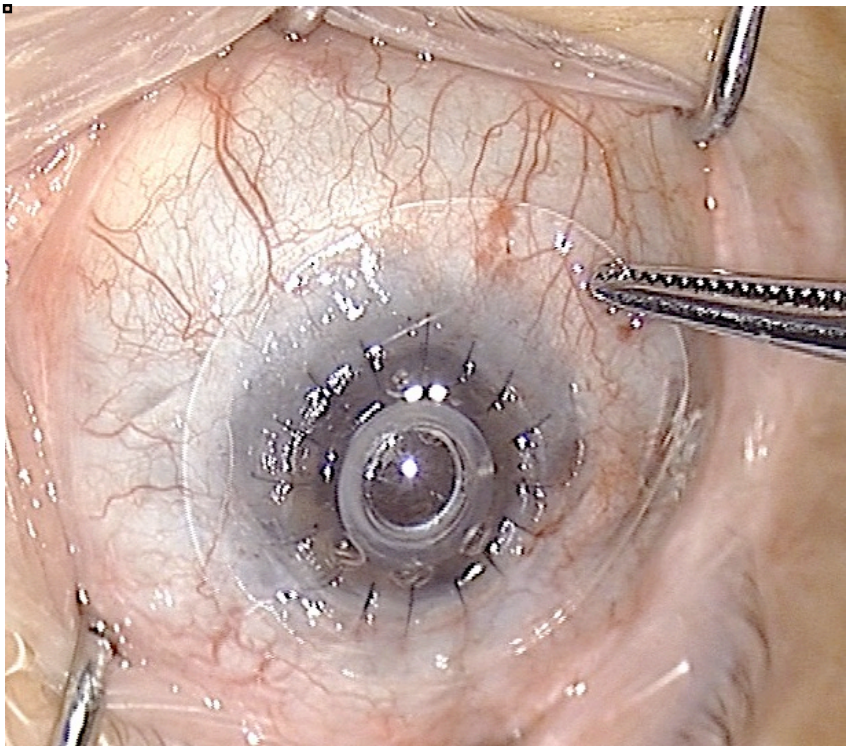


Figure 46. A large bandage contact lens is placed at the end of the surgery.

2.4.2 Boston KPro Type II

The principle of assembly of the Boston KPro type II is similar to that of Boston KPro type I where a donor cornea is needed. Since this prosthesis is trans-palpebral, the mounted KPro will be covered with lid skin. After exposing the ocular surface, all pannus and conjunctival fibrous tissue is dissected to expose bare sclera as far as possible all the way to the fornices. Cauterization in the area of the trephination is crucial so as to avoid bleeding towards the vitreous cavity. Trephination is performed as described above for the Boston KPro type I. The retina and vitreous cavity are examined using a vitrectomy lens and necessary procedure should be done at this point by the retina surgeon since once the trans-palpebral prosthesis is in place, anatomical landmarks are lost and posterior segment surgery will be very difficult to perform. The rest of the procedure, until fixation of the mounted KPro using nylon sutures as in the Boston KPro type I, is followed.

The next step is to evert the lower and upper lids to remove all conjunctival tissue towards the fornices. The idea is to remove all epithelium so that the bulbar and tarsal surfaces would fuse together and to prevent epithelial encystment beneath closed eyelids. Bleeding is expected since these eyes have end-stage ocular surface dryness, fibrosis and keratinization that judicious use of cautery is required. The lid margins are then excised making sure that no eyelash follicles are left in place. Trephination of the host cornea is performed and the rest of the surgery proceeds in similar fashion to a Type 1 surgery (whether phakic, aphakic or pseudophakic).

Once the prosthesis is sutured on the host cornea, peribulbar injection of wide spectrum antibiotics and triamcinolone is done. Closure of the lids is performed with vicryl sutures to fuse the upper and lower tarsi and the eyelid

margins are sutured with nylon sutures over plastic bolsters. Vannas scissors are used to create a notch on the edge of the upper lid to allow the keratoprosthesis nub to protrude thru the closed lids (Palioura, 2015).

2.5 Post-operative care of the Boston KPro

The success of the surgery not only lies in the correct indication and surgical procedure, but more importantly in the post-operative care and follow-up of the patient.

The protocol at our eye center is to see the patient the following day, after one week, weekly for the first month and every two to three months thereafter for life. If there are problems, then the follow-up schedule may be modified accordingly.

Post-operative medication consists in oral steroids like prednisone 0.5-1.0 mg per kilogram body weight depending on the amount of inflammation expected per case-to-case basis. This is tapered over a two to three week period. Eye drops include prednisolone acetate 1% or dexamethasone phosphate 4-5 times a day then switched to a milder steroid like fluorometholone over several months according to the amount of inflammation present. Wide spectrum antibiotic drops should be used as prophylaxis against infection and is likewise tapered to once a day over several months. In single eyes or in autoimmune or chemical burn cases, 14 mg/ml vancomycin is added. Topical antibiotic use is for life and compliance is key to success, such that patients or caregivers must have the same commitment as the surgeon to religiously comply with the treatment protocol.

3. AIMS

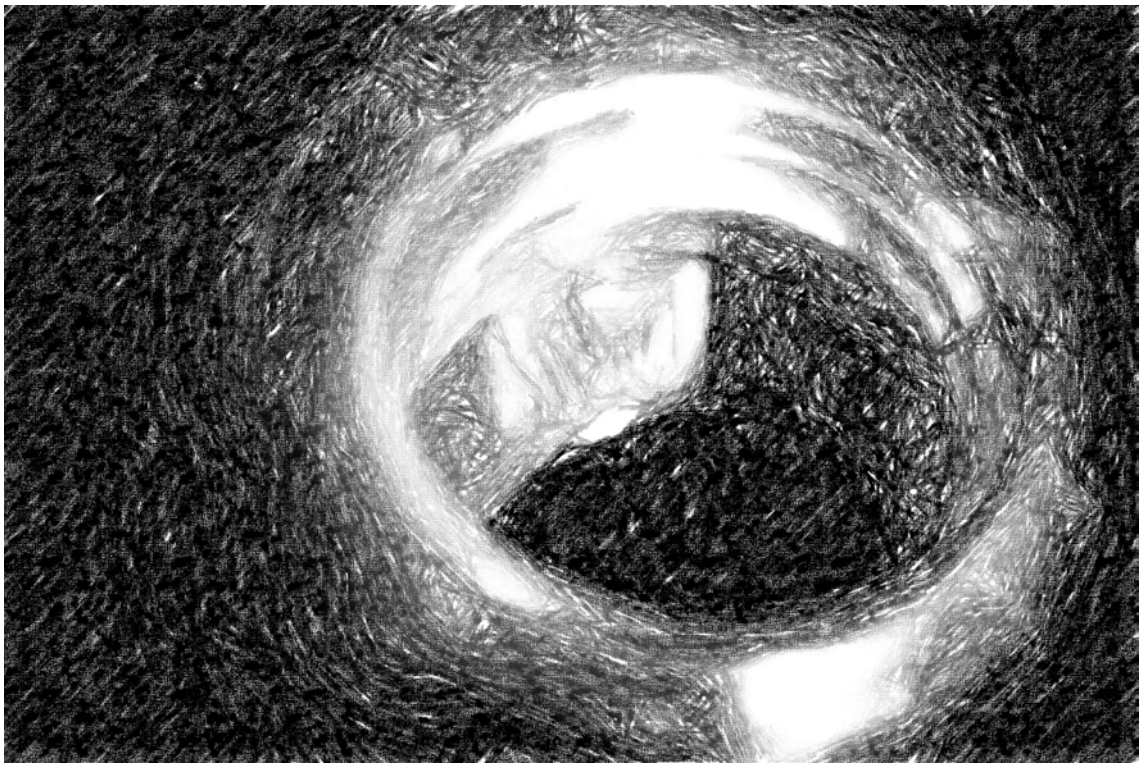
1. What are the anatomical and visual outcomes in challenging indications for the Boston KPro Type I like chemical burns or autoimmune cases?

2. How do primary diagnosis and post-operative complications affect the visual acuity results of the Boston KPro Type I over time?

3. What are the most common post-operative complications of the Boston KPro Type I?

4. Can the Boston KPro Type I be used as a primary surgery for cases wherein a conventional keratoplasty is predicted to fail?

5. How do the anatomical and visual outcomes, and post-operative complications of the Boston KPro Type I compare with other artificial corneas in the long-term?



4. METHODOLOGY

The success of the Boston KPro Type 1 has been demonstrated over the years, since its approval by the FDA in 1992. In the last 5 years, there has been an exponential increase in its use outside the United States (Cruzat, 2015) (Figure 47).

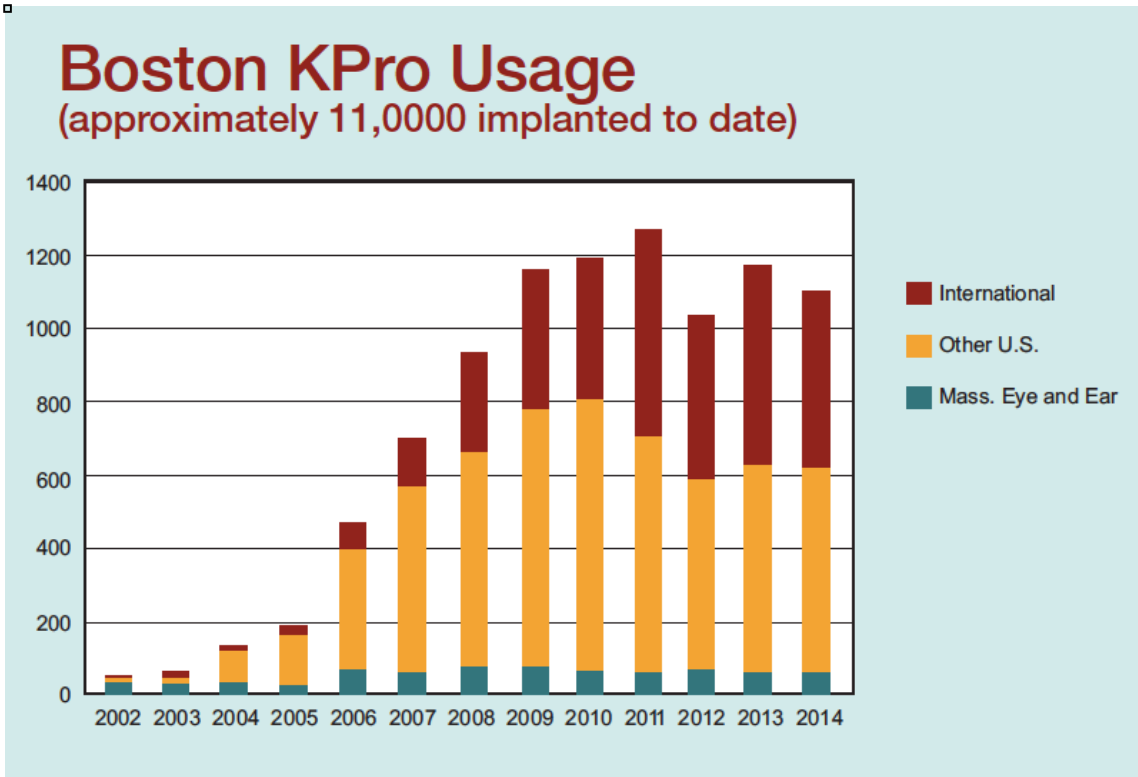


Figure 47. The continuous rise of the use of the Boston KPro Type 1 worldwide (taken from the Boston KPro Newsletter, 2015).

In Spain, our eye center, the Centro de Oftalmología Barraquer, is the first one to implant the Boston KPro Type 1 in May 2006. Few other eye centers have followed since then. In parallel fashion, the University Eye Clinic in Salzburg, Austria started implanting it at about the same time. Like our eye center, the Salzburg team has years of experience with the biological KPro´s like the OOKP and their criteria of indications and post-operative care are similar to ours.

We reviewed all the cases of Boston KPro type 1 implanted at the two eye centers from May 2006 up to December 2014. A total of 117 operated eyes were encountered. 89 cases were from the Barcelona (B) team and 29 cases were from the Salzburg (S) team. The surgeons from the Barcelona team were Juan Alvarez de Toledo, Rafael Barraquer and Maria Fideliz de la Paz, while the surgeons from the Salzburg team were Günther Grabner and Joseph Stoiber.

All patients signed an informed consent for "compassionate use" prior to the prosthesis' approval by the EMA in 2013. After which time, all patients signed a standard informed consent where the kind of surgery, anesthesia, possible complications and alternatives are explained in detail. The KPro refractive power was chosen based on each patient´s lens status. The surgical procedure was performed according to the technique explained in Section 2.4.1 (Surgical Steps for the Boston KPro Type I). The post-operative standard treatment regimen was a third generation quinolone (levofloxacin) or aminoglycoside (tobramycin), vancomycin 14 mg/ml antibiotic drops, and prednisolone acetate or dexamethasone phosphate steroid drops. Bandage contact lens was fitted and changed every three to four weeks. Majority of patients wore disposable bandage contact lens, while a few others needed large diameter non-disposable silicone contact lens for better fitting. Patients with pre-existing glaucoma were treated with topical medication or surgery. All complications were treated medically or surgically immediately after diagnosis. Age, gender, number of previous corneal transplants and previous co-morbidities were noted for descriptive statistics.

Anatomical success was defined as permanent retention of the prosthesis. All cases that underwent exchange of the first prosthesis were considered to be anatomical failures.

Visual acuity was measured in decimal units and later on translated to LogMar units. No light perception was defined as 0.001 in the decimal scale (3.00 LogMar), light perception only as 0.002 (2.7 LogMar), hand motion as 0.005 (2.3 LogMar), and counting fingers as 0.015 (1.82 LogMar) (Schulze-Bonsel, 2006). Functional success in our study was defined as visual acuity better ≥ 0.05 decimal units. Legal blindness according to the World Health Organization is defined as best corrected visual acuity of 0.05 decimal units in the best eye or visual field limited to 20 degrees.

Primary diagnosis for each case was noted and this was determined as the main disease of the patient that initially led to the first corneal graft, or of the keratoprosthesis surgery if no previous corneal graft was performed. We divided our patients into three main categories: autoimmune, chemical or thermal burn, and "others". Primary diagnosis was taken into account to evaluate if it had any implication on visual acuity and retention of prosthesis.

Post-operative complications were noted and correlated with visual acuity and retention of prosthesis. Only those that may directly affect visual acuity in the post-operative period were considered relevant for analysis. They were grouped accordingly: retroprosthetic membrane, posterior segment complications, infections and stromal necrosis, "de novo" or worsened glaucoma and no complications.

Paper 1 (Anatomical survival and visual prognosis of Boston Type 1 keratoprosthesis in challenging cases), published in January 2014 was a retrospective study on 67 cases from the Barcelona (B) and Salzburg (S) teams. 41 eyes were from the B team and 26 eyes were from the S team. We chose only one eye in bilateral cases to avoid statistical bias and excluded the case of

one child (2 years old). Visual acuity data until the first anatomical failure was included for statistical analysis. One case was excluded from analysis due to lack of visual acuity data. Therefore a total of 61 cases were included for the final statistical analysis. Anatomical survival in this paper was studied for all cases grouped together, as well as in separate groups according to primary diagnosis and according to post-operative complications. Visual acuity or functional success was analyzed at 1, 2 and 3 years for all cases grouped together, separately according to the primary diagnosis and separately according to complications. In the results sections, we present the findings on the same 61 cases whose data have been updated until December 2014.

Paper 2 (Influence of primary diagnosis and complications of visual outcomes in patients receiving a Boston Type 1 keratoprosthesis), published in May 2014 was a review on 67 eyes from the B and S teams. 41 eyes were from the B team and 26 eyes were from the S team. Cases with follow-up less than 3 months were not included. Visual acuity results until last follow-up (even if exchange of prosthesis had to be performed), were included for analysis. 6 cases were excluded due to follow-up data less than 3 months and 2 other cases were excluded due to lack of visual acuity results after KPro exchange. Therefore, a total of 59 cases were included for final statistical analysis. This paper was written as a continuation of Paper 1 since we were able to demonstrate statistically that visual acuity results were influenced by primary diagnosis and post-operative complications. We also found out that that patients with multiple complications were difficult to analyze statistically. Therefore, we evaluated our functional results by grouping our cases based on the evolution of post-operative visual acuity, with subsequent analysis of the primary diagnosis and post-operative complications in each group. The cases

were grouped accordingly: those whose visual acuity improved to better than 0.05 and was maintained until the last follow-up, those whose visual acuity of 0.05 was reached at one point in time but later on worsened, and those without any relevant improvement in visual acuity.

Paper 3 (Pronóstico visual y complicaciones posquirúrgicas en queratoprótesis de Boston tipo 1), published in February 2013 was a review on 42 eyes operated by the B team. Patients with follow-up less than 3 months were excluded from analysis. Therefore, a total of 41 eyes were included for final statistical analysis. This paper presents the visual prognosis by presenting the best-ever achieved visual acuity as well as the visual acuity at last follow-up. We also enlist in detail the post-operative complications that were encountered.

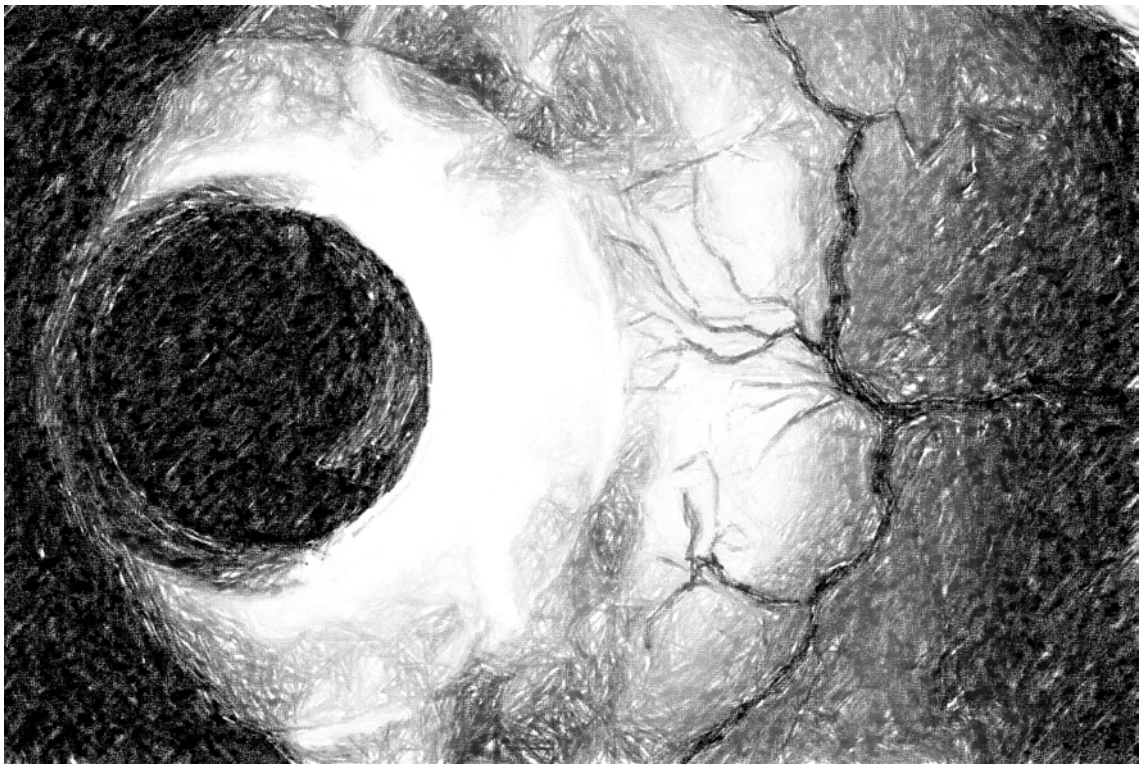
Data Analysis

In Paper 1, statistical analysis on anatomical and visual acuity results was performed using Kaplan-Meier survival analysis. The Kaplan-Meier is a non-parametric test to estimate the survival function from lifetime data. Log-rank test was performed on all Kaplan-Meier results to compare the survival distributions of the time-stratified samples based on primary diagnosis and on post-operative complications. Log-rank test is a non-parametric test that reports a chi-square value. A p-value less then 5% indicated statistically significant difference between groups. Box-plots were also done to visually display visual acuity data at 1, 2 and 3 years follow-up, and compare groups according to primary diagnosis and post-operative complications. Box plots

are also non-parametric tests. The median values are also presented together with the box plots as the band inside each box.

In Paper 2, the evolution of individual cases are presented as line graphs according to the aforementioned grouping based on visual acuity progress. Cross tabulations were done on primary diagnosis, number of previous graft failures, post-operative complications against groupings based on visual acuity evolution. A Kruskal-Wallis test was performed to see if there was statistically significant difference when comparing the number of previous grafts before Boston KPro Type I implantation. The Kruskal-Wallis test is a non-parametric method for comparing two or more independent samples of equal or different sample sizes.

In Paper 3, a scatter plot was performed to summarize the visual acuity results at two different points in time: the pre-operative visual acuity and the post-operative visual acuity. One scatter plot was performed on the pre-operative visual acuity against the best ever-achieved visual acuity in the post-operative period, and another scatterplot on the pre-operative visual acuity against the visual acuity at final follow-up. A scatter plot is a type of a mathematical diagram using Cartesian coordinates to display values for two variables for a set of data. With these two graphs we show the general visual prognosis of the all cases.



5. RESULTS AND DISCUSSION

5.1 Patient Demographics

The average age of the patients was 54 years (range: 2-89 years). 62% were male and 38% were female. In bilateral cases, only one eye was included in the final statistical analysis to avoid bias.

Mean follow-up time was 37 months (range: 1-54 months) or 3.1 years.

The mean number of previous grafts prior to Boston KPro Type I implant was 2.27 (range: 0-9 grafts). A total of 11 patients underwent surgery as a primary procedure. 15 patients had 1 previous graft, 15 patients had 2 previous grafts and 22 patients had three or more previous grafts.

The primary diagnoses, accordingly grouped as mentioned in the methodology section were (in increasing order of frequency):

1) Chemical or thermal burn = 12 eyes.
2) Autoimmune disease = 16 eyes (*Stevens-Johnson/ Lyell Syndrome/ mucous membrane pemphigoid/ graft-versus-host disease/ immune tactoid keratopathy).*
3) Other diagnoses = 33 eyes (aphakic or pseudophakic bullous keratopathy, congenital aniridia, leukoma post-infectious keratitis, ocular trauma, congenital corneal opacities, corneal ectatic disease, calcific keratopathy due to collagen vascular disease, neurotrophic keratopathy, limbal stem cell deficiency due to contact lens abuse, congenital glaucoma and cicatricial trachoma.

5.2 Anatomical Outcomes

Our almost 60 years of experience with different kinds of keratoprosthesis has taught us that retention of the prosthesis is our gauge of success. However, we have also learned that several factors significantly affect anatomical retention and we were able to demonstrate this in two papers about our long experience on the biological keratoprosthesis OOKP and Tibia KPro. (Michael, 2008; de la Paz, 2011). Following these two publications, we analyzed our Boston KPro Type I data in a similar fashion by measuring the anatomical outcomes, taking into account all cases altogether, taking into account the primary clinical diagnosis, and taking into account the complications encountered in the post-operative period.

As mentioned in the methodology section, anatomical success was defined as retention of the prosthesis. The anatomical survival rate for all cases, as shown in Paper 1 was 95% at 1 year, 85% at 2 years, 82% at 3 years and 78% at 5 years. Updated data shows a 77% survival at 3 years (**Figure 48).**

Taking into account the primary diagnosis based on the categories mentioned above, the outcome of autoimmune cases was similar to the group with "other diagnoses" and better than those with chemical/thermal burn **(Figure 49).** The survival rates at three years are as follows: 84% for "other diagnoses", 69% for autoimmune cases and 61% for chemical/thermal burn cases. There was a tendency for the chemical/thermal burn group to worsen from three years onwards, whereas the autoimmune cases and the group with "other diagnoses" showed stable results thru time. However, using the log rank test to compare the anatomical success in the three diagnostic categories,

there was no statistically significant difference (p value = 0.083). **Figure 50** shows the anatomical survival of cases taking into account the impact of complications encountered in the post-operative period. It appears that retroprosthetic membrane barely affects anatomical retention while infection and stromal necrosis have the worst impact on anatomical success. The survival rates at three years are as follows: 100% for retroprosthetic membrane, 92% for no complications, 86% for posterior segment complications, 83% for glaucoma, 61% for multiple complications and 50% for infection/stromal necrosis. Results are consistent thru time. Log rank test to compare the anatomical success in the six categories showed no statistically significant difference between groups (p value = 0.197).

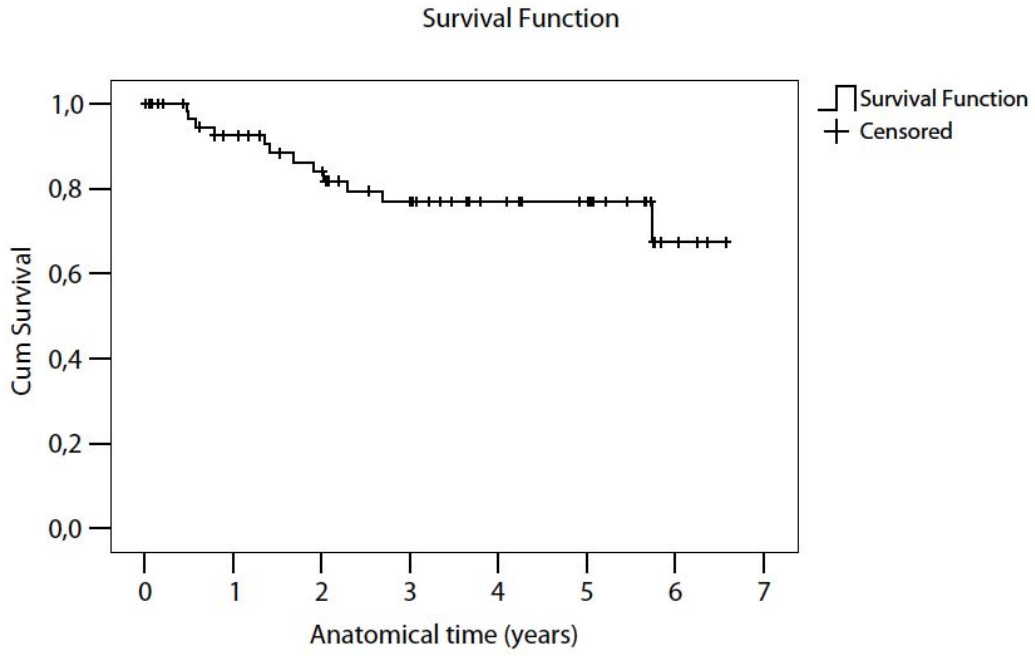


Figure 48. Kaplan-Meier anatomical survival curve (retention of the prosthesis) for all cases showing updated data of 77% survival rate at 3 years. (from Paper 1 with presently updated data).

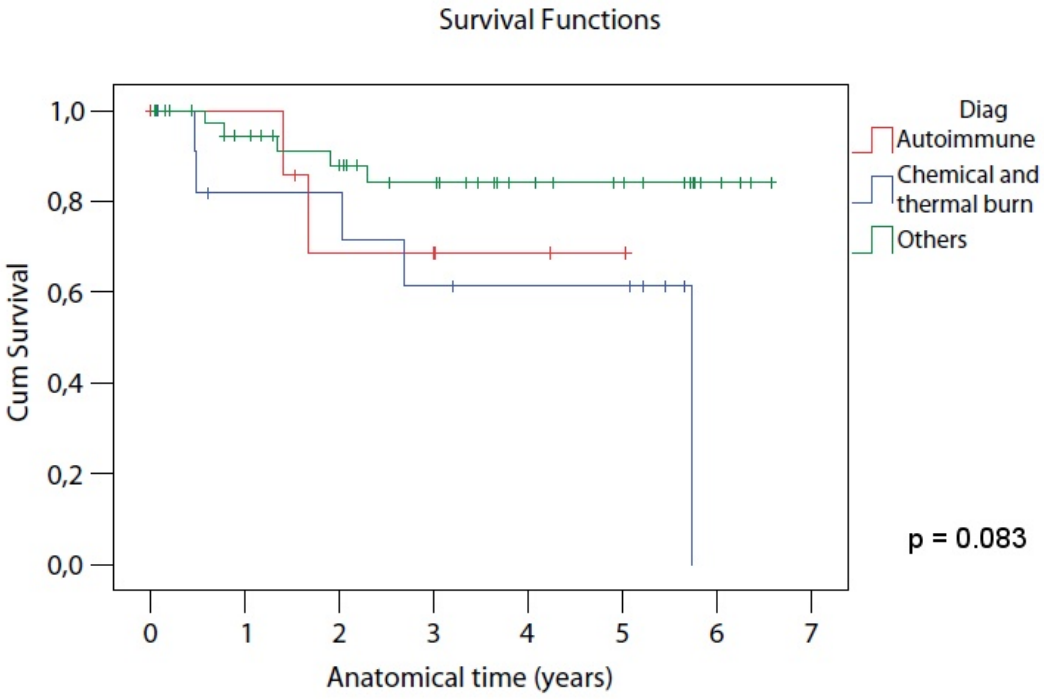


Figure 49. Kaplan-Meier anatomical survivals (retention of the prosthesis) taking into account the primary diagnosis. Tendency is worse result for chemical and thermal burn cases after 5 years. However, Log rank test showed no statistically significant difference from autoimmune case and "other" diagnoses (from Paper 1 with presently updated data).

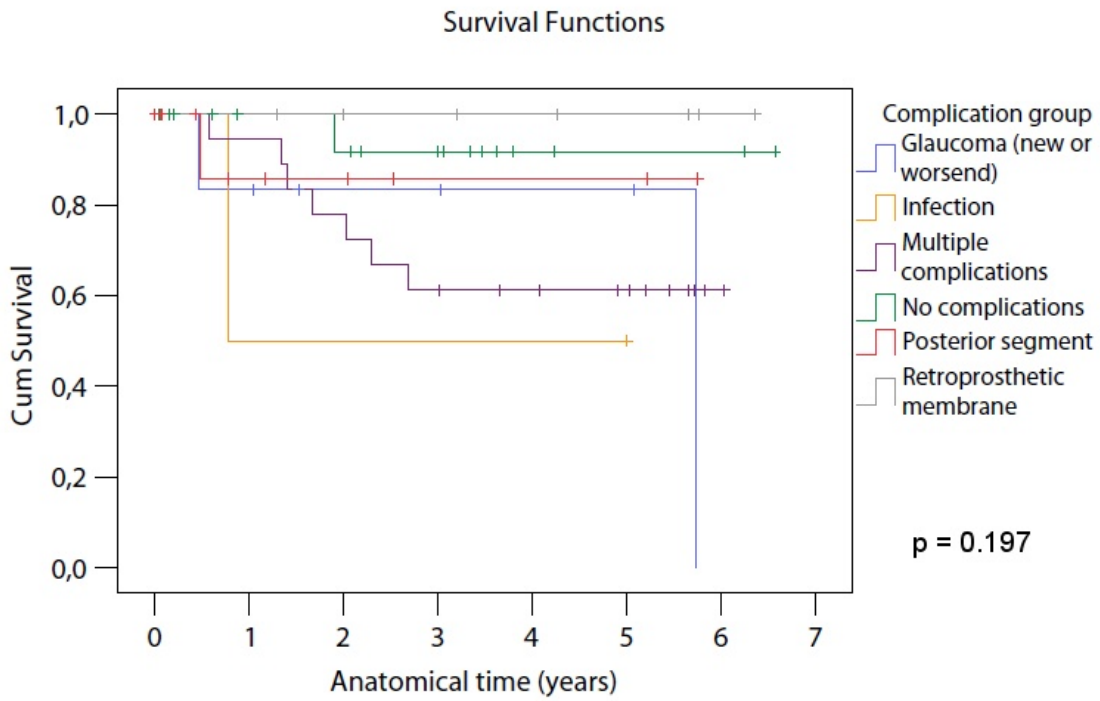


Figure 50. Kaplan-Meier anatomical survivals (retention of the prosthesis) taking into account the post-operative complications. Tendency is for best results in cases with retroprosthetic membrane and worst results for cases with infection. However, Log rank test showed no statistically significant difference compared to other post-operative complications.

5.3 Visual Acuity Outcomes

As mentioned in the methodology section, functional success was defined as visual acuity better or equal to 0.05 decimal units. The median pre-operative visual acuity was 2.3 LogMar units (hand movement), 1.0 at 1 year, 1.0 at 2 years and 0.96 at 3 years. The functional survival rate taking into account all cases was 45% at 3 years (**Figure 51**).

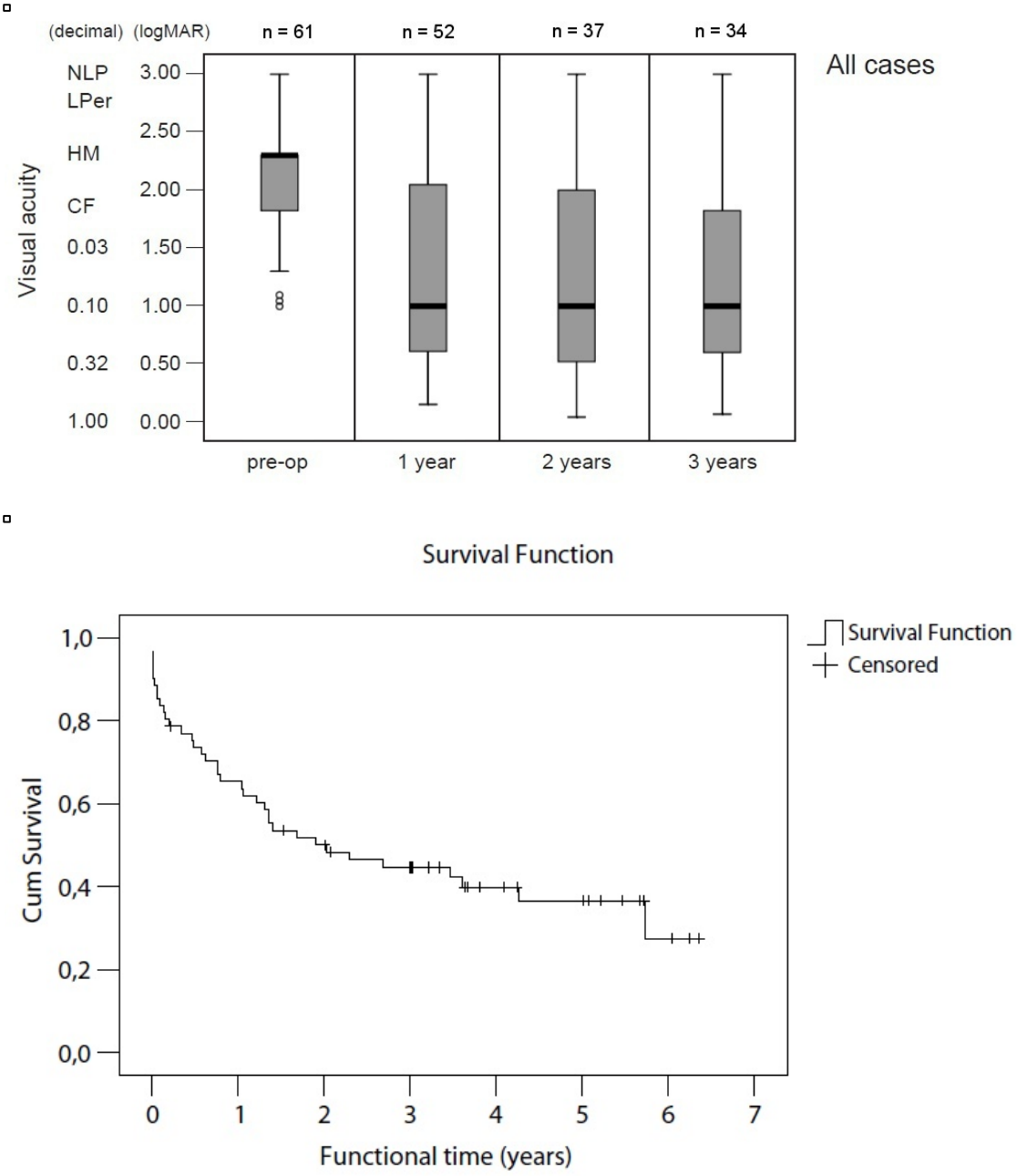


Figure 51. Visual acuity progression thru time of all cases showing improvement and stability thru the years using boxplots (upper), and using Kaplan-Meier functional survival (VA ≥ 0.05 decimal units) we can see a decline in the first 2 years with stability from 3 to 5 years (lower) (from Paper 1 with presently updated data).

Taking into account the primary diagnosis, the chemical/thermal burn and autoimmune groups had better visual acuity results at 1 year post-operatively compared to the group with "other diagnoses". However, there was worsening of results in autoimmune cases and "other diagnoses" at 3 years. Comparing all three diagnostic categories thru time, the chemical/thermal burn group had the best improvement from 2.3 LogMar units pre-operatively, 0.69 at 1 year, 0.52 at 2 years and 0.39 at 3 years. The group with "other diagnoses" also showed improved visual acuity, with 2.2 pre-operatively, 1.18 at 1 year, 1.52 at 2 years and 1.54 at 3 years. The autoimmune group showed initially marked improvement, with 2.3 pre-operatively, 0.65 a 1 year, 0.15 at 2 years and eventual worsening with 1.5 at 3 years. These are median values. The updated Kaplan Meier curves show quite similar long-term results for all three groups. Survival rates at three years are as follows: 50% for chemical/thermal burn, 47% for autoimmune cases and 43% for "other diagnoses". Log rank test with p value of 0.73 showed no statistically significant difference (Figure 52).

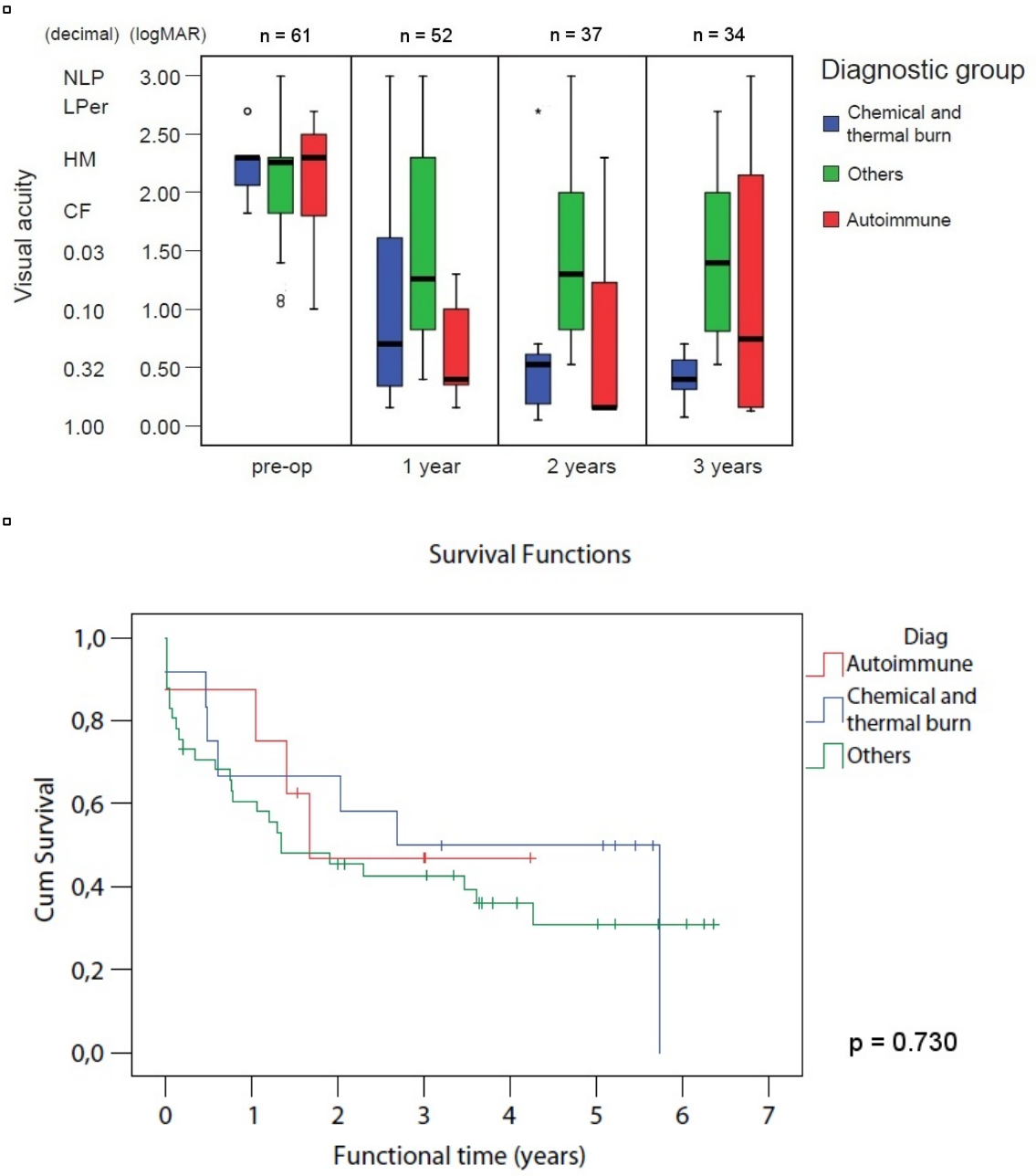


Figure 52. Visual acuity progression thru time of different diagnostic categories showing stable improvement in chemical and thermal burn cases using box plots (upper) and in the Kaplan-Meier functional survival (VA ≥ 0.05 decimal units) we can see a decline in the first 2 years with stability from 3 to 5 years (lower). Log rank test showed no statistically significant difference between groups (taken from Paper 1 with presently updated data).

Cases with only one kind of complication were analyzed separately to better investigate the impact of each complication on visual acuity. Cases with multiple complications, meaning more than one kind of post-operative complication, were put under the group of "multiple complications". The best visual acuity in the long-term was found in patients with no complications, only glaucoma or only retroprosthetic membrane. Much worse visual acuity was found in patients with posterior segment complications or multiple complications. Analyzing the visual acuity results thru time in each of the complications, patients with no complications had the best results, with 2.3 pre-operatively, 0.82 at 1 year, 1.26 at 2 years and 0.92 at 3 years. Patients with only glaucoma also showed stable visual acuity, with 2.3 pre-operatively, 0.89 at 1 year, 0.15 at 2 years and 0.41 at 3 years. Patients with retroprosthetic membrane showed improved results with 2.0 pre-operatively, 1.19 at 1 year, 1.1 at 2 years and 0.60 at 3 years. The two cases with only infection had similar results with 1.9 pre-operatively and 2.0 at 1 year. In 18 eyes with multiple complications, visual acuity improved from 2.3 pre-operatively to 1.0 at 1 year, 1.3 at 2 years and 1.3 at 3 years. Patients with posterior segment complications showed the worst visual acuity results, with no change in visual acuity of 2.3 pre-operatively until 3 years. These are median values. The updated Kaplan-Meier survival curves show that posterior segment complications worsely affected the visual results while retroprosthetic membrane least affected visual acuity. Survival rates at three years are as follows: 71% for retroprosthetic membrane, 67% for glaucoma, 51% for no complications, 50% for infection/stromal necrosis, 44% for multiple complications and 9% for posterior segment complications. Log rank test showed statistically significant difference with p value = 0.008 (**Figure 53**).

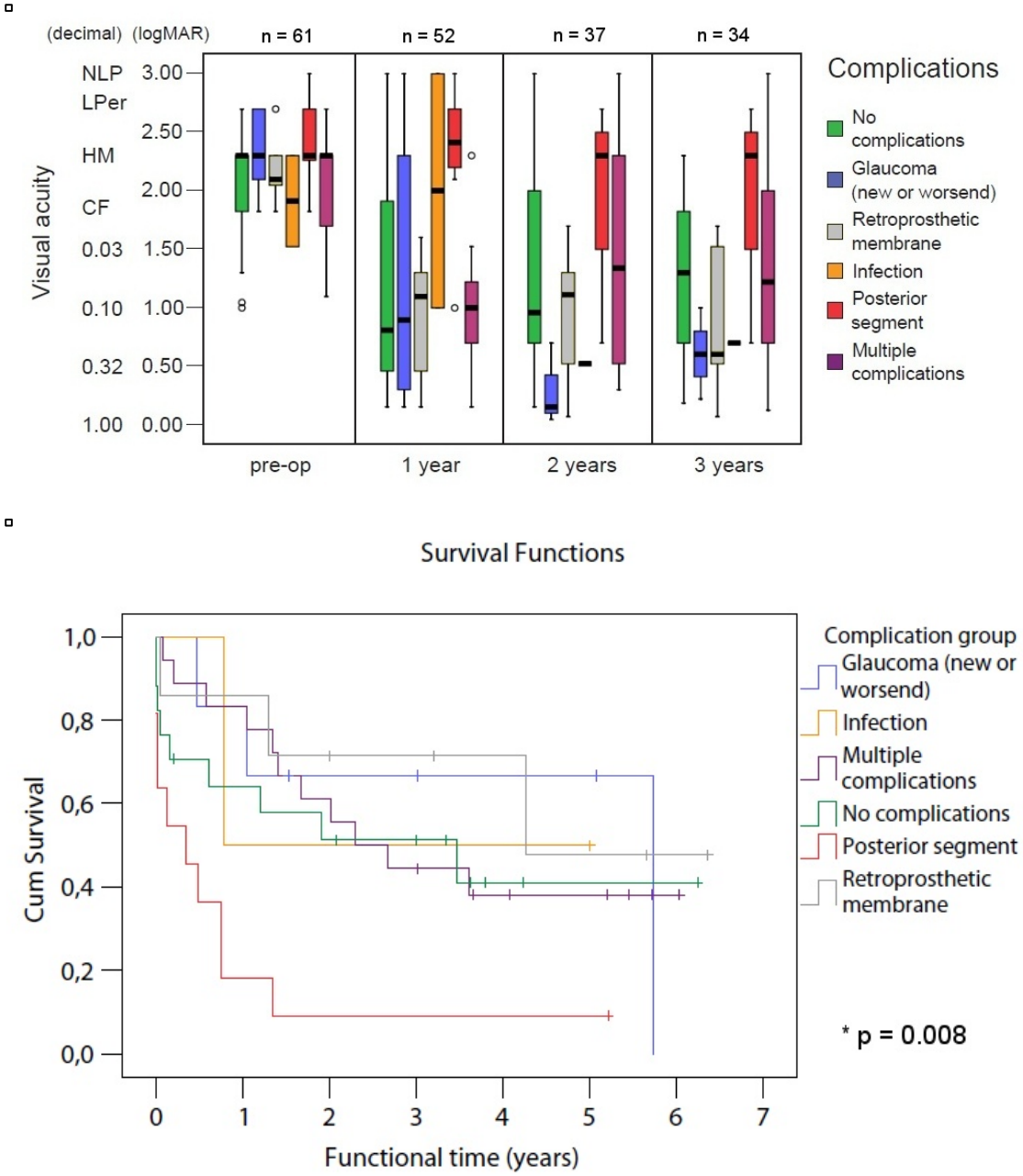


Figure 53. Visual acuity progression thru time based on post-operative complications showing worst results in patients with posterior segment complications in box plots (upper) and corroborated by Kaplan Meier survival curves where statistically significant difference between groups is shown by p value (lower) (from Paper 1 with presently updated data).

It is generally accepted that the Boston Type I keratoprosthesis is best indicated in cases of repeated failed graft, where a conventional full-thickness corneal transplant is bound to fail (Colby, 2011; Greiner, 2011; Zerbe, 2006; Chan, 2012; Chodosh, 2011; Chan, 2012; Chew, 2009; Patel, 2012). Colby mentions that increasing experience with the Boston KPro type I has expanded its indications to cases with herpetic keratitis, aniridia, autoimmune ocular disorders, and pediatric corneal opacities (Colby, 2011). Yaghouti and colleagues first discussed the influence of the pre-operative diagnosis on the success rate of the prosthesis (Yaghouti, 2001). Back then, post-operative protocols, such as the use of wide-spectrum antibiotics and fungal infection prophylaxis, were not as well defined as they are today. They were already able to demonstrate that cicatrizing causes of graft failure had a fairly better outcome compared to conditions with pre-operative inflammation, such as chemical burn, ocular cicatricial pemphigoid and Stevens-Johnson syndrome.

Taking into account our experience with biological keratoprosthesis such as OOKP and Tibia KPro (de la Paz, 2011; de Araujo, 2012; Michael, 2008), we have been very selective in our indication when we started with the Boston Type I KPro in 2006. We have also been very strict with the recommended topical post-operative regimen, using a third/fourth generation quinolone, vancomycin 14 mg/ml, steroids, medroxyprogesterone, and bandage contact lens. In addition to this, we administered oral immune suppressive treatment, such as oral cyclosporine or tacrolimus, when the ocular surface inflammation seemed to be uncontrolled with only topical anti-inflammatory drops. In other cases, we continued topical therapy with blood derivatives, such as autologous serum, when it was already preoperatively used to cure and prevent persistent epithelial defects or trophic ulcers.

This might explain the very good results in the autoimmune group compared to the results of other authors (Ciralsky, 2010). In the literature reviewed on Boston Type I KPro at the time of publishing Paper 1, the most common autoimmune diagnoses have been Stevens-Johnson syndrome and ocular cicatricial pemphigoid. To our knowledge, Paper 1 presented the highest number of patients with Stevens-Johnson syndrome as primary diagnosis, compared with other publications in early 2014 (Greiner, 2011; Zerbe 2006; Chew, 2009; Kang, 2012). The study of Sayegh presents good anatomical results in patients with SJS in the long-term, combining results of Type I (six eyes) and Type II (ten eyes) Boston KPro (Sayegh, 2008). Based on our experience with both biological and non-biological keratoprosthesis, we believe that ocular cicatricial pemphigoid is a contraindication for Boston Type I keratoprosthesis. As of writing, we are performing a comparison of our outcomes using biological (modified OOKP and Tibia KPro) versus the Boston Type I KPro in autoimmune and chemical/thermal burn cases to have evidence-based results. The presence of severe dry eye, symblepharon and progressive ocular surface fibrosis will make a bandage contact lens difficult to adapt. Our experience corroborates findings that a biological keratoprosthesis may be the surgery of choice for the end-stage disease of ocular cicatricial pemphigoid, as a severely dry ocular surface is replaced by oral buccal mucosa (De Araujo, 2012; de la Paz, 2012; Michael, 2008). However, in cases of Stevens- Johnson, before deciding on whether to implant a biological or non-biological artificial cornea, we preoperatively check for the presence of stable ocular surface, good lid closure, and the absence of excessive symblepharon wherein a bandage contact lens can be fitted properly (Boston Type I KPro). If this is not the case, then we proceed with a biological keratoprosthesis such as an OOKP or Tibia KPro. Another possible option may be the trans-palpebral Boston Type II keratoprosthesis.

In paper 1, 18% of eyes had history of chemical or thermal burn. These cases had very good anatomical and visual acuity results at 3 years post-operatively. In fact, this diagnostic group had the best visual acuity results compared with autoimmune cases and other diagnostic groups. This parallels the publication of the multi-center Boston Type I KPro study with the highest number of chemical burns included for analysis (20 eyes/15%), with favorable visual improvement, although their study had a shorter follow-up time of 8.5 months (Zerbe, 2006). Greiner and his colleagues presented the results of a large number of patients with chemical burn (ten eyes/25%), and also described good long-term anatomical retention and visual improvement, corroborating the results of Paper 1 (Greiner, 2011). The study of Magalhaes, on the other hand had a high incidence of corneal melt (40%) in patients with a history of ocular burn (Magalhaes, 2013). The aforementioned publication by Yaghouti on Boston Type I KPro, which took into account the impact of the preoperative diagnosis on anatomical retention showed a decline in visual acuity from 2 to 5 years post-operatively in eyes with chemical burns. However, this pioneer study was performed in the 1990's. We must consider that at present, due to improved post-operative protocols and better treatment of post-operative complications, we may now expect better overall results in this diagnostic category.

After analyzing the anatomical and visual acuity outcomes based on primary diagnosis and post-operative complications in Paper 1, we can see that it is not easy to determine how much impact these factors have on the visual acuity results. Moreover, statistical tests become difficult to apply since diagnoses are varied and post-operative complications are complex. Therefore we decided to analyze the results of the visual acuity using a different approach. This is what we investigated in Paper 2. Instead of analyzing the

visual acuity results based on groupings of diagnosis and postoperative complications, we tried to study the evolution of visual acuity thru time in all cases.

As mentioned in the methodology section, functional outcomes were also analyzed depending on the course of visual acuity thru time, and cases were classified accordingly: Group A are cases where visual acuity improved to 0.05 (decimal units) or better and maintained thru the last follow up or "stable VA improvement"; Group B are cases that had visual acuity improvement to 0.05 or better at one point in the post-operative period but with eventual worsening or "lost VA improvement"; and Group C are cases that never achieved visual acuity of 0.05 or "no significant VA improvement". In each of these three groups, we studied the incidence of the different primary diagnoses, as well as the post-operative complications to analyze their relevance in the evolution of visual acuity.

Almost half of the cases fell into group A with stable VA improvement (27 cases or 46%), 19 fell into group B with lost VA improvement (32%), and 13 cases fell into group C with no significant improvement in VA (22%).

Figure 54 shows the progress of cases that had stable VA improvement where the median best visual acuity was 0.30 (decimal units). However, patients in this group lost an average of one line until last follow-up. This group includes 9 cases that lost more than 2 lines, but maintained VA better than 0.05.

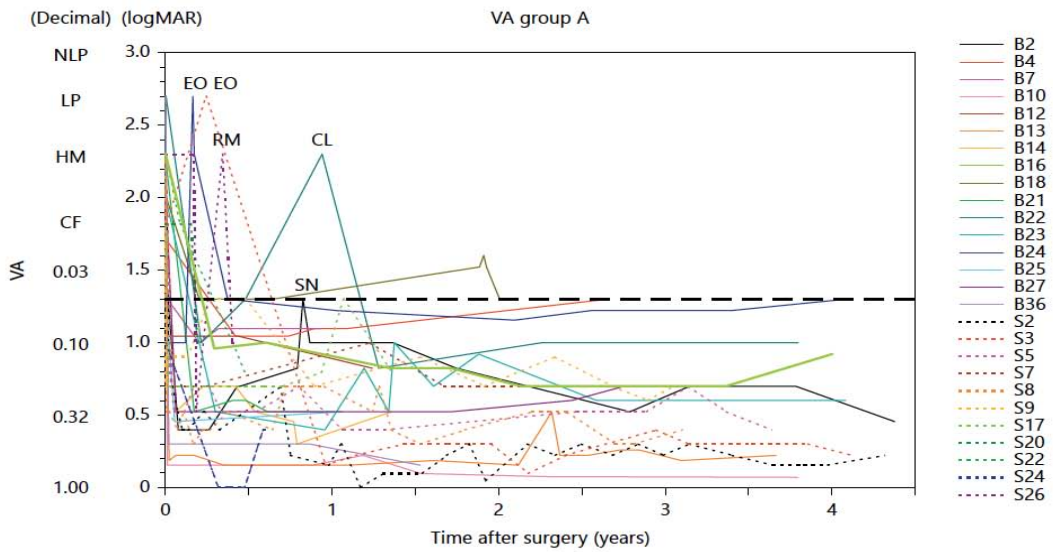


Figure 54. Evolution of VA in cases where improvement remained better than 0.05 decimal units (dotted line) until last follow-up. Complications at the time of major temporary worsening of VA are specified as follows: EO=endophthalmitis (B24, S3), CL=dirty contact lens (B22), RM=retroprosthetic membrane (S26); SN=stromal necrosis (B2) (taken from Paper 2).

Figure 55 shows cases where the median best VA reached was 0.10 decimal units but lost their improved VA values to less than 0.05 at the end of follow-up.

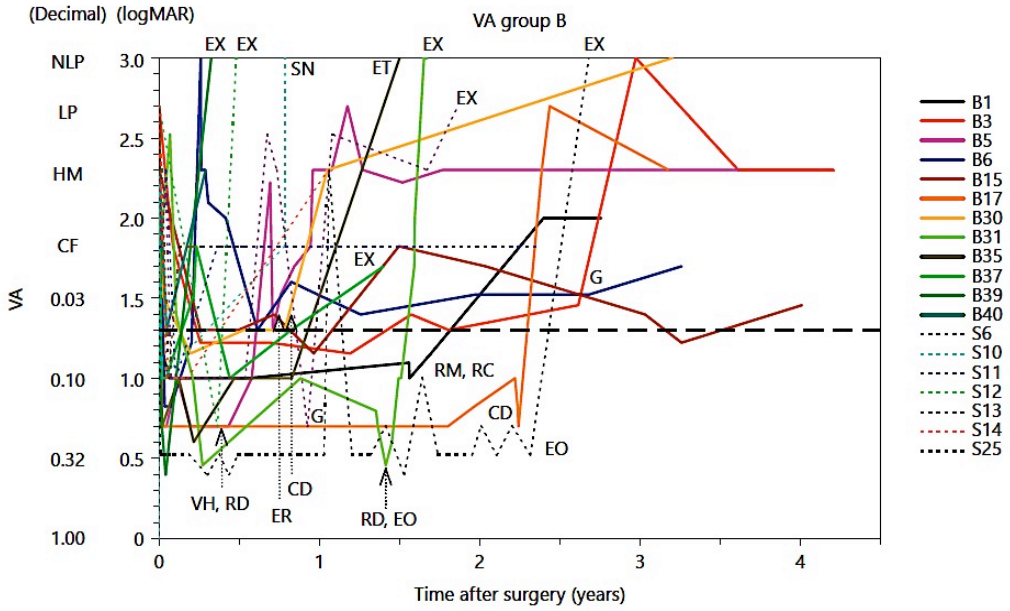


Figure 55. Evolution of VA in cases where improvement to 0.05 decimal units (dotted line) was reached at one point in time in the post-operative period, but later on worsened. Complications at the time of unresolved major worsening of VA are specified as follows: EO=endophthalmitis (S6, B31), ET=extrusion (B35), ER=epiretinal membrane (B5), EX=KPro exchange (B31, B37, B39, S6, S12, S13), CD=choroidal detachment (B30, B27), G=glaucoma (S13, B3), RD=retinal detachment (S12, B31), RM=retroprosthetic membrane (B1), SN=stromal necrosis (S10), VH=vitreous hemorrhage (S12) (taken from Paper 2).

Figure 56 shows the cases where VA improvement never reached 0.05, although there were 4 patients who improved from LP or HM to CF and 1 case to 0.04 decimal units.

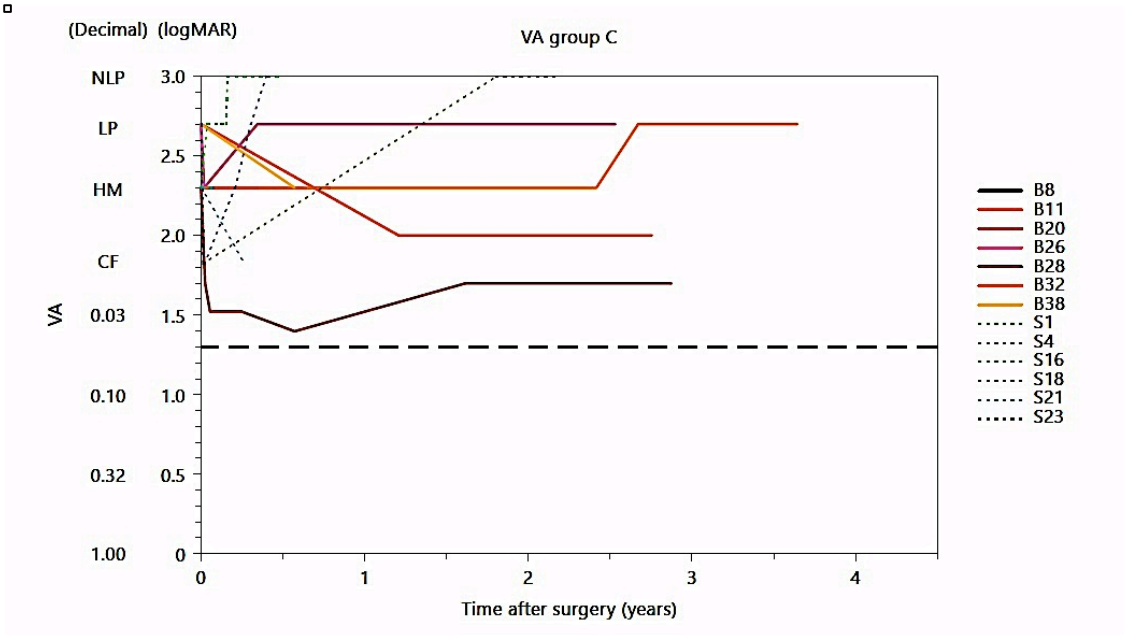


Figure 56. Evolution of VA in cases that did not show any improvement or never reached 0.05 decimal units (dotted line) (taken from Paper 2).

Regarding primary diagnosis, 58% of chemical/thermal burn patients and 47% of patients with autoimmune diseases or with bullous and aniridic keratopathy were in group A. A few other cases like immunetactoid keratopathy, calcific keratopathy and congenital glaucoma were also found in group A. Cases of trauma, post-keratitis leukoma and congenital opacities were evenly distributed throughout all three groups. As for corneal ectasia, corneal dystrophy and degeneration, limbal stem cell deficiency due to contact lens abuse, neurotrophic keratopathy and trachoma, most cases were concentrated in group B (**Figure 57).**

The number of previous graft failures does not seem to have influence on the VA outcome. The following percentages of these patients in group A were: 11% of cases had the Boston Type KPro implant as a primary procedure, 22% of cases with 1 graft failure, 33% of cases had 2 graft failures and another

33% with 3 or more failed grafts. As for group B, 30% had Boston Type 1 KPro as primary procedure, 15% had 1 failed graft, 10% had 2 failed grafts and 45% had 3 or more failed grafts. As for group C, 13% had Boston Type I KPro as a primary procedure, 31% had 1 failed graft, 20% had 2 failed grafts and 27% had 3 or more failed grafts. A Kruskal-Wallis test on the number of graft failures and visual outcome gave a χ^2 value of 0.41, showing no statistically significant difference across groups. Even after 3 or more failed grafts, patients can have good visual outcome. On the other hand, Boston Type I KPro implantation as a primary procedure can be a good alternative in patients with poor prognosis for primary penetrating keratoplasty (Kang, 2012). This is corroborated by our results wherein 30% belonged to group A and 50% belonged to group B (Figure 57).

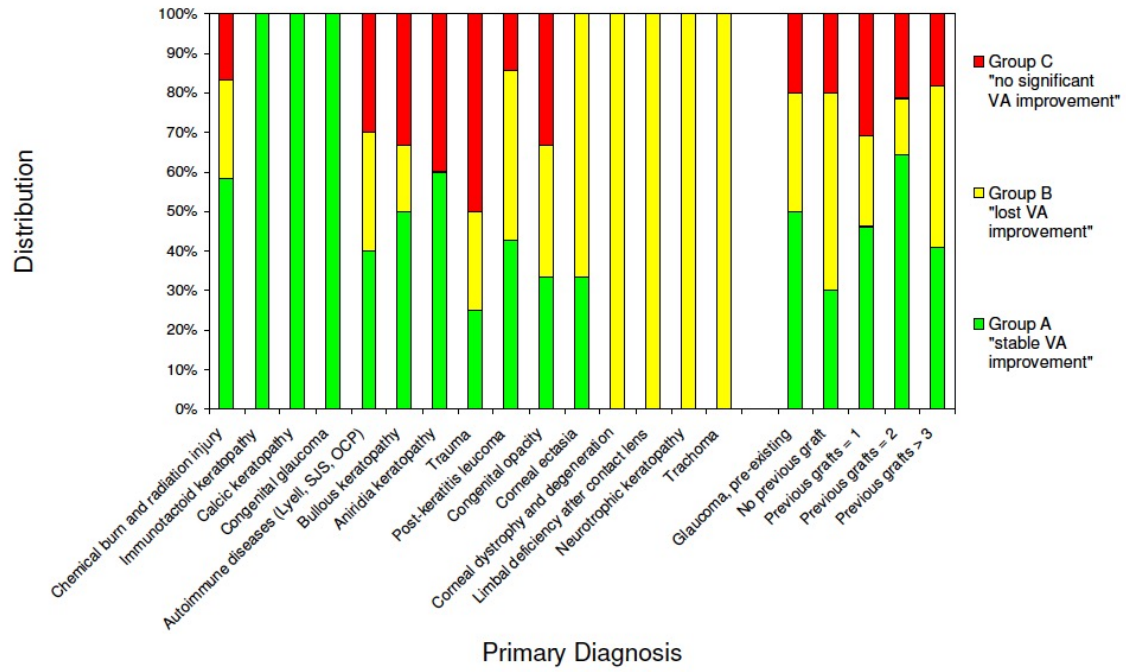


Figure 57. Bar graph of the distribution of the different diagnostic categories in relation to the evolution of visual acuity thru time showing that the diagnosis has no influence on the final functional outcome (left hand side), and that the presence of pre-existing glaucoma and number of previous grafts likewise have no influence on the final functional outcome (right hand side). This graph is based on Table 2 of Paper 2.

Regarding complications, patients with pre-existing glaucoma (n=31) were similarly distributed among all three groups. Patients with retroprosthetic membrane fell mostly into group A (50%) and group B (40%). Those with posterior segment complications mostly fell into groups B or C. Retinoschisis cases were all found in group B. Choroidal detachment was found in groups A or B. Vitreous hemorrhage was distributed over all three groups. The only case of epiretinal membrane appeared in group B. Retinal detachment cases were evenly distributed between groups B and C. Non-infectious vitritis, central artery occlusion and retinal necrosis all fell in group C. Endophthalmitis,

keratitis and stromal necrosis, present in 25% of our cases were predominantly found in group B, with only 1 case in group C. Only 4 of the patients recovered their visual acuity after this complication and remained in group A. New or worsened glaucoma was most frequently found in group A, this corroborates our findings in Paper 1 that glaucoma, when properly controlled in time scarcely affects the final visual outcome (Figure 58).

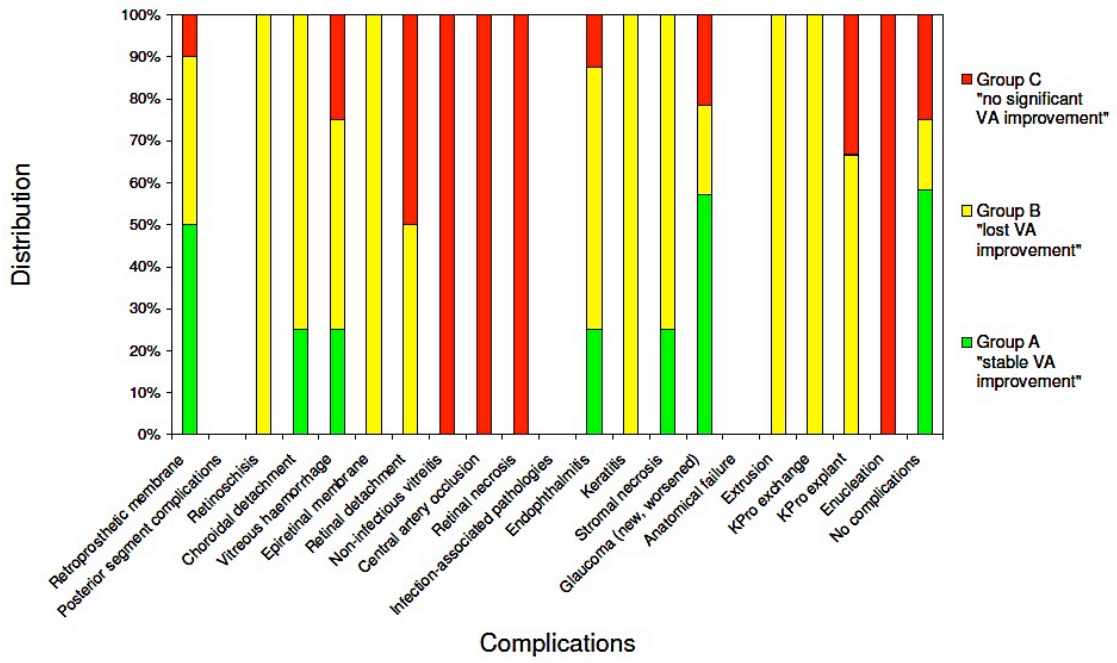


Figure 58. Bar graph of the distribution of the different post-operative complications and their impact on the evolution of visual acuity thru time showing that retroprosthetic membrane and glaucoma have the least negative influence, and that the posterior segment complications have the most negative influence of the final visual outcome. This graph is based on Table 3 of Paper 2.

A post-operative period free of complications does not necessarily correlate with good visual outcome. There were 12 eyes without documented complications, 7 of which were in group A and 2 in group B. One had a primary diagnosis of trauma, history of glaucoma and retinal detachment and 5 prior

keratoplasties. Visual loss in these cases could be attributed to optic nerve atrophy. The other case was a patient with high myopia and visual field examination confirmed central scotoma due to myopic maculopathy, which probably worsened thru time.

In Paper 3, we presented the general visual prognosis of our cases by comparing the best-corrected visual acuity (BCVA) pre-operatively versus the best-ever achieved BCVA values in LogMar units. The mean pre-operative value was 2.05 (range: 1.10 -2.52), while the mean best-ever achieved visual acuity was 1.16 (range: 0.08 – 2.70) showing overall improvement. Figure 59 We also presented the BCVA pre-operatively versus the BCVA in the last follow-up. The BCVA value at last follow-up was 1.47 (range: 0.08 – 3.00). In all 41 eyes, visual improvement was achieved although if we compare it to the final follow-up values, we can see that some patients eventually lost some lines (Figure 60).

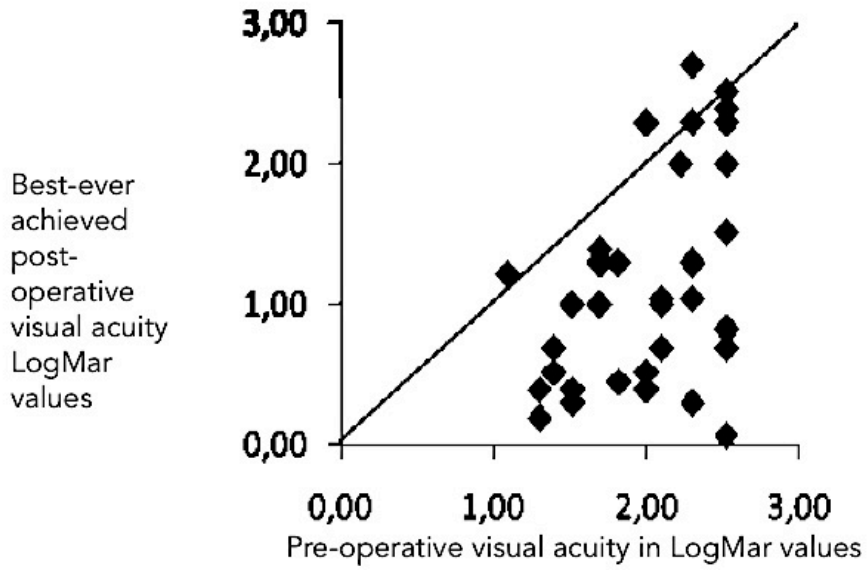


Figure 59. Scatterplot comparing the pre-operative BCVA versus the best ever achieved BCVA in the post-operative period showing improvement (taken from Paper 3).

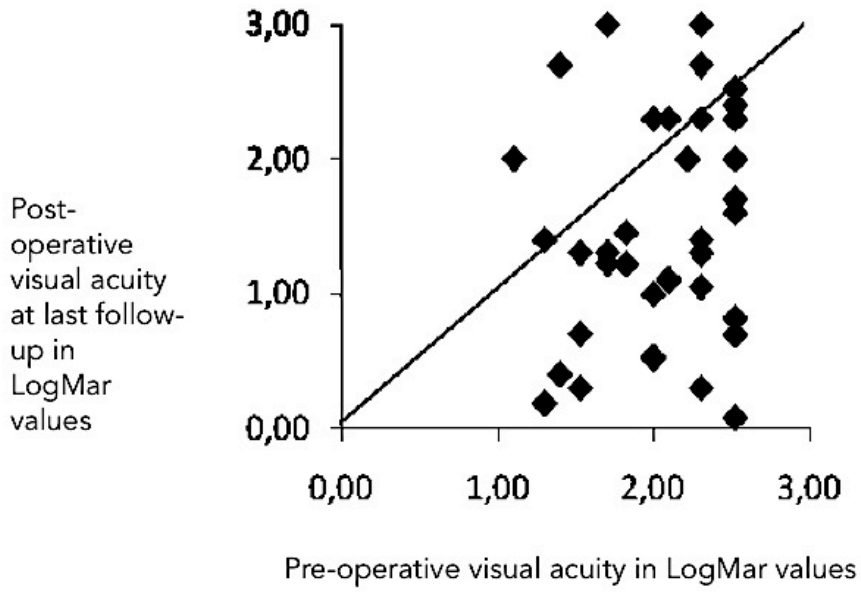


Figure 60. Scatterplot comparing the pre-operative BCVA versus the values at final follow-up showing improvement, although if compared to the previous figure, we can see worse results in this scatterplot indicating that some patients eventually lost VA (taken from Paper 3).

5.4 Post-operative Complications

Only post-operative complications that may directly affect visual acuity in the post-operative period were considered relevant for this study. Extraocular ones like palpebral ptosis, or those that were not related to the Boston KPro type I implant were not included for statistical analysis.

Retroprosthetic membrane

A retroprosthetic membrane is a thin opaque membrane behind the optical part of the front plate (Figure 61). It is made up of a layer of inflammatory cells along with proliferation of host cells that grow behind the back plate of the prosthesis (Jou, 2014). This is probably a subtle sign of the tendency of the eye to expulse a prosthesis trying to create an exoprosthesis as explained in the introduction section.

Retroprosthetic membrane occurred in 34% of cases as shown in Paper 1. Like other series, this is the most common complication encountered in all three papers. Reports are between 25%-65% occurrence in the post-operative period (Greiner, 2011; Zerbe, 2006; Chew, 2009; Patel, 2012; Yaghouti, 2001). This complication is usually not sight threatening, as it can be easily treated by performing YAG laser membranotomy. Close observation when not too dense or not affecting visual acuity is a valid option. However, surgical membranectomy with sub-tenon injection of triamcinolone maybe needed in recalcitrant or recurrent cases. A larger back plate of 9.5 mm made of titanium seems to lower the incidence of retroprosthetic membrane formation, as observed by the Dohlman group (Guell, 2015). They postulate that the membrane is formed due to unrestricted swelling of the host cornea wound, allowing stromal keratocytes to migrate onto the optical part of the prosthesis (Colby, 2012).

It has been observed that retroprosthetic membrane formation seems to correlate with the degree of ocular inflammation (Guell, 2015). Titanium is a more biocompatible material and might be the best material for the Boston KPro type I back plate, decreasing host cornea immune reaction to the

prosthesis. An infrequently recognized complication that may be related to a retroprosthetic membrane is the formation of a retro-back plate membrane. Sivaraman and colleagues describe this entity as related to sterile keratolysis or melting, as its formation may impede the nutrition of the donor cornea by aqueous humor (Sivaraman, 2013). They suggest that anterior segment ocular coherence tomography (AS-OCT) might be useful to monitor retro-back plate membrane thickness.

At present, we perform AS-OCT periodically on post-operative controls, and thus hope to further evaluate the implication of this entity and its relationship to membrane formation on the optical part of the prosthesis (**Figure 62**). **Figure 63** shows the evolution of a patient with recurrent retroprosthetic and retro back plate formation due to autoimmune uveitis.

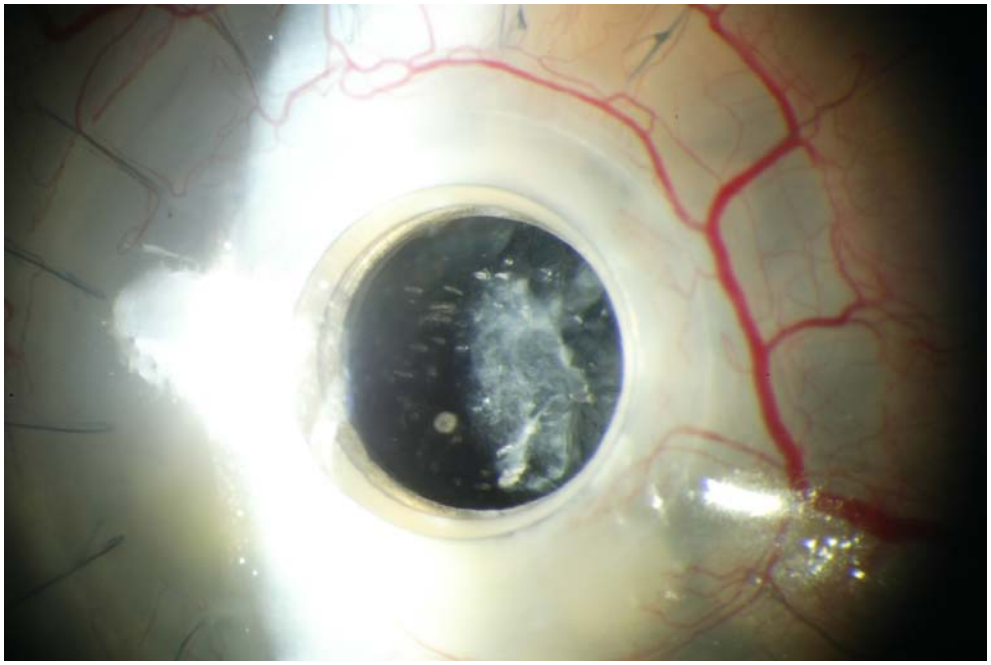


Figure 61. Dense retroprosthetic membrane that was recalcitrant to YAG laser membranotomy. Note the pits on the back part of the optic due to laser shots.

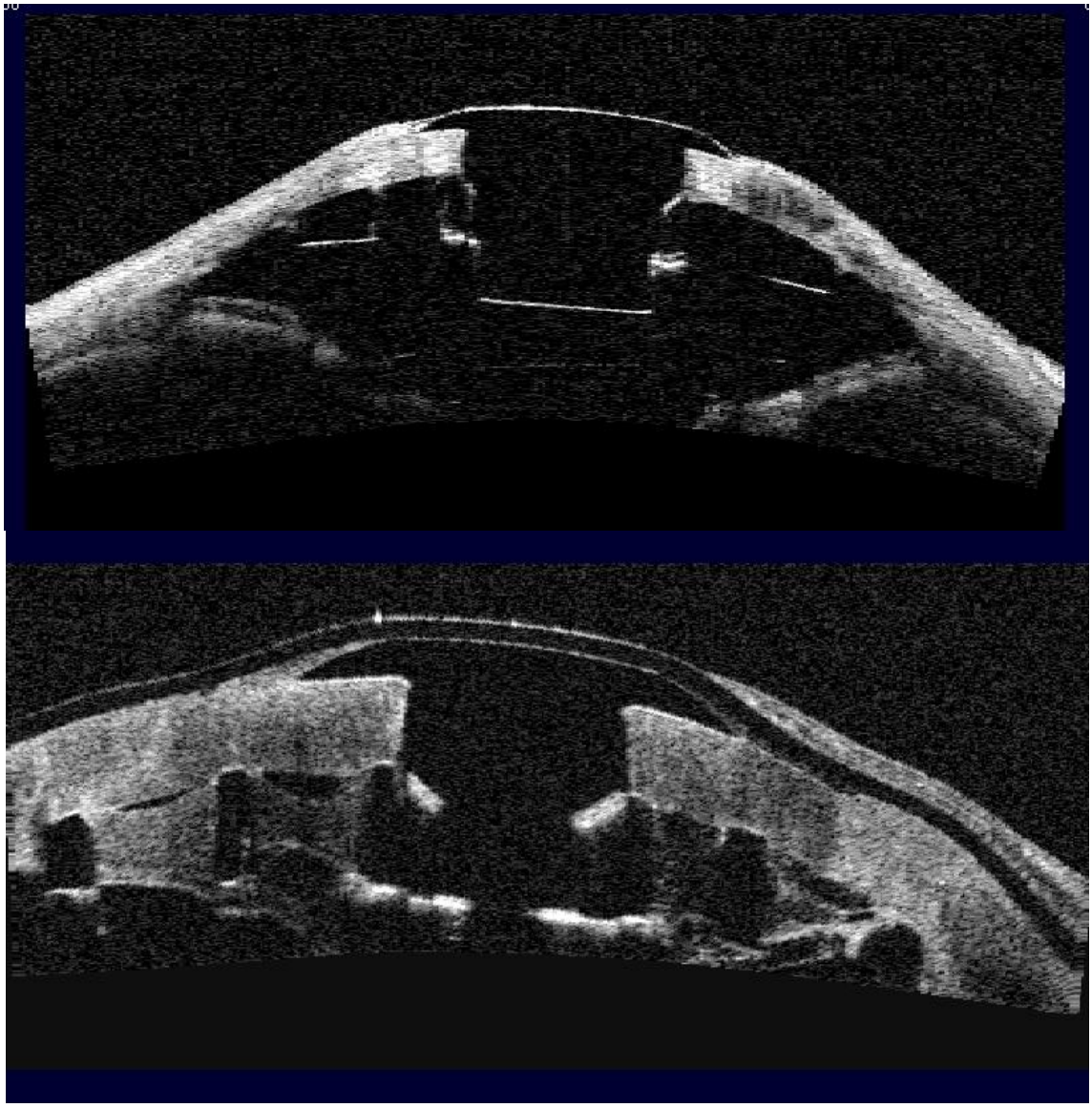


Figure 62. Anterior segment OCT showing the profile of the Boston KPro Type I optic and haptic. In the case above we can see the angle structures and no retro-back plate formation. In the case below, we can see a dense retroprosthetic and retro backplate membrane, and adhesions behind the donor cornea.

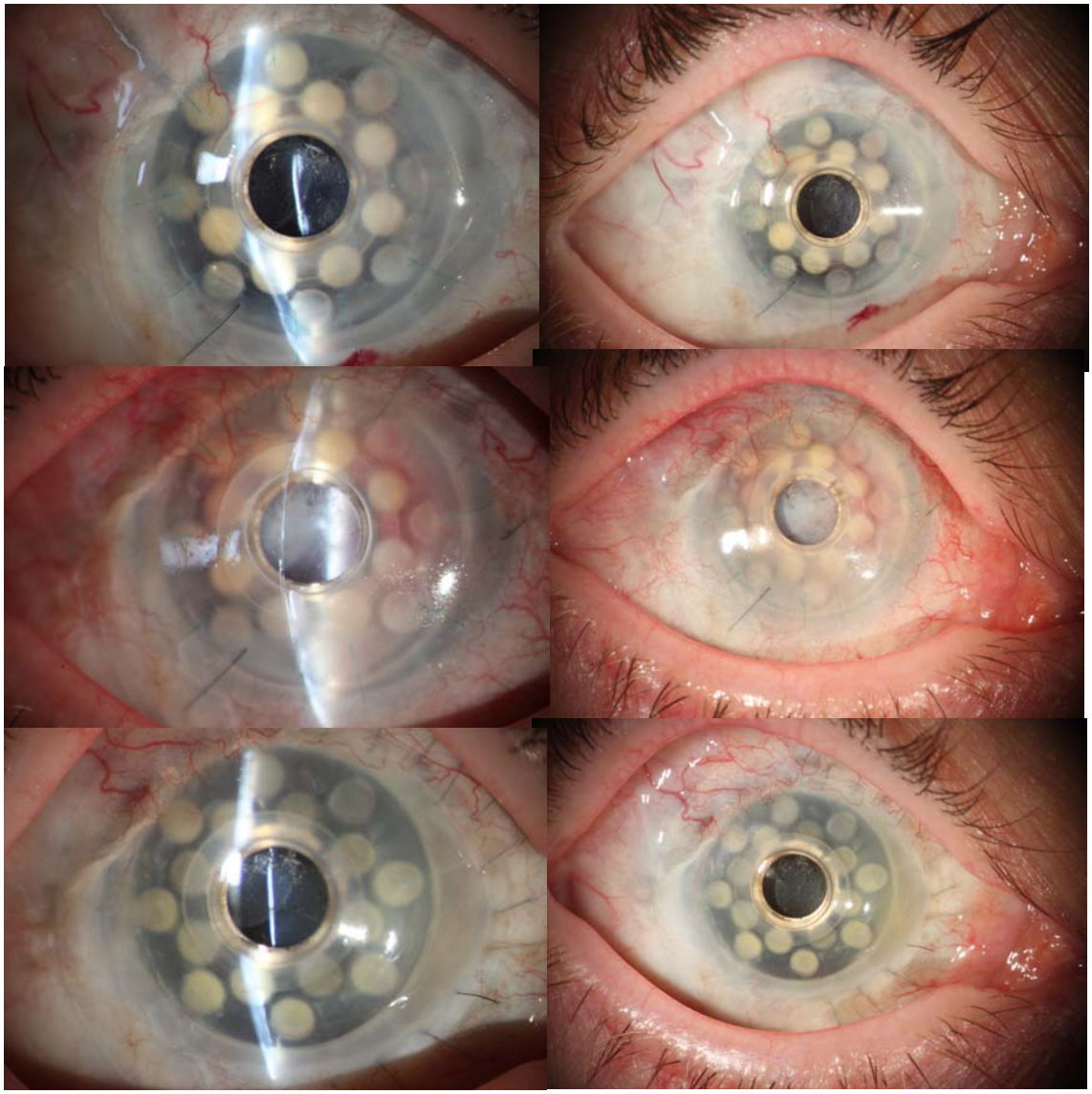


Figure 63. Evolution of a patient with recurrent dense retroprosthetic membrane, as well as dense retro-back plate formation due to autoimmune uveitis. Patient underwent repeated laser and surgical membranotomies. Images from 2013 (upper), images from 2014 (middle) and images from 2015 (lower).

Glaucoma

The majority of patients who undergo a keratoprosthesis implantation already have a history of glaucoma, or may even have undergone glaucoma surgery previously (Greiner, 2011; Zerbe, 2006; Chew, 2009; Patel, 2012; Kamyar, 2012; Banitt, 2011). In Paper 3, 86.8% of patients already were under medical treatment or had previously undergone glaucoma surgery. Its existence prior to keratoprosthesis surgery affects visual prognosis in the long-term, especially if there is progression and poor control of the disease. In Paper 2 we defined glaucoma as a complication if there was worsening of a pre-existing glaucoma or if there was "de novo" appearance of the said disease after Boston KPro Type I implantation. This occurred in 25% of our cases in Paper 2. Some authors recommend the implantation of a glaucoma drainage device simultaneous to the KPro surgery, or cyclophotocoagulation, if medical treatment is not sufficient to control glaucoma progression (Netland, 1998; Rivier, 2009).

Development of glaucoma after keratoprosthesis surgery may be due to several mechanisms such as: steroid responsiveness (as most patients need to be on topical steroids for a very long period of time), chronic inflammation (especially in auto-immune or chemical burn patients), or progressive fibrosis causing angle closure.

Anterior segment optical coherence tomography (AS-OCT) or ultrasound biomicroscopy (UBM) may serve as useful tools to rule out the presence of synechia or progressive angle closure. With such tests, glaucoma progression may be detected earlier, prior to clinical detection using standard techniques like finger palpation, visual field studies and optic nerve imaging (Qian, 2015). At the Barcelona and Salzburg centers we perform refraction,

visual field exams **(Figure 64)** and AS-OCT studies every 3-6 months with regular consultation at the glaucoma department to detect early glaucoma progression. The importance of refraction cannot be underestimated, as progressive myopization of the eye can be a subtle sign of progressive rising of intraocular pressure. Finger palpation is quite unreliable, especially in cases where eyes have undergone multiple surgeries and have been on chronic use of topical steroids, resulting in marked scleral thinning. The reverse would apply for patients with severely inflamed eyes and thick Tenon´s capsule, previous scleral buckling or presence of glaucoma drainage device. Currently we hope for the benefit of a novel device to directly measure intraocular pressure (Colby, 2011).

In the post-operative follow-ups when a patient has elevated intraocular pressure we recommend topical beta-blockers, carbonic anhydrase inhibitors and alpha-agonists. We prefer to avoid prostaglandin analogues as much as possible due to its undesired inflammatory side effect causing redness and dry eye. If there is preservative free formula, then we also prefer them to the ones with preservatives for the same reasons mentioned above.

Oral intraocular pressure lowering agents are used for a short period of time due to possible systemic side effects. When medical treatment seems to be inadequate in halting glaucoma progression, we prefer trans-scleral diode cyclo-photocoagulation to glaucoma drainage device, especially when the ocular surface is very fragile pre-empting possible complications like tube extrusion. Should the glaucoma surgeon, however, decide to place a glaucoma drainage device, the tube is placed in the vitreous cavity and not in front of the iris as there may be tube occlusion by fibrotic membranes in the long-term. This may explain the fairly better anatomical and functional results, if the only complication after keratoprosthesis surgery is glaucoma, compared to other

devastating complications like infection, necrosis and posterior segment complications.

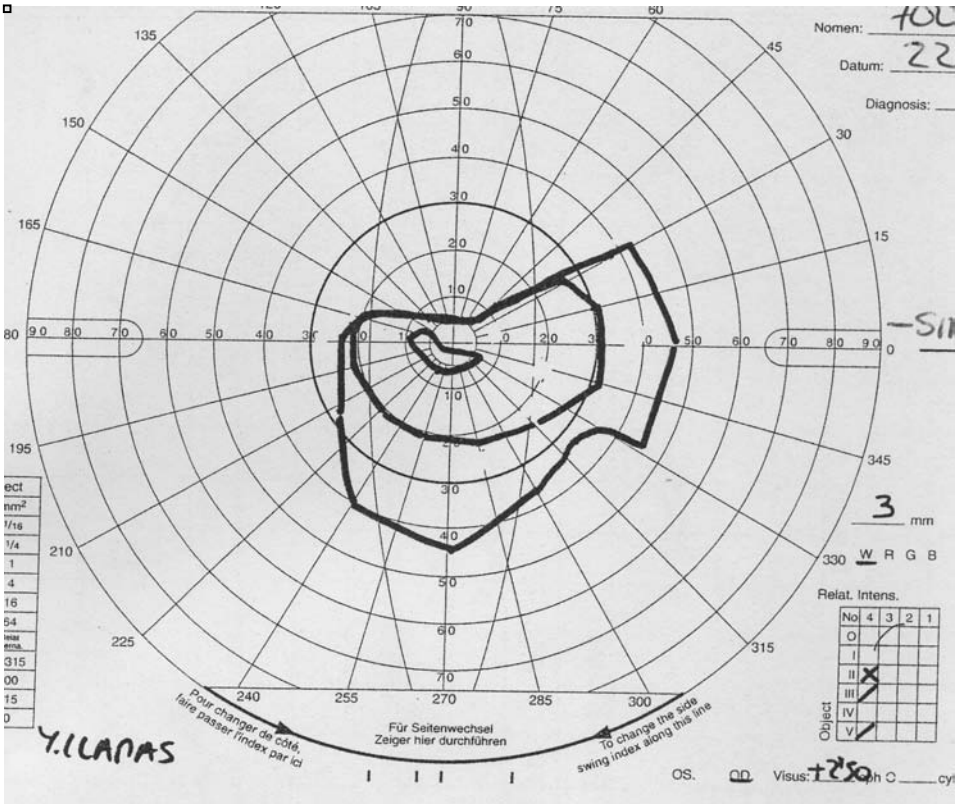


Figure 64. Goldmann visual field perimetry on a patient with congenital glaucoma showing superior nasal scotoma respecting central vision.

Posterior segment complications

Visualization of the posterior segment is not complicated in a Boston KPro Type I patient. In fact, fundus imaging is possible as long as all media is clear **(Figure 65).** Even retinal imaging studies are possible as long as the patient has good collaboration.

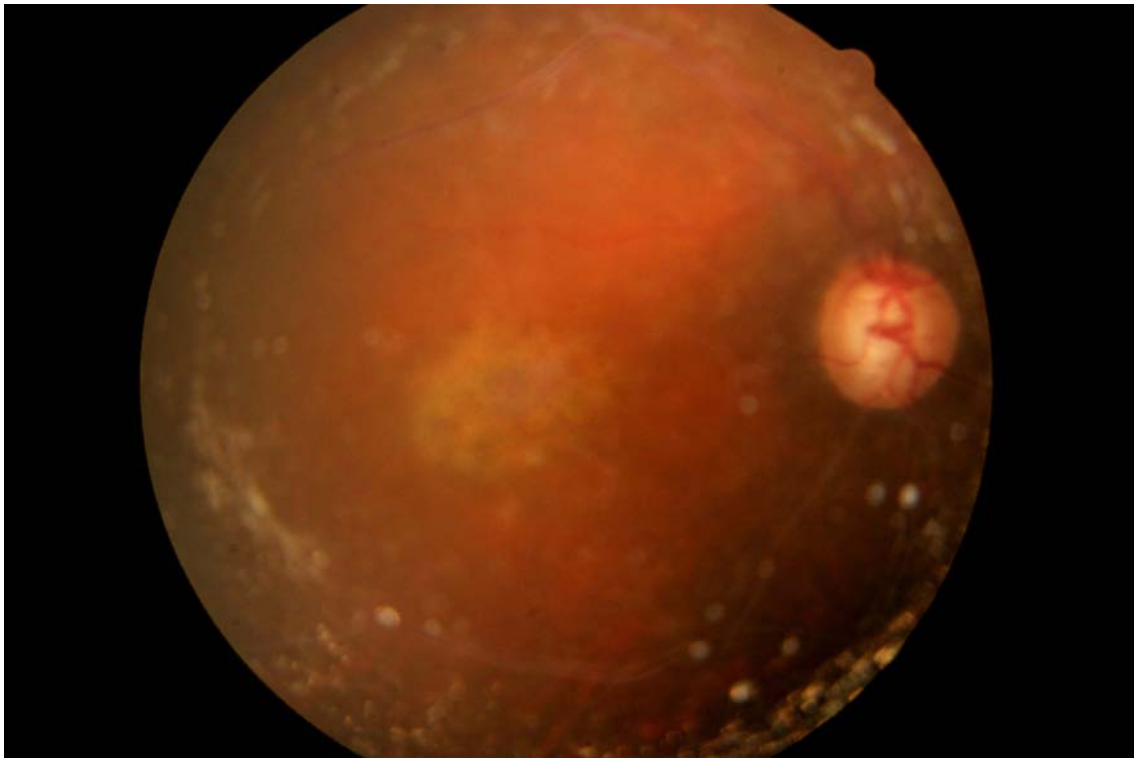


Figure 65. Fundus exam three months post implantation of Boston Type I KPro of a patient with asteroid hyalosis, chronic macular edema and glaucoma.

Paper 1 demonstrated a high incidence of posterior segment complications (37%). This category included (in decreasing order of frequency): retinal detachment, choroidal detachment, vitreous hemorrhage, retinal necrosis, retinoschisis, sterile vitritis, pre-retinal membrane and central retinal artery occlusion. In Paper 3, the incidence was 26.82%. These complications are the ones that most affected visual acuity compared to other aforementioned complications. This is in accordance with the study of Goldman et al with an incidence slightly higher than ours (Goldman, 2013). Whereas under normal circumstances, retinal or choroidal detachment can be successfully treated, our KPro patients did not regain vision after surgery. Other series mention related complications like cystoid macular edema, chronic hypotony not due to retinal detachment nor leakage, and vascular occlusion (Greiner, 2011; Kang, 2012; Dokey, 2012). Care must be taken in

patients with history of macular degeneration, as they may not improve significantly from keratoprosthesis due to limited visual fields. Such conditions severely affect visual outcome, thus it is important to perform pre-operative exams to assess visual potential as we have demonstrated in our series on biological keratoprosthesis (de Araujo AL, 2012). Patients must therefore be aware of these feared complications, which may impact the visual prognosis in the short term or long term.

With regard to surgery, pars plana vitrectomy may be performed in a standard fashion, but the surgeon must keep in mind that peripheral visualization may be difficult due to the limited 3.35 mm size of the optic (Figure 66).

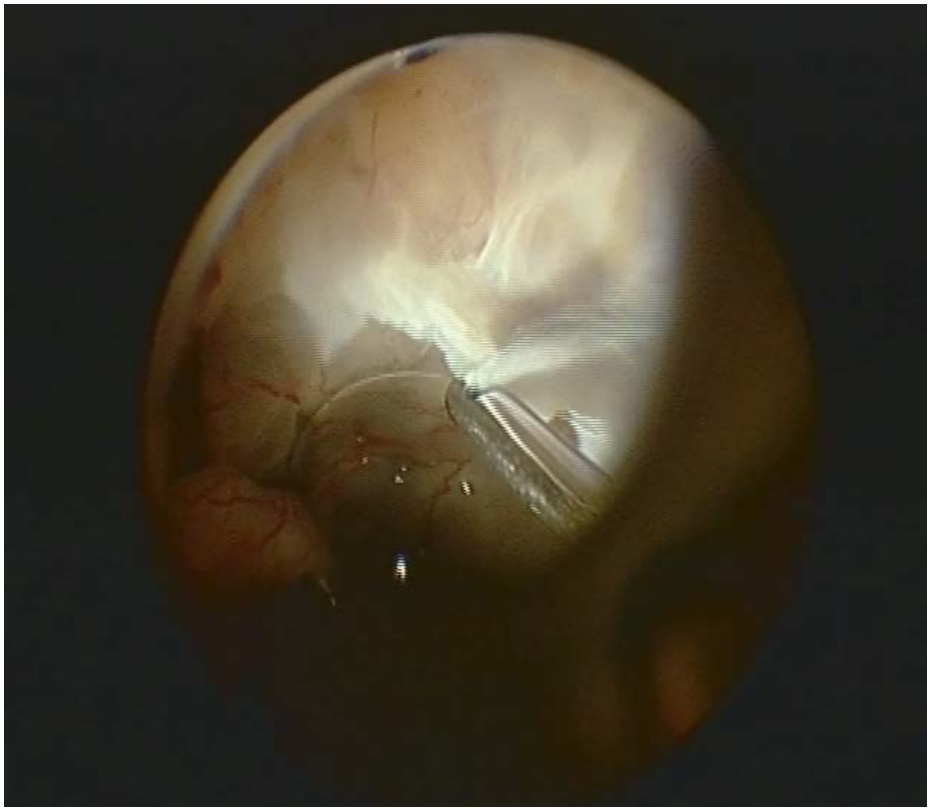


Figure 66. Intra-operative surgeon´s view of patient with advanced proliferative vitreo-retinopathy. Retinal detachment surgery may be performed in a standard fashion, only that the view is limited by the 3.35 mm optical cylinder of the Boston Type I KPro.

Infection and Stromal Necrosis

These are sight-threatening complications where early diagnosis and intervention are crucial to preserve anatomical integrity and visual results. Paper 1 showed an incidence of 13% of endophthalmitis, which is slightly higher than those of other series, ranging from 0 to 12.5% (Greiner, 2011; Zerbe, 2006; Chan, 2012; Chew, 2009; Aldave, 2009; Kamyar, 2012; Fintelmann, 2009). In Paper 3, infections occurred in 17.07% of cases. We follow the recommended protocol, with application of bandage contact lens that is changed at least every month, instillation of topical 14 mg/ml vancomycin, third or fourth generation quinolone, and strong topical steroids, which are tapered from the first month onwards to 1-2 times daily, depending on the inflammatory status of each case. In cases where topical 14 mg/ml vancomycin is not available to the patient, as it is not commercially available in any country, and has to be prepared under sterile conditions by a specialized pharmacy, wide spectrum antibiotics are given.

It is important to point out that compliance and patient education are critical, since non-compliance in therapy might lead to this complication. Being both the Centro de Oftalmología Barraquer in Barcelona and the University Eye Clinic of Salzburg top referral centers in Europe, a majority of the patients live far from the eye center, or even live abroad, such that patient follow-up becomes an issue. In Paper 3, three of the patients who developed endophthalmitis had cultures positive for candida; one was positive for streptococcus viridans, one was positive for Brachnibacterium paraconglomeratum, and three were culture negative **(Figure 67).** Polymerase chain reaction (PCR) testing of the vitreous tap may be more

reliable, albeit more expensive, since false negative results in conventional cultures may occur due to chronic use of antibiotics.

Presenting symptoms were acute or progressive injection, blurry vision, and sometimes pain. B-scan ultrasound may help us to assess the status of the posterior segment. However performing emergency vitrectomy and intra-vitreal tap to get material for culture, followed by intra-vitreal injections with fortified antibiotics or antifungals (depending on the suspected pathogen) increases the chance of restraining infection and avoiding necrosis of the retina. The studies of Chan on infectious endophthalmitis and infectious keratitis in Boston KPro Type I patients concluded that gram negative and fungal pathogens are the most frequent causes, since these patients are on chronic topical antibiotic and steroid use (Chan, 2012). Moreover, resistance to broad-spectrum antibiotics may be an issue despite their lower dosage (Fintelmann, 2009). Since we started in 2010 with 5% povidone-iodine wash at each visit to our eye center, we have noticed a dramatic decrease in the incidence of infections.

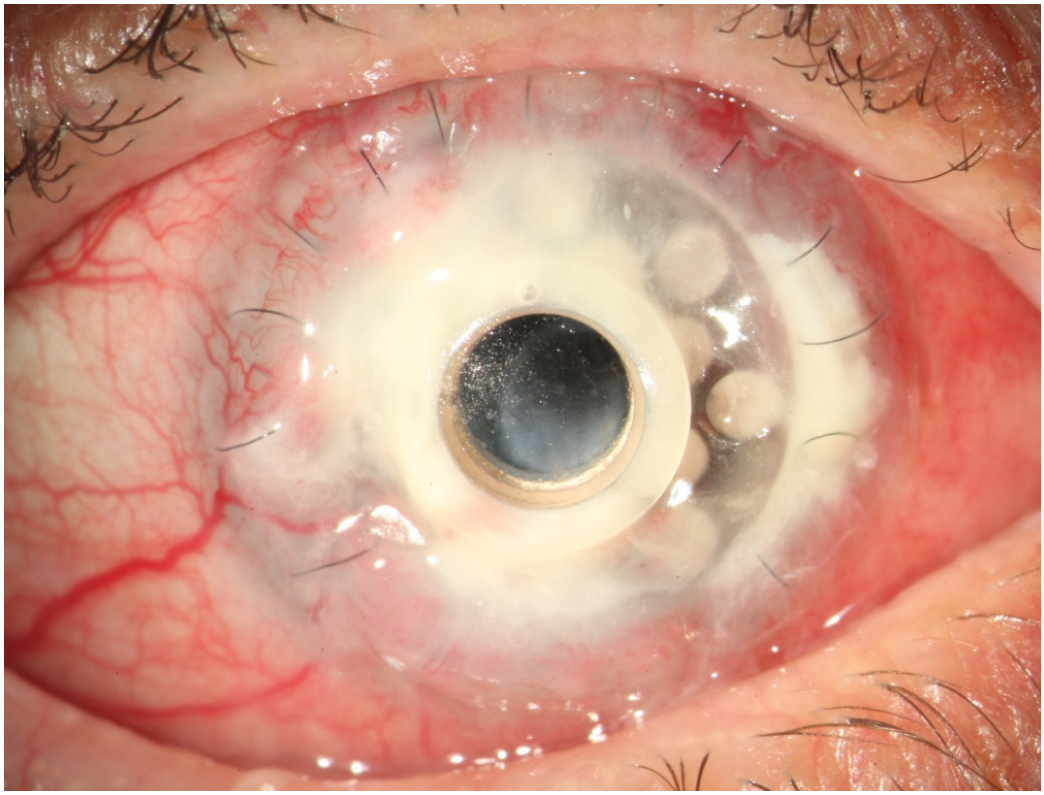


Figure 67. Infectious keratitis in a patient whose culture turned out positive for candida albicans. Notice the thinning of the donor cornea in the three o-clock area where the holes of the prosthesis become visible and thru which iris tissue can be seen.

Stromal necrosis is another devastating complication, which can lead to extrusion of the implant. Therefore, its early detection and treatment is crucial. The incidence of this complication in Paper 1 (6%) in Paper 3 (4.87%), is less than those mentioned in other series (Ciralsky, 2010; Aldave, 2009). One case was due to blepharophimosis and KPro exposure due to poor contact lens fit (eight previous corneal transplants). Another patient had persistent epithelial defects, which led to failure of the four previous corneal grafts. This patient underwent Boston KPro exchange for corneal melting of her first implant, the second implant unfortunately ended up in extrusion with panophthalmitis due to Brachnibacterium paraconglomeratum and eventual enucleation (**Figure 68).** Two patients developed stromal melting after prolonged epithelial

defects. In contrast to previous reports, our cases in Paper 1 that developed stromal necrosis did not suffer from autoimmune disorders (Greiner, 2011; Ciralsky, 2010) (Figure 69).

Ocular burns seem to be risky cases for development of corneal melting (Magalhaes, 2013). We fully agree with the recommendation of using a soft bandage contact lens to improve surface hydration, and the application of topical medroxyprogesterone. In selected cases we prescribe oral doxycycline to enhance anti-collagenolytic activity, as described previously by other authors (Chew, 2009). Dohlman and his team are continuously improving material and design of the prosthesis. The titanium back plate, which is thinner than its PMMA counterpart seems to have promising results (Guell, 2015). Also, crosslinking of the donor cornea seems to increase corneal resistance to enzymatic degradation, at least in animal studies (Robert, 2014; Kanellopoulos, 2014).

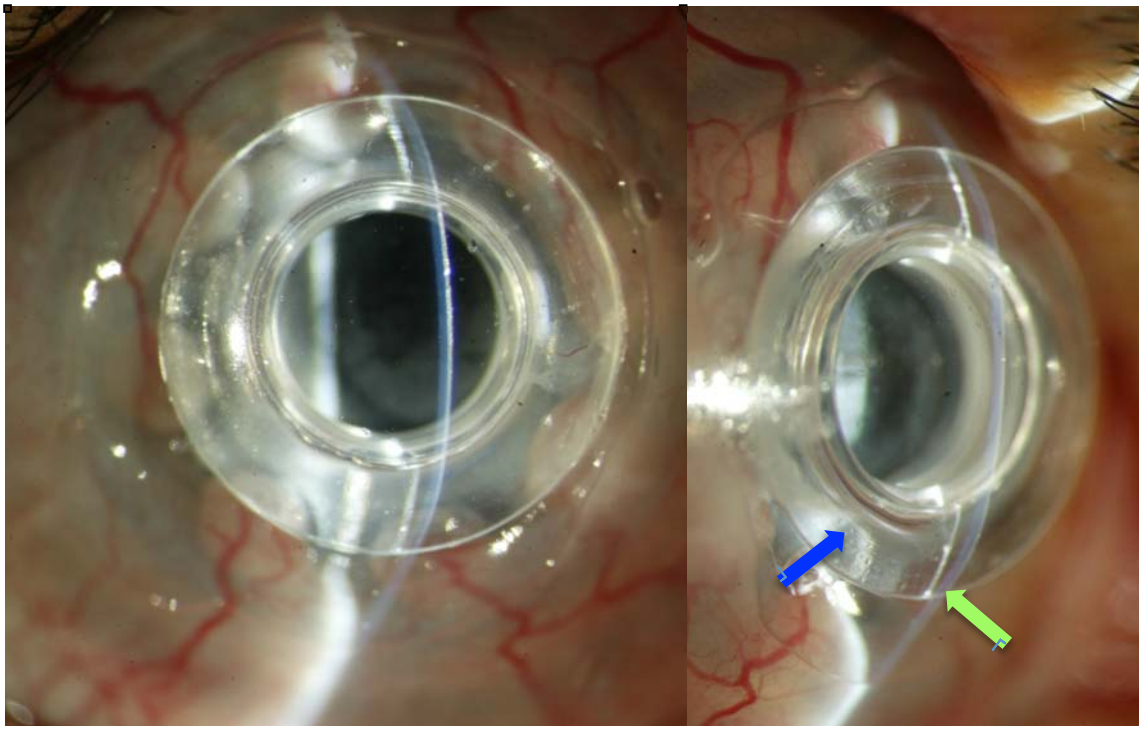


Figure 68. Severe thinning of donor cornea with partial exposure of the prosthesis near the stem (blue arrow), in spite of bandage contact lens use (green arrow). Also notice the retroprosthetic membrane developing behind the optic. This patient had ectrodactyly, cleft lip and palate and ectodermal dysplasia (EEC syndrome), underwent 4 penetrating keratoplasties and 2 Boston KPro Type 1 surgeries, which ended up in enucleation due to panophthalmitis.

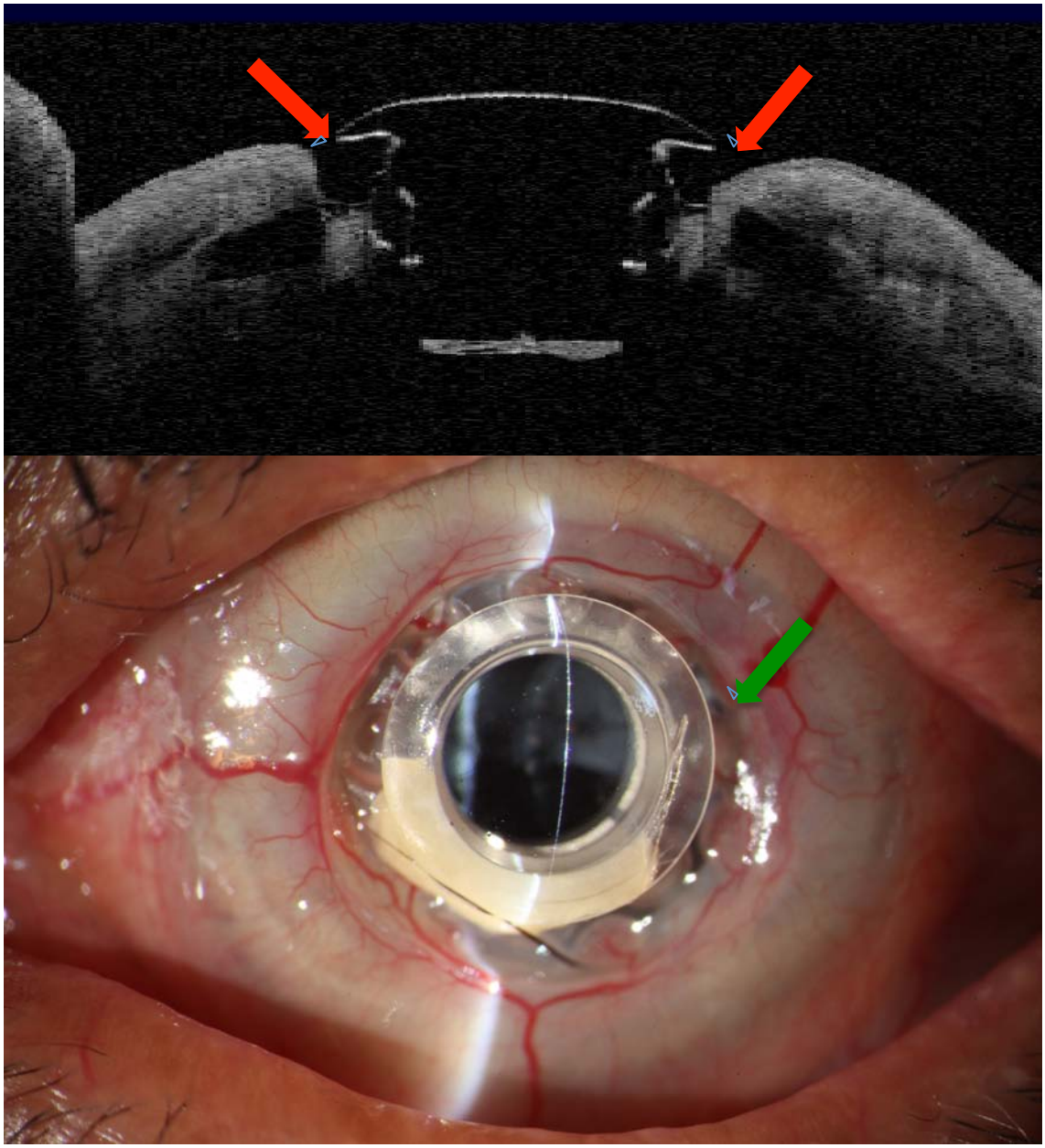


Figure 69. 360 degree loss of corneal tissue around the front plate stem as seen on OCT (upper image, red arrows) and slit lamp (lower image, green arrow). This patient with non-autoimmune repeated graft failure had poor follow-up in another country and did not wear bandage contact lens nor instilled topical medications. Salvaging procedure using 360-degree dissection and full thickness corneal graft without explanting the keratoprosthesis was successfully performed.

5.5 Comparison to other artificial corneas

Comparison of artificial corneas is not that easy since indications are different, surgeon experiences are presented in different manners, especially when we talk about visual acuity results. Perhaps the simplest and most logical way of comparing artificial corneas is looking into results of anatomical retention thru time, and evaluating the different complications that we may encounter in each kind in the post-operative period. If we are to compare the results of the Boston Type I KPro to other artificial corneas, we can see why it is gaining popularity on a global basis.

Perhaps the only other artificial cornea for wet blinking eyes, which has been used on a wide scale over the last few decades, is the AlphaCor®. In a series of 322 eyes after mean follow-up of 16 months, the anatomical loss was 34% (Hicks, 2006). This is worse compared to our results of anatomical loss of 18% at 3 years. Stromal melting was the most important complication of the AlphaCor® ranging from 26% up to 60% in some series (Hicks, 2006; Trichet, 2013; Jiraskova, 2011). Endophthalmitis was less frequent with AlphaCor, ranging between 1 - 7% according to the said publications. These complications are quite expected as the AlphaCor® is an intracorneal device, unlike the Boston KPro, which is a trans-corneal device. It has no physical contact with the interior part of the anterior segment, such that retroprosthetic membrane (the most common complication of the Boston Type I KPro) does not occur. The same reason would explain why endophthalmitis is much less in the AlphaCor® compared to the Boston Type I KPro. As for stromal melting, the incidence is much less in Boston Type I KPro due to the presence of holes in the back plate allowing nutrition of the donor cornea, which is impeded in the intracorneal device AlphaCor®.

Prior to the popularity of the Boston Type I KPro, only a handful of surgeons performed what is considered the gold standard for end-stage cicatricial corneal disease, the modified OOKP. Our experience at the Centro de Oftalmología Barraquer over the last few decades shows that a biological keratoprosthesis using tooth or tibia have comparable anatomical results in the long-term until 10 years follow-up (de la Paz, 2011; Michael, 2008). Compared to the Boston Type I KPro, anatomical retention is slightly less at 87% at 1 year, 82% at 2 years and 78% at 3 years, 70 % at 5 years, as presented in Paper 1 (**Table 1).** Notwithstanding, a successful artificial cornea must have good anatomical retention for a long period of time such as we have seen with the OOKP and Tibia KPro with 62% anatomical retention at 10 years and 52% retention at 20 years according to our experience. Only with years and years of experience will we be able to assess if the Boston Type I KPro will stand the test of time as to anatomical retention.

Table 1. Comparison of anatomical retention thru time of biological keratoprostheses (modified OOKP and Tibia KPro) and the Boston Type I KPro updated data taken from papers published by our team (De la Paz, 2011; Michael, 2008).

Follow-up	OOKP and Tibia KPro	Boston Type I KPro
1 year	87%	95%
2 years	82%	85%
3 years	78%	82%
5 years	70%	78%
10 years 20 years	62% 52%	no data available as of writing

As for complications, the encountered post-operative complications are comparable but with different incidences **(Table 2).** The low incidence of retroprosthetic membrane in the biological keratoprosthesis is because of its autologous origin and that it is a meso-prosthesis, such that inflammation is less than in the Boston Type I KPro. Extrusion, though, a feared complication which compromises the anatomical retention, is higher in the biological keratoprostheses since these eyes are anatomically more dysfunctional with shallow fornices, symblepharon, severe keratinized dry eye and poor lid closure. These may compromise the health of the oral mucosa covering the autologous lamina. This is where our experience on Paper 1 demonstrates that poor lid function and severe dry eye in cases like autoimmune diseases and severe chemical burns may have a difficult post-operative course **(Figure 70)**. As for glaucoma, the higher incidence in Boston Type I KPro may be due to the need for chronic use of steroids, progressive angle closure, long-standing inflammation. With the biological counterparts, steroids are not mandatory in the long-term and iridodialysis is performed precluding the possibility of angle closure.

Table 2. Comparison of post-operative complications between biological keratoprosthesis and the Boston Type I KPro data taken from papers published by our team (De la Paz, 2011; Michael, 2008).

Major complications	MOOKP and Tibia KPro	Boston Type I KPro
Extrusion	28%	6%
Retroprosthetic membrane	5%	34%
Retinal detachment	16%	19%
Uncontrolled glaucoma	11%	24%
Infections	9%	13%

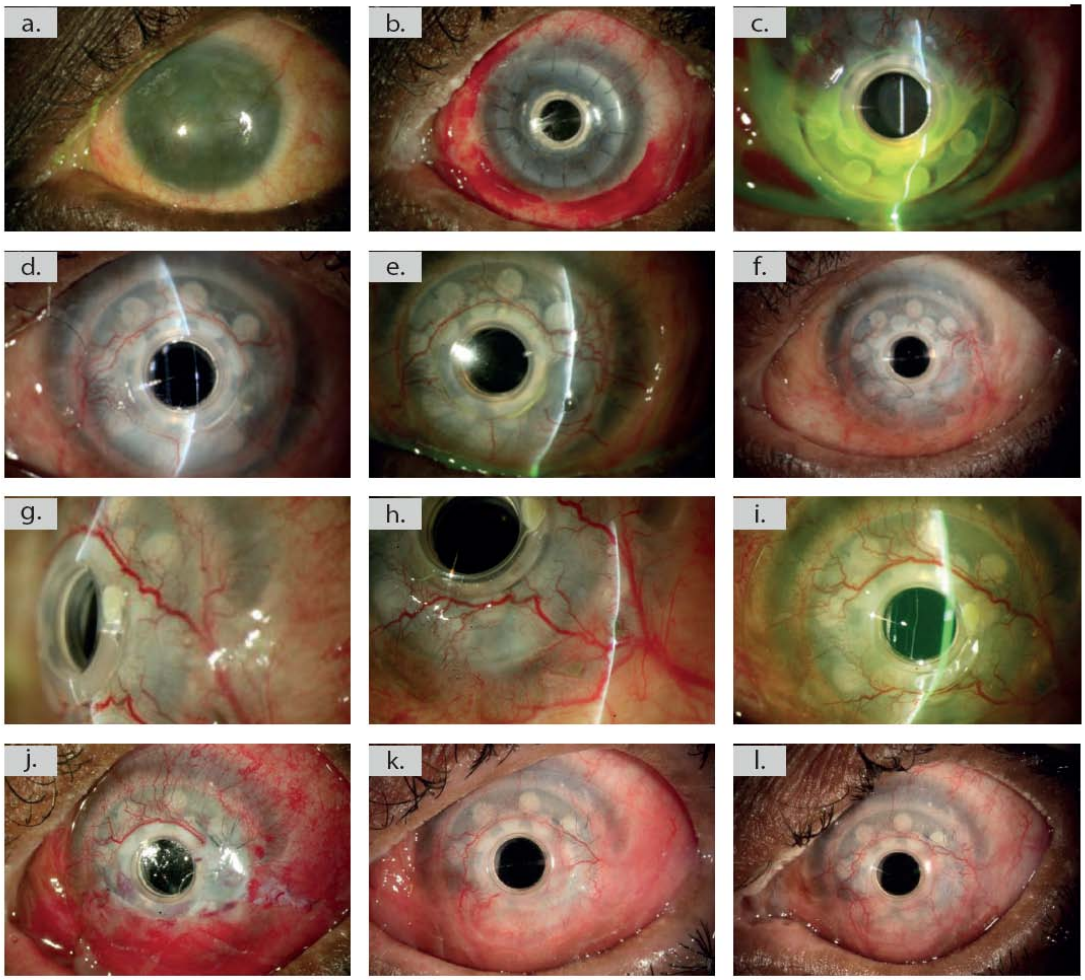


Figure 70. Stevens-Johnson syndrome patient with only seeing eye a: preoperative image of the eye with no symblepharon and no keratinization. b: one month post-implant of Boston KPro Type I as a primary procedure. c: Extrusion of the inferior half of a Boston Type I KPro 4 months after surgery and retroprosthetic membrane. d: 5 months after successful KPro exchange with best-corrected visual acuity (BCVA) of 0.6. e: 1 year after KPro exchange presenting with descemetocoele and positive Seidel test at 4 o'clock area. f: lamellar keratoplasty and conjunctivoplasty in the infero-temporal quadrant as salvaging procedure. g, h, i: 6 months after lamellar procedure, there is extrusion in the infero-temporal area from 3-7 o'clock area. The patient would refer frequent loss of bandage contact lens. j: repeat lamellar keratoplasty from the 2:30 to 8 o'clock area with conjunctivoplasty and mini-lateral tarsorraphy. k: 4 months after the last surgery. l: 6 months after the last procedure, Boston KPro Type I in place with BCVA 0.6. Since the very first surgery, this patient had been on systemic immunesuppresion, heterologous serum, prednisolone acetate, medroxyprogesterone, vancomycin, fourth generation quinolone and anti-glaucoma drops. Total follow-up time to writing of this thesis is 48 months/ 4 years.

Compared to the biological KPro´s, the advantages of the Boston KPro Type I are:

- Simplicity of surgery performed in a single stage.
- Easy learning curve for any experienced corneal transplant surgeon.
- Reversibility of the surgery. The implant may be removed and a conventional keratoplasty be performed afterwards to restore the anatomical integrity of the eye.
- Repeatability of the surgery. In cases of extrusion or infection, the Boston KPro Type I may be explanted and replaced with a new one.
- Wider visual field.

The disadvantages are:

- High cost of the prosthesis.
- Waiting time for ordering and shipping of the prosthesis from the Massachusetts Eye and Ear infirmary, as there are no suppliers in the other countries.
- Need for a viable donor cornea.
- In certain diagnosis, like autoimmune cases or chemical burns, the post-operative complications are more frequent and more sight-threatening, therefore strict follow-up and compliance of treatment are mandatory.

As of writing, our group is making a retrospective study on the anatomical and visual results of comparable cases of chemical burn using biological (modified OOKP and Tibia KPro) versus Boston KPro Type I. We intend to find out long-term anatomical and visual results in these cases.

6. CONCLUSIONS

1. The best indications for a Boston KPro Type I are non-inflamed eyes with good lid closure and no severe dry eye, meaning non-autoimmune graft failure. It may be a viable option in the treatment of challenging cases such as autoimmune diseases and chemical burns. Anatomical retention maybe achieved in the long-term as long as there is a stable ocular surface and recommended post-operative protocols are strictly followed. Visual outcomes may be affected by sight-threatening complications such as infections and stromal necrosis, which are more common in these complex cases.

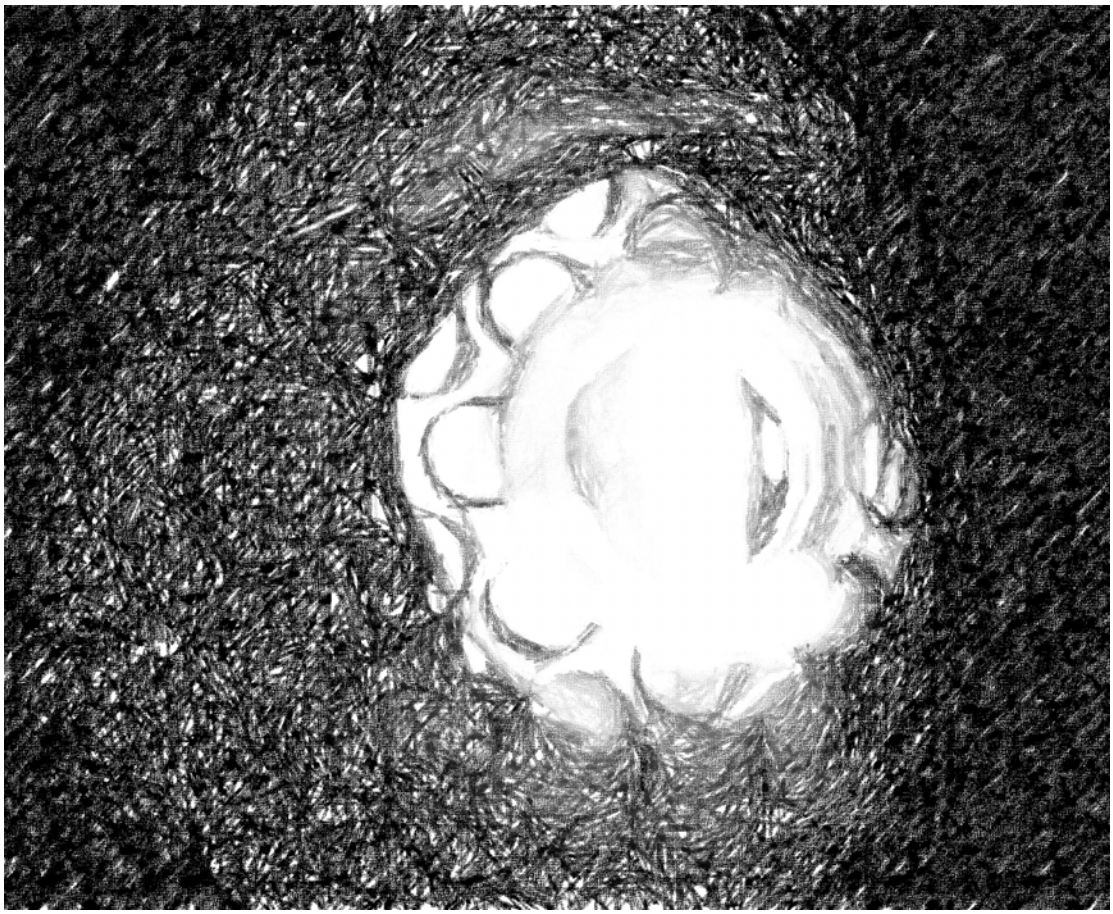
2. The Boston Type I KPro provides visual improvement in most patients with corneal blindness not amenable to penetrating keratoplasty. Primary diagnosis does not appear to affect the final visual outcome, but the type of post-operative complications does affect the final visual outcome.

3. The post-operative complications of the Boston KPro Type I in decreasing order of frequency are retroprosthetic membrane, glaucoma, infection and stromal necrosis, and posterior segment complications such as retinal detachment, choroidal detachment, vitreous hemorrhage, retinal necrosis and sterile vitritis. Of the above-mentioned complications, retroprosthetic membrane has the least impact on visual acuity and anatomical retention.

4. The Boston KPro Type I is a viable option as a primary procedure in patients otherwise condemned to a high risk of failure with a conventional corneal graft such as cases of total limbal stem cell deficiency and marked corneal neovascularization. The post-operative

visual acuity results, compared with cases having had 1, 2, 3 or more previous penetrating keratoplasties, did not show any difference.

5. The good anatomical and visual outcomes of the Boston KPro Type I are comparable with other artificial corneas whether biological or non-biological at 5 years follow-up, although longer term follow-up must be continued in order to compare it with our results of the modified OOKP and Tibia KPro. The most common complications, like retroprosthetic membrane and glaucoma in the Boston KPro Type I, are much less common in the biological keratoprosthesis owing to the difference in material and fixation. Compared to the modified OOKP and Tibia KPro, the post-operative complications (except for glaucoma) are milder and surgically easier to resolve with fairly good anatomical and visual outcomes afterwards.



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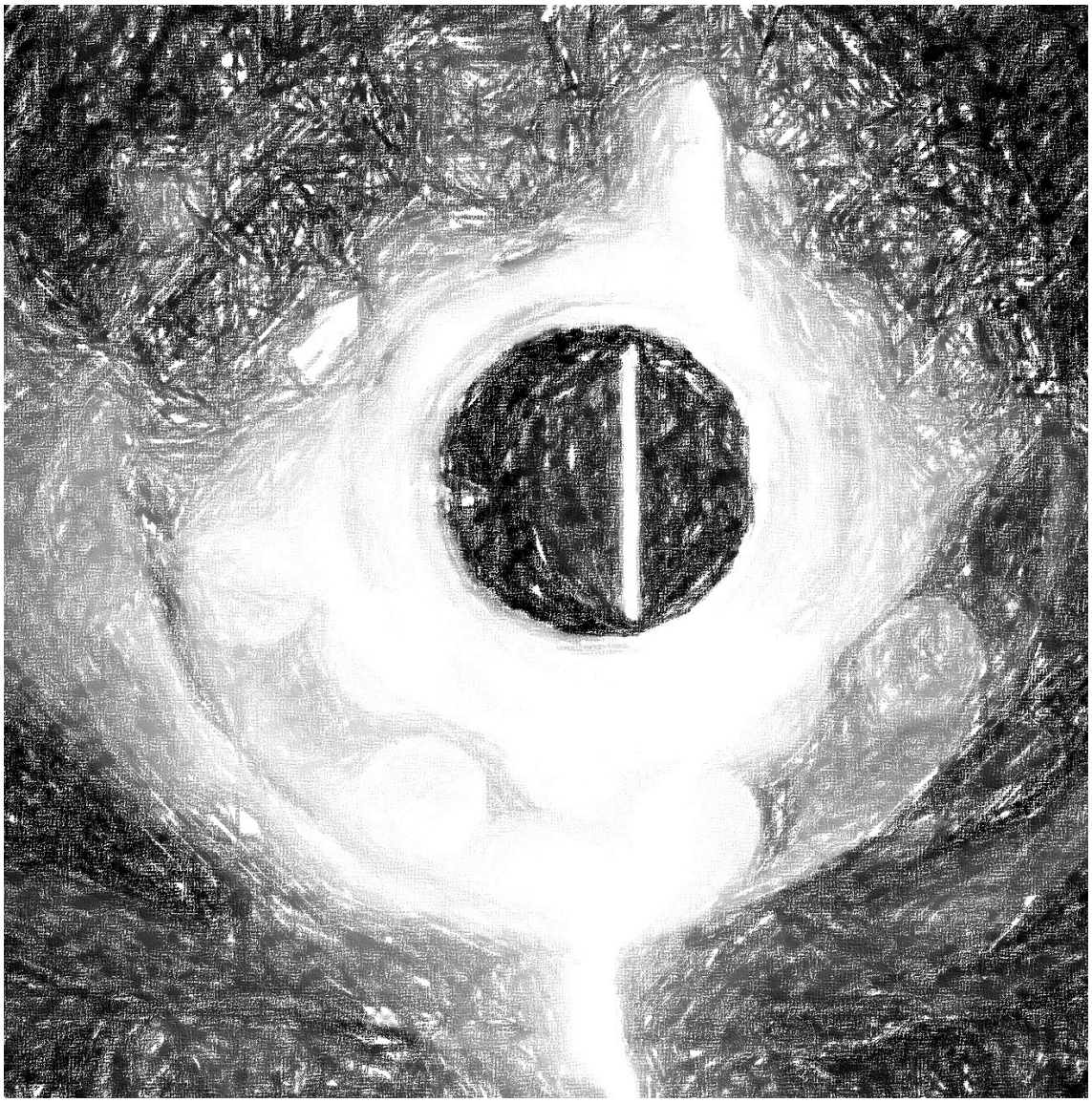

8. APPENDIX

8.1 Paper 1

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Anatomical survival and visual prognosis of Boston type I keratoprosthesis in challenging cases.

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CORNEA

Anatomical survival and visual prognosis of Boston type I keratoprosthesis in challenging cases

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Abstract
Purpose To describe the outcome of patients with Boston type 1 keratoprosthesis, with regard to anatomical and visual success.
Methods Retrospective case series of patients who underwent Boston type I keratoprosthesis surgery at the Centro de Oftalmología Barraquer in Barcelona and at the University Eye Clinic in Salzburg between May 2006 and December 2011. Sixty-seven eyes were included. Anatomical success, visual acuity, and complication rate were evaluated and correlated with the initial diagnosis.
Results The mean age of patients was 54 years; 62 % were male and 38 % were female. Eleven patients underwent Type I Boston Kpro implantation as a primary procedure, while the other 52 patients had previous graft failure. The most frequent diagnoses were autoimmune diseases (16 eyes), severe chemical or thermal burn (12 eyes), leukoma post-infectious keratitis (seven eyes) and bullous keratopathy (six eyes). The mean follow-up time was 26 months. Retention of the prosthesis was achieved in 95 % at 1 year and 78 % at 4.5 years. Two eyes suffered extrusion of the KPro, six underwent successful exchange of the prosthesis either due to infection, necrosis or extrusion, three KPro's had to be explantated, and two eyes ended up in enucleation due to panophthalmitis. The outcome of the autoimmune cases was similar to the group with "other diagnoses" and better than those with chemical/thermal burn. The most frequent complication was development of a retroprosthetic membrane in 21 eyes (34 %). Visual acuity (LogMAR) in the chemical/thermal burn group was 2.30 preoperatively, 0.69 at 1 year, 0.52 at 2 years and 0.39 at 3 years; in the autoimmune group visual acuity was 2.3 preoperatively, 0.65 at 1 year, 0.15 at 2 years, and 1.5 at 3 years.
Conclusions Boston type 1 keratoprosthesis is a viable option for patients with repeated graft failure, even for those with challenging diagnoses such as ocular burns and autoimmune syndromes.

Keywords Keratoprosthesis · Visual outcome · Primary diagnosis · Postoperative complications

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Introduction

The Boston Keratoprosthesis is the most widely implanted artificial cornea at present [1–4]. Due to the simplicity of the surgical technique and accessibility in developed countries, and more recently in developing countries, it is fast becoming a procedure highly appealing to any corneal surgeon. It was developed in the 1970s by Claes Dohlman [5], and has undergone several improvements in terms of design [1] as well as post-operative regimen, thereby improving its anatomical retention, and decreasing sight-threatening complications such as retroprosthetic membrane [6] and endophthalmitis [7, 8].

Having nearly 50 years experience with biological keratoprosthesis such as Strampelli´s osteo-odonto keratoprosthesis (OOKP) and Temprano´s tibial bone keratoprosthesis (Tibal Kpro), we have demonstrated that a biological keratoprosthesis might be a viable option for

end-stage corneal disease complicated by severe dry eye [2, 9]. However, due to the challenging technique and the sometimes unfavorable results of keratolimbal allografts [10], we decided to look for biocompatible alternatives that might replace such tedious procedures such as OOKP or Tibia Kpro.

When we started implanting the Boston Type I KPro at our institutions in 2006, the main recommended indication at that time was two or more failed grafts [11]. With time and increasing experience, we have expanded the indications for this procedure: in selected cases we use it as primary procedure, if we consider a corneal graft at high risk to fail due to the presence of marked corneal neovascularization. In a recent publication by Colby [1], expanded indications and their anatomical results for the Boston Type I Kpro were presented. After nearly 6 years of experience at our institution, our indications have become more extensive than those previously described [1, 4, 11]. We present anatomical as well as visual results of our patients with Boston Type I KPro. In all our cases, we considered a biological keratoprosthesis as too aggressive and the potential results of a conventional penetrating keratoplasty as too poor.

Material and methods

We reviewed the charts of 63 patients who underwent Boston Type I Keratoprosthesis implantation at two major eye referral centers in Europe (Centro de Oftalmología Barraquer, Barcelona and University Eye Clinic, Paracelsus Medical University, Salzburg) from May 2006 to December 2011. A total of 67 eyes were included. This retrospective study was approved by the appropriate ethics committee, and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Visual acuity was measured in decimal units and transcribed into LogMAR values. No light perception was defined as 0.001 (decimal visual acuity), light perception only as 0.002, light projection as 0.003, hand motion as 0.005, and counting fingers as 0.015 [12]. Visual acuity measurements were performed regularly, and all data were tabulated pre-operatively and at all succeeding postoperative follow-ups.

Boston Type I Keratoprosthesis implantation was performed as previously described by the Dohlman group [11]. The post-operative treatment protocol at the two eye centers did not differ significantly from that of the Boston Type I Keratoprosthesis Group.

Anatomical success was defined as permanent retention of the first prosthesis. All cases that underwent exchange of the first prosthesis were considered to be anatomical failures. With regard to the primary diagnosis, we divided our patients into three categories: autoimmune, chemical or thermal burn, and "others". Primary diagnosis was taken into account to evaluate if it had any implication on visual acuity results. Post-operative complications were noted and correlated with the visual acuity. They were grouped accordingly: retroprosthetic membrane, posterior segment complications, infections and stromal necrosis, new or worsened glaucoma and no complications.

Analysis was performed using Kaplan–Meier survival curves with 95 % confidence intervals (CI). A p-value less than 5 % indicated a statistically significant difference.

Results

Patient demographics

The mean age of patients was 54 years (range: 13–87 years); 62 % were male and 38 % were female. Mean follow-up time was 26 months (range: 1–54 months). All patients less than 12 years old were excluded from our statistical analysis. Therefore, we excluded one eye of a patient with bilateral implantation and one pediatric case at 2 years of age. Sixty-one eyes were included for the final statistical analysis.

The mean number of corneal grafts prior to Boston Type I Keratoprosthesis implantation was 2.27 (range: 0–11). A total of 11 patients underwent Type I Boston Kpro implantation as a primary procedure, while the other 52 patients had previous graft failure. Fifteen patients had one previous graft, 15 patients had two grafts, and 22 patients had three or more previous grafts. The primary diagnoses (meaning the main disease of the patient which initially led to the first corneal graft) were (in decreasing order of frequency): 1) chemical/thermal burn in 12 eyes, 2) autoimmune diseases (Stevens–Johnson/Lyell syndrome, graft versus host disease, ocular cicatricial pemphigoid, and immunetactoid keratopathy) in 16 eyes, and 3) other diagnoses: bullous keratopathy in six eyes, congenital aniridia keratopathy in five eyes, leukoma post keratitis in seven eyes, ocular trauma in four eyes, congenital opacities in three eyes, corneal ectatic disease in three eyes, calcific keratopathy in one eye, neurotrophic keratopathy in two eyes, limbal stem cell deficiency due to contact lens abuse in one eye, cicatricial trachoma in one eye, and congenital glaucoma in one eye.

Complications

The incidence of complications was as follows: 1) retroprosthetic membrane in 21 eyes (34 %), 2) posterior segment complications: retinal or choroidal detachment in 12 eyes (19 %), vitreous hemorrhage in three eyes (5 %), retinal necrosis in two eyes (3 %), sterile vitritis in one eye (2 %), pre-retinal membrane in one eye (2 %), central retinal artery occlusion in one eye (2 %), 3) infection and necrosis such as endophthalmitis in eight eyes (13 %), stromal necrosis in four eyes (6 %), and infectious keratitis in three eyes (5 %), and 4) new or worsened glaucoma in 15 eyes (24 %).

Eighteen eyes developed multiple complications (30 %), while in 17 eyes (28 %) no complications were found during the follow-up period. For the statistical analysis, we analyzed cases with only one complication, to avoid confounding variables in analysing each complication´s impact on visual acuity, i.e., only retroprosthetic membrane in seven eyes (11 %), only glaucoma in six eyes (10 %), only infection in two eyes (3 %), and only posterior segment complications in ten eyes (16 %).

Retention of the prosthesis was achieved in 95 % at 1 year and 78 % at 4.5 years. Two eyes suffered extrusion of the KPro, six underwent successful exchange of the prosthesis either due to infection, necrosis or extrusion, three KPro's had to be explantated, and two eyes ended up in enucleation due to panophthalmitis.

Anatomical results

The anatomical survival rate in our study group at 1 year was 95 %, at 2 years 85 %, at 3 years 82 %, and at nearly 5 years 78 % (Fig. 1 — All cases). Taking into account the primary diagnosis based on the categories mentioned above, the outcome of the autoimmune cases was similar to the group with "other diagnoses" and better than those with chemical/thermal burn (Fig. 1 - Diagnostic group). There was a tendency for the chemical/thermal burn group to worsen from 3 years onwards, whereas the autoimmune cases and the group with "other diagnoses" showed stable results . However, using the chi-squared test to compare the anatomical success of the three diagnostic categories, it was not possible to find any statistically significant difference at any point in time in the post-operative period.

Visual acuity results

The median visual acuity in LogMAR was preoperatively 2.30 (equivalent to hand motion), 1.0 at 1 year post-op, 1.0 at 2 years and 0.96 at 3 years (Fig. 2 - All cases).

Taking into account the primary diagnosis, the chemical/thermal burn and autoimmune groups had better visual acuity results at 1 year post-op. However, there was worsening of results in the autoimmune and other diagnoses at 3 years. Comparing all three diagnostic categories through time, the chemical/thermal burn group had the best improvements, from 2.30 at pre-op, 0.69 at 1 year, 0.52 at 2 years and 0.39 at 3 years. The group with "other diagnoses" also showed improved visual acuity, with 2.2 at pre-op, 1.18 at 1 year, 1.52 at 2 years and 1.54 at 3 years. The autoimmune group showed initially marked improvement, with 2.3 at pre-op, 0.65 at 1 year and 0.15 at 2 years, but eventual worsening with 1.5 at 3 years (Fig. 2 — Diagnostic group).

Cases with only one kind of complication were analyzed separately, to better investigate the impact of each

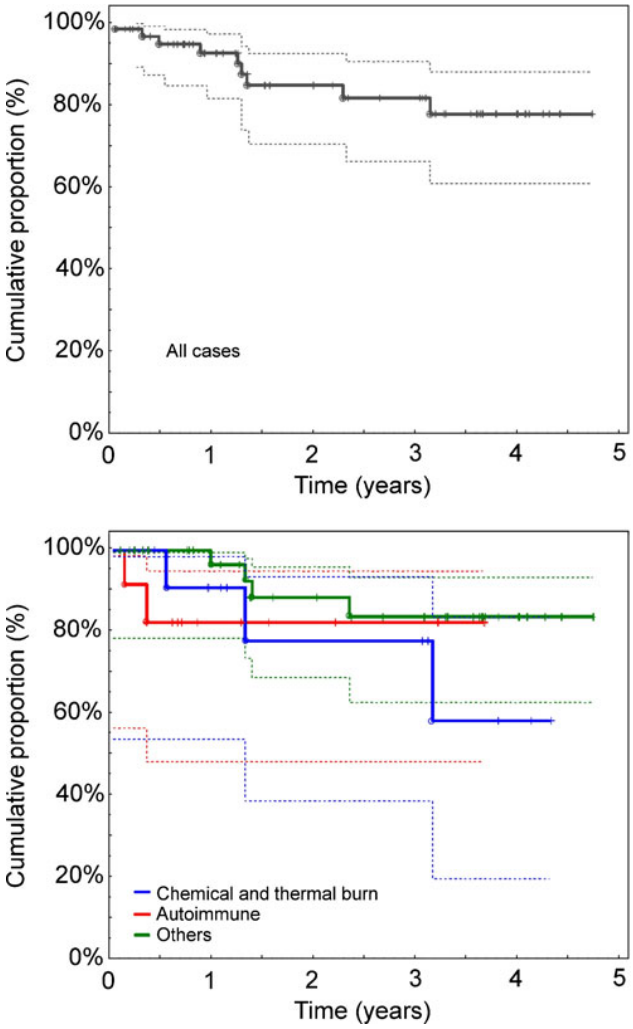

Fig. 1 Kaplan–Meier anatomic survival curves for Boston Type I keratoprosthesis; for all cases (*top*) and according to primary diagnosis (*bottom*). *Dotted lines* are 95 % confidence intervals. Differences for primary diagnosis groups are not significant; chi-square test $p = 0.26$

complication on visual acuity. The best visual acuity in the long term was found in patients with no complications, only glaucoma, or only retroprosthetic membrane. Much worse visual acuity was found in patients with posterior segment complications or multiple complications. Analyzing visual acuity through time in each of the complications, patients with no complications had the best visual results, with 2.30 pre-op, 0.82 at 1 year, 1.26 at 2 years and 0.92 at 3 years. Patients with only glaucoma also showed stable visual acuity, with 2.3 pre-op, 0.89 at 1 year, 0.15 at 2 years and 0.41 at 3 years. Patients with retroprosthetic membrane showed improved results with 2.0 pre-op, 1.19 at 1 year, 1.1 at 2 years and 0.60 at 3 years post-op. The two cases with only infection had similar results, with 1.9 pre-op and 2.00 at 1 year. In the 18 eyes with multiple complications, visual acuity improved from 2.3 pre-op, to 1.00 at 1 year, 1.3 at 2 years and 1.3 at 3 years. Patients with posterior segment complications showed the worst visual

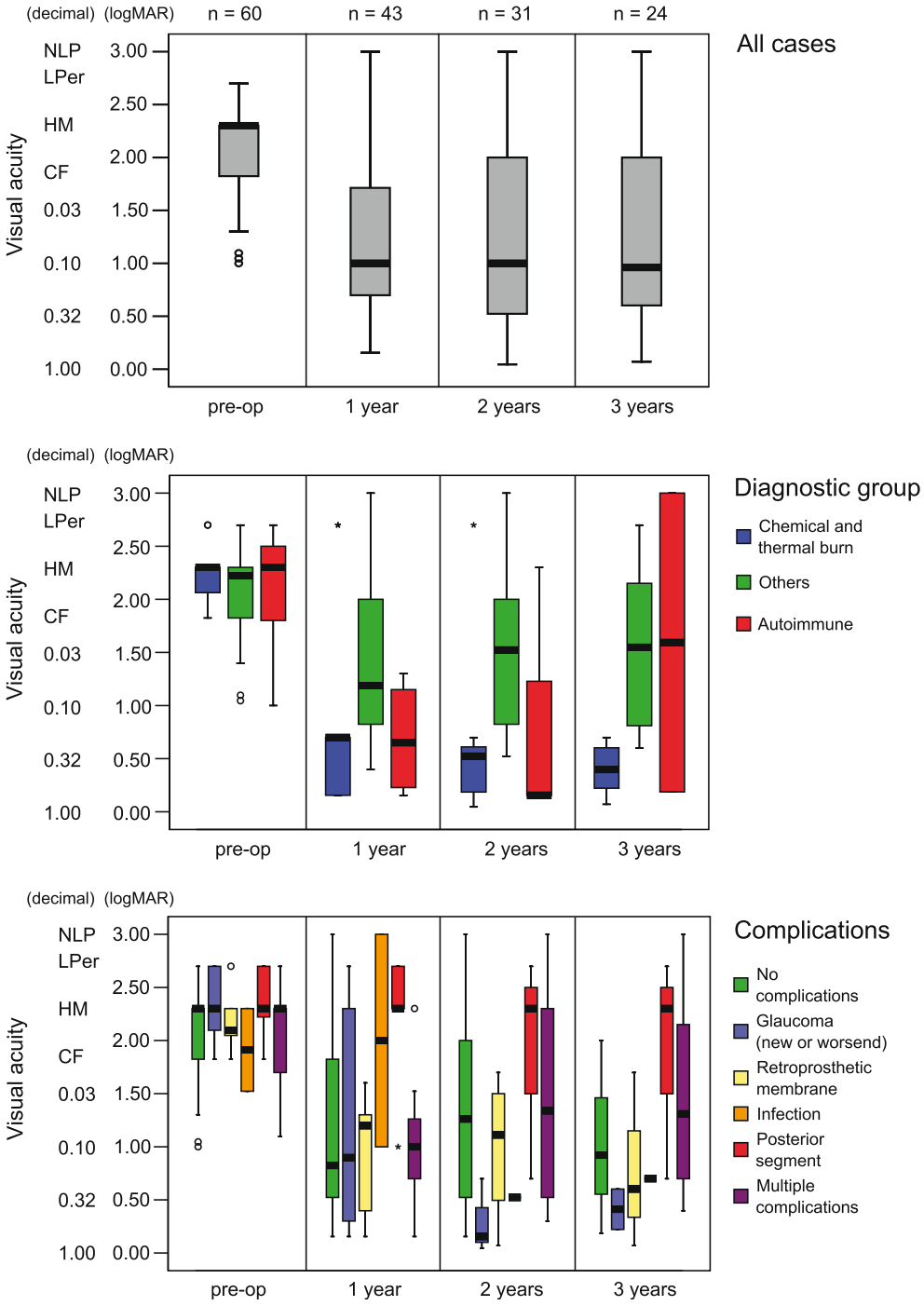

Fig. 2 Visual acuity for Boston Type I keratoprosthesis cases; for all cases (*top*), according to primary diagnosis (*centre*) and according to postoperative complications (*bottom*). Data given as box plots preoperatively, 1 year, 2 years, and 3 years postoperatively

results, with no change in visual acuity of 2.3 pre-op until 3 years post-op (Fig. 2 — Complications).

Discussion

It is generally accepted that the Boston Type I keratoprosthesis is best indicated in cases of repeated graft failure, where a conventional full-thickness corneal transplant usually fails [1, 3, 4, 8, 11, 13–15]. Colby mentions that increasing experience with the Boston KPro has expanded its indications to cases with herpetic keratitis, aniridia, autoimmune ocular disorders, and pediatric corneal opacities [1]. Yaghouti et al. first discussed in 2001 the influence of the preoperative diagnosis on the success rate of the prosthesis. Back then, post-operative protocols, such as the use of wide spectrum antibiotics and fungal infection prophylaxis, were not as well-defined as they are today. They were already able to demonstrate that non-

cicatrizing causes of graft failure had a fairly better outcome compared to conditions with pre-operative inflammation, such as chemical burn, ocular cicatricial pemphigoid, and Stevens–Johnson syndrome [16].

Taking into account our experience with biological keratoprosthesis such as OOKP and Tibia KPro [2, 9, 17], we have been very selective in our indications when we started with the Boston Type I KPro in 2006. We have also been very strict with the recommended topical post-operative regimen, using a third/fourth generation quinolone, vancomycine 14 mg/ml, steroids, medroxyprogesterone, and a bandage contact lens. In addition to this, we administered oral immunosuppressives, such as oral cyclosporine or tacrolimus, when the ocular surface inflammation seems to be uncontrolled with only topical anti-inflammatory drops. In other cases, we continued topical therapy with blood derivatives, such as autologous serum, when it was already preoperatively used to cure and prevent persistent epithelial defects or trophic ulcers (Fig. 3).

This might explain the very good results in the autoimmune group compared to the results of other authors [18]. In the literature that has so far been published on the Boston Kpro, the most common autoimmune diagnoses have been Stevens–Johnson syndrome and ocular cicatricial pemphigoid. To our knowledge, this study presents the highest number of patients with Stevens-Johnson syndrome as primary diagnosis, compared to other publications implanted with Boston Type I keratoprosthesis [3, 4, 14, 19]). The study of Sayegh presents good anatomical results in patients with SJS in the long term, combining results of Type I (six eyes) and Type II (ten eyes) Boston KPro. [20]. Based on our experiences with both biological and biocompatible keratoprosthesis, we believe that ocular cicatricial pemphigoid is a contraindication for Boston Type I keratoprosthesis. The presence of severe dry eye, symblepharon, and progressive ocular surface fibrosis will make a bandage contact lens difficult to adapt. Our experience shows that a biological keratoprosthesis may be the surgery of choice for the end-stage disease of ocular cicatricial pemphigoid, as a severely dry ocular surface is replaced by oral bucal mucosa [2, 9, 17]. However, in cases of Stevens–Johnson, before deciding on whether to implant a biological or a biocompatible keratoprosthesis, we preoperatively check for the presence of stable ocular surface, good lid closure, and absence of excessive symblepharon wherein a bandage contact lens can be fitted properly (Boston Type I Kpro). If this is not the case, then we proceed with a biological keratoprosthesis such as an OOKP or Tibial bone KPro. Another possible option may be the transpalpebral Boston Type II keratoprosthesis.

In our series, 18 % of eyes had a history of a chemical or thermal burn. Our results show very good anatomical and

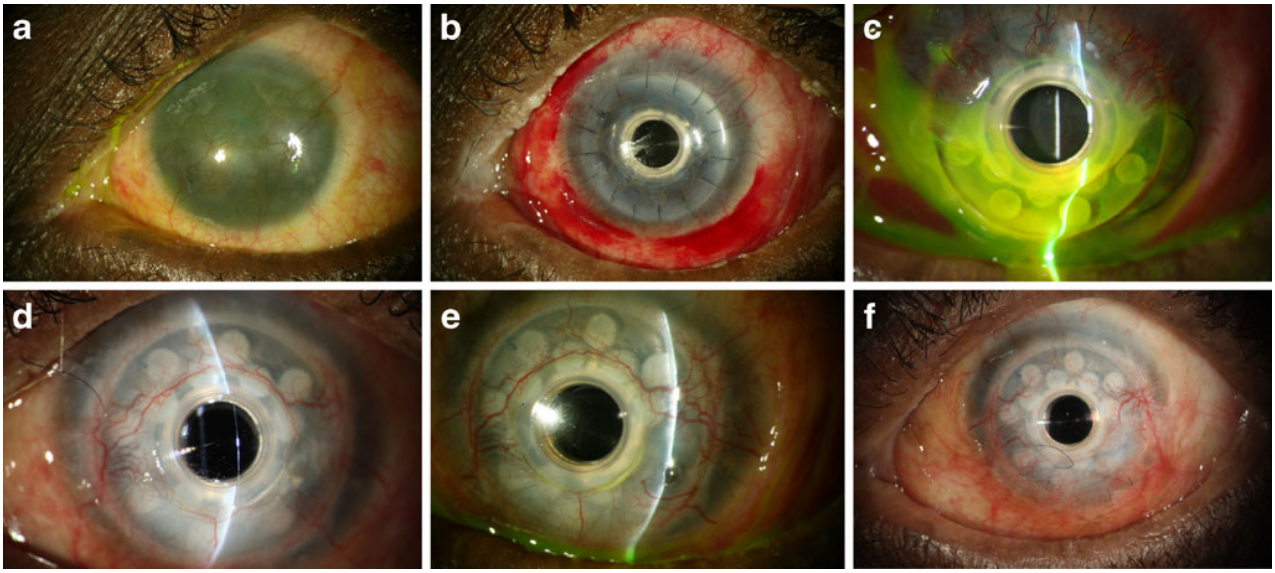

Fig. 3 Case of 50-year-old male with Stevens–Johnson syndrome and end stage renal disease. **a** There was good lid function and stable dry eye. Preoperative BCVA was 0.05. OD had symblepharon and advanced optic nerve excavation due to long-standing glaucoma. **b** Four months after Boston KPro implant with cataract extraction and IOL implantation with stable contact lens and incipient retroprosthetic membrane. BCVA 0.4. Follow-up is limited to every 4–6 months since patient lives outside Europe. **c** Eight months after surgery with extrusion of the inferior half of the prosthesis and dense retroprosthetic membrane. **d** Five months after KPro exchange with BCVA 0.6. **e** One year after KPro exchange with impending perforation of a small descemetocoele in the inferior temporal quadrant. BCVA 0.6. **f** A lamellar segment keratoplasty of the inferior temporal quadrant with conjunctival flap was performed since the rest of the prosthesis was intact. Present BCVA is 0.7. All this time, the patient has been maintained on oral immunesuppresants, autologous serum, topical steroids and medroxyprogesterone, vancomycine, fourth generation quinolone, and glaucoma medications

visual acuity results at 3 years post-op. In fact, this group had the best visual prognosis compared with auto-immune cases and other diagnosis groups. This parallels the publication of the multicenter Boston Type I KPro study with the highest number of chemical burns included (20 eyes/15 %), with favourable visual improvement, although their study had a shorter follow-up time of 8.5 months [4]. Greiner et al. presented the results of a large number of patients with chemical burn (ten eyes, 25 %), and also described good long-term results in terms of anatomical retention and improved visual acuity, which corroborates the results of our study [3]. The study of Magalhaes, on the other hand, had a high incidence of corneal melt (40 %) in patients with a history of an ocular burn [21]. The aforementioned publication by Yaghouti on Boston Type I Kpro, which took into account also the impact of the preoperative diagnosis on anatomical retention [16], showed a decline in visual acuity from 2 to 5 years postoperatively in eyes with chemical burns. However, their study was performed in the 1990s. We must consider that at present, due to improved postoperative protocols and improvements in the treatment of postoperative complications, we might expect better overall results in this diagnostic category.

Retroprosthetic membrane

Our study is in accordance with the majority of case series, finding retroprosthetic membrane to be the most common postoperative complication following a Boston Type I KPro implantation, with rates ranging from 25 %-65 % [3, 4, 14–16, 19, 21, 22]. In our series, retroprosthetic membranes developed in 34 % of our cases. This complication is usually not sight-threatening, as it can be easily treated and cured by performing YAG laser membranotomy; however, surgical membranectomy or subtenon injection of triamcinolone might be needed in a very few cases [3, 4, 14]. A larger backplate of 9.5 mm made of titanium seems to lower the incidence of retroprosthetic membrane formation, as observed by the Dohlman group (unpublished results). They postulate that the membrane is formed due to unrestricted swelling of the host cornea wound, allowing stromal keratocytes to migrate onto the optical part of the prosthesis (Shukla ARVO 2012 abstract). We have observed that retroprosthetic membrane formation seems to be related to the degree of ocular inflammation. Titanium is a more biocompatible material and might be the future material for the Boston Kpro backplate, decreasing host cornea immune reaction to the prosthesis. An unfrequently recognized complication that may be related to a retroprosthetic membrane is the formation of a retro backplate membrane. Sivaraman et al. describes that this entity might be related to sterile keratolysis or melting, as its formation may impede the nutrition of the donor cornea by aqueous humor [23]. They suggest that ocular coherence tomography might be useful to monitor retro backplate membrane thickness. At present, we perform AS-OCT on all post-operative controls, and thus hope to further evaluate the implication of this entity and its relationship to membrane formation on the optical part of the prosthesis.

Glaucoma

The majority of patients who undergo a keratoprosthesis implantion already have a history of glaucoma, or may even have undergone glaucoma surgery previously [3, 4, 14, 15, 24, 25]. Its existence prior to keratoprosthesis surgery affects visual prognosis in the long-term, especially if there is progression and poor control of the disease. The implantation of a glaucoma drainage device simultaneously to the Kpro surgery, or cyclophotocoagulation, if medical treatment is not sufficient to control glaucoma progression, has been suggested by some authors. Development of glaucoma in keratoprosthesis patients may be due to several mechanisms, such as: steroid responsiveness (as most patients had to be on topical steroids for a very long time), chronic inflammation (especially in autoimmune or chemical burn cases), or progressive fibrosis causing angle closure. Anterior segment optical coherence tomography (OCT) or ultrasound biomicroscopy (UBM) may serve as useful tools to rule out the presence of synechia or progressive angle closure. In such a way, glaucoma progression might be picked up earlier, prior to clinical detection with standard diagnostic techniques as digital palpation, visual field studies, and optive nerve imaging (Qian, Pallás, Panarelli posters ARVO 2012). At our centers we perform refraction, visual field studies, and Visante-OCT at least every 3 months, with regular consultation of our glaucoma department to early detect glaucoma progression. The importance of refraction cannot be underestimated, as progressive myopization of the eye can be a subtle sign of progressively raised intraocular pressure. Digital tonometry is quite unreliable, especially in cases where patients had undergone multiple surgeries and had been on chronic use of topical steroids, resulting in marked scleral thinning. Currently, we hope for the benefit of a novel device to directly measure intraocular pressure [1]. When medical treatment seems to be inadequate for halting progression, we prefer transscleral diode cyclophotocoagulation to glaucoma drainage devices, especially when the ocular surface is very fragile. This may probably explain the fairly better results, if the only complication after keratoprosthesis surgery is glaucoma, compared to the other more devastating complications as infection, necrosis, and posterior segment complications.

Infection and stromal necrosis

These are sight-threatening complications, where early diagnosis and intervention are crucial to preserve anatomical integrity and visual results. Our incidence of endophthalmitis is 13 %, which is slightly higher than those of other series (0–12.5 %) [3, 4, 8, 14, 22, 24, 26]. We follow the recommended protocol, with

application of a bandage contact lens changed every month, topical vancomycine 14 mg/ml, third or fourth generation topical quinolone, and strong topical steroids, which are tapered from the first month onwards to 1–2 times daily, depending on the inflammatory status of each case. It is important to point out that patient compliance and education are critical, since non-compliance in therapy might lead to complications. Being referral centers in Europe, a majority of our patients live far from our eye clinic, or they even live abroad, such that patient follow-up becomes an issue. Three of the patients who developed endophthalmitis had cultures positive for candida; one was positive for streptococcus viridans, one was positive for Brachinebacterium paraconglomeratum, and three were culture-negative. Presenting symptoms were acute or progressive injection, blurry vision, and sometimes pain. B-scan ultrasound may help us to assess the status of the posterior segment. However, performing emergency vitrectomy and intravitreal tap to get material for culture, followed by intravítreal injections with fortified antibiotics or antifungals — depending on the suspected pathogen — increases the chances of restraining infection and avoiding necrosis of the retina. The studies of Chan on infectious endophthalmitis and infectious keratitis in Boston Kpro patients conclude that gram negative and fungal pathogens are the most frequent causes, since these patients are on chronic topical antibiotic and steroid use [8, 13]. Moreover, resistance to broad spectrum antibiotics may be an issue despite their low dosage [26]., Since we started in 2010 with 5 % povidone–iodine wash at each visit to our eye center, we have noticed a dramatic decrease in the incidence of infections.

Stromal necrosis is another devastating complication, which can lead to extrusion of the implant. Therefore, its early detection and treatment is crucial. The incidence of this complication in our series (6 %) is less than those mentioned in other studies [18, 22]. One case was due to blepharophimosis and Kpro exposure with poor contact lens fitting (eight previous corneal transplants). Another patient had persistent epithelial defects, leading to failure of the previous four corneal grafts. This patient underwent Boston KPro exchange for corneal melting of her first implant; the second implant unfortunately ended up in extrusion with panophthalmitis due to Brachnibacterium paraconglomeratum and eventual enucleation. Two patients developed stromal melting after prolonged epithelial defects. In contrast to previous reports, our cases developing stromal necrosis did not suffer from autoimmune disorders [3, 18]. Ocular burns seems to be a risk factor for developing corneal melting [21]. We fully agree with the recommendation of using a soft bandage contact lens to improve surface hydration, and the application of topical medroxyprogesterone. In selected cases, we prescribe oral doxycycline to enhance anti-collagenolytic activity, as previously described by other authors [14]. Dohlman and his team are continuously improving material and design of the prosthesis. Thus, a titanium backplate, which is slightly larger in diameter, seems to have promising results (Shukla ARVO poster 2012, Salvador EVER poster 2012). Furthermore, crosslinking of the donor cornea seems to increase corneal resistance to enzymatic degradation, at least in animal studies (Arafat ARVO 2012 poster).

Posterior segment complications

Our series showed a high incidence of posterior segment complications (37 %). Retinal detachment, choroidal detachment, vitreous hemorrhage, retinal necrosis, retinoschisis, sterile vitritis, pre-retinal membrane, and central retinal artery occlusion were the complications identified (in decreasing order of frequency). These cases end up with the worst visual prognosis, when compared to the other aforementioned complications. This is in accordance with a study by Goldman et al., with an incidence slightly higher than in our series [27]. Whereas under normal circumstances retinal or choroidal detachment can successfully treated with posterior segment surgery, our KPro patients did not regain vision. Other mentioned post-operative complications are cystoid macular edema [19], chronic hypotony not due to retinal detachment nor leakage [3, 28], and vascular occlusion [3]. Visual acuity in patients with pre-existing macular degeneration may not improve from keratoprosthesis [4]. These conditions severely affect visual outcome; thus, the importance of performing preoperative exams to assess the visual function in severely opacified corneas cannot be underestimated, as we have demonstrated in cases of biological keratoprosthesis [2]. Patients must therefore be aware of these feared complications, which may impact the visual prognosis in the short or long term.

Years of experience with keratoprosthesis demonstrate that the Boston Type I keratoprosthesis may be a viable option in the treatment of challenging cases such as ocular burns and autoimmune syndromes. However, a stable ocular surface is absolutely essential to strictly adhere to the recommended post-operative treatment protocols. Retention rates are good in the long term, and patients have good chances for improved and stable visual acuity, provided that posterior segment pathologies are ruled out preoperatively. Patients have to be aware of potential complications, which may be either reversible or sight-threatening. We consider the procedure a viable option in patients otherwise condemned to high risk of failure of a conventional corneal graft.

Conflict of interest There is no conflict of interest for any of the authors.

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8.2 Paper 2

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Influence of Primary Diagnosis and Complications on Visual Outcome in Patients Receiving a Boston Type 1 Keratoprosthesis

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Influence of Primary Diagnosis and Complications on Visual Outcome in Patients Receiving a Boston Type 1 Keratoprosthesis

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Key Words
Keratoprosthesis · Visual outcome · Primary diagnosis · Post-operative complications

Abstract
Purpose: To analyse how primary diagnosis and complications affect the evolution of post-operative visual acuity (VA). ***Methods:*** We performed retrospective chart analysis on 59 eyes in 57 patients with various diagnoses, most of which were non-standard indications for Boston type 1 keratoprosthesis (Kpro) implantation. The follow-up period was at least 3 months. Patients were classified based on the evolution of post-operative VA: group A demonstrated stable VA improvement, group B lost VA improvement and group C no significant VA improvement. ***Results:*** We assigned 46% of our cases to group A with stable VA improvement, 32% to group B with lost VA improvement, and 22% to group C with no VA improvement. The number of graft failures before Kpro implantation did not influence VA outcome. Except for the relatively good VA outcome in chemical burn and radiation injury patients, there seems to be no association between primary diagnosis and positive or negative VA outcome. Only 9% of patients with posterior segment complications and 20% with infections and associated pathologies were assigned to group A. ***Conclusion:*** Most cases (78%) showed improvement in VA after Boston type 1 Kpro (groups A and B). Posterior segment complications and infections mostly resulted in persistent loss of vision. These complications should be prevented and carefully treated.

Introduction

Treating corneal blindness is challenging in patients undergoing multiple penetrating keratoplasties. Visual outcome in these cases is inversely related to the number of re-graftings [1, 2]. The Boston type 1 keratoprosthesis (Kpro) was developed to treat patients with corneal blindness and poor prognosis after full-thickness corneal transplantation. It provides a clear visual axis through the optical cylinder and rapid visual recovery [3–5]. This method offers an alternative technique for improving vision in patients with multiple graft failures [6]. Satisfactory outcomes correlate with the underlying pre-operative pathology [7].

Eyes receiving this device must have reasonable tear and lid function and the ability to protect the ocular surface. General indications are corneal allograft rejection, corneal vascularization, opacity with limbal stem cell deficiency (aniridia and others) and chemical burns [2, 8, 9]. Modified Kpro design, routine use of soft con-

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tact lens after surgery and long-term use of antibiotics have significantly reduced complication rates, leading to improved final visual outcomes with this procedure [10].

In our study, patients who underwent Kpro had varied primary diagnoses and post-operative complications. This makes classification by diagnosis and complication difficult. Therefore, we evaluated our results by grouping patients based on the evolution of post-operative visual acuity (VA) and subsequent analysis of the primary diagnoses and complications in each VA group.

Materials and Methods

We performed retrospective chart analysis on 59 eyes in 57 patients who underwent Kpro implantation at the Centro de Oftalmología Barraquer, Barcelona (33 patients) or the University Eye Clinic, Paracelsus Medical University, Salzburg (24 patients) between May 2006 and May 2011. The average age of the patients is 54 years (range: 2–89), including 61% male and 39% female. The follow-up period was at least 3 months (median: 27 months; range: 4–54 months). Follow-up continued after exchanging the Kpro. Both clinics used exactly the same pre- and post-operative procedures according to the Boston Keratoprosthesis International Protocol [11, 12]. We conducted this study in accordance with the guidelines of the Declaration of Helsinki.

The Kpro refractive power was chosen based on each patient's lens status. The post-operative standard treatment regimen was ofloxacin or tobramycin, vancomycin 14 mg/ml and prednisolone acetate 1% [12–14]. Other medications were administered based on clinical needs. Intra-ocular pressure was measured by digital palpation at follow-up visits. Patients with pre-existing glaucoma were treated with topical medication or surgery. All complications were treated medically or surgically immediately after diagnosis.

Best corrected VA was measured pre-operatively and post-operatively using decimal scale values that were converted to logMAR scale values. No light perception (NLP) was defined as 0.001 in the decimal VA scale (3.00 logMAR), light perception (LP) 0.002 decimal VA scale (2.70 logMAR), hand movement (HM) 0.005 decimal VA scale (2.30 logMAR) and counting fingers (CF) 0.015 decimal VA scale (1.82 logMAR) [15].

In accordance with the World Health Organization definition of blindness, we defined functional success of the implant as best corrected VA ≥0.05 (≤1.30 logMAR). Patients were grouped based on post-operative VA outcome: Group A included eyes with improved VA that remained better than 0.05 until the end of follow-up. Group B included eyes with improved VA that reached 0.05 at least once during follow-up but later worsened. Group C included eyes with no improvement of VA, never reaching higher than 0.05. In summary, group A means 'stable VA improvement', group B 'lost VA improvement' and group C 'no significant VA improvement'. In each of the three groups, we studied the incidence of the different primary diagnoses, as well as post-operative complications to analyse their relevance in the evolution of VA.

Results

The evolution of VA in all 59 cases is shown in figures 1–3, grouped according to VA outcome as described in the 'Materials and Methods' section. Almost half of our cases (27 patients, 46%) fell into group A with stable VA improvement, 19 (32%) into group B with lost VA improvement and 13 (22%) into group C with no significant VA improvement. The overall best VA reached was 0.15 (median in decimal values; range HM–1.00; table 1). In group A, the best visual acuity was 0.30. However, patients lost on average one line during follow-up (0.1 logMAR). These included 9 cases which lost more than two lines, but kept a VA better than 0.05. In group B, the best median VA was 0.10. However, these patients lost their improved VA to values below 0.05 at the end of follow-up (table 1). Although the cases in group C never reached a VA better than 0.05, there were 4 patients who improved from LP or HM to CF (B11, S4, S18, S23) and 1 case to 0.04 decimal VA (B28).

Regarding primary diagnosis, 58% of chemical/thermal burn patients and 47% of patients with autoimmune diseases or with bullous and aniridia keratopathy were in group A. Immunotactoid and calcic keratopathy and congenital glaucoma cases were all found in group A, but there were few cases of these primary diagnoses (table 2).

Cases of trauma, post-keratitis leucoma and congenital opacity as primary diagnoses were distributed over the three VA groups. For corneal ectasia, corneal dystrophy and degeneration, limbal deficiency due to contact lens misuse, neurotrophic keratopathy and trachoma, most cases were concentrated in group B (table 2).

Patients with pre-existing glaucoma (n = 31) were similarly distributed among all three VA groups. The number of graft failures before Kpro does not seem to have influenced VA outcome. The following percentages of these patients were in group A: 30% of patients with no prior keratoplasty, 46% of patients with 1 graft failure, 64% of patients with 2 graft failures and 41% of patients with more than 3 graft failures (table 2). A Kruskal-Wallis test on the cross-tab data about graft failures before Kpro gave a χ^2 value of 0.41, and hence was not significant.

Figures 1–3 are not intended to follow individual cases, but we indicated acute changes in VA in group A (which later improved) and group B (which lost improved vision and did not improve subsequently). Major temporary worsening of VA in group A was due to endophthalmitis (n = 2), retroprosthetic membrane (n = 1), vitreous haemorrhage (n = 1) and stromal necrosis (n = 1).

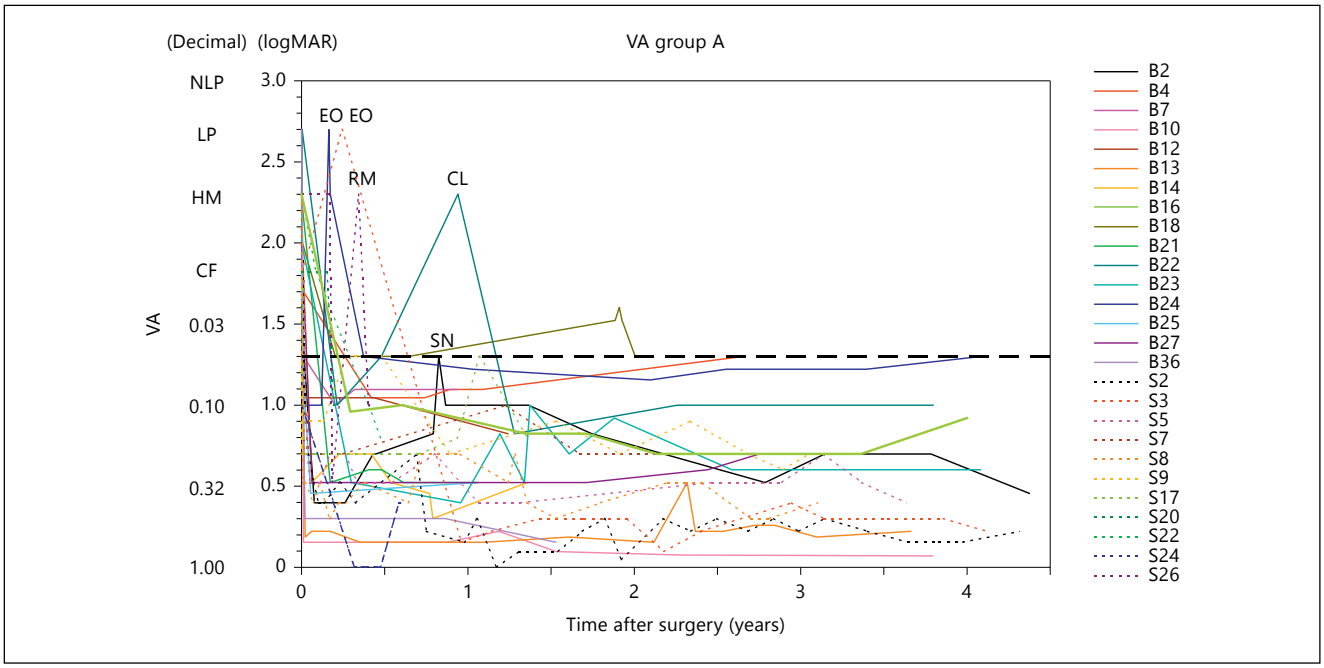

Fig. 1. Evolution of VA for all cases with improvement that remained better than 0.05 until the end of follow-up. Complications at the time of major temporary worsening of VA are specified: EO = endophthalmitis (B24, S3); CL = contact lens dirty (B22); RM = retroprosthetic membrane (S26); SN = stromal necrosis (B2).

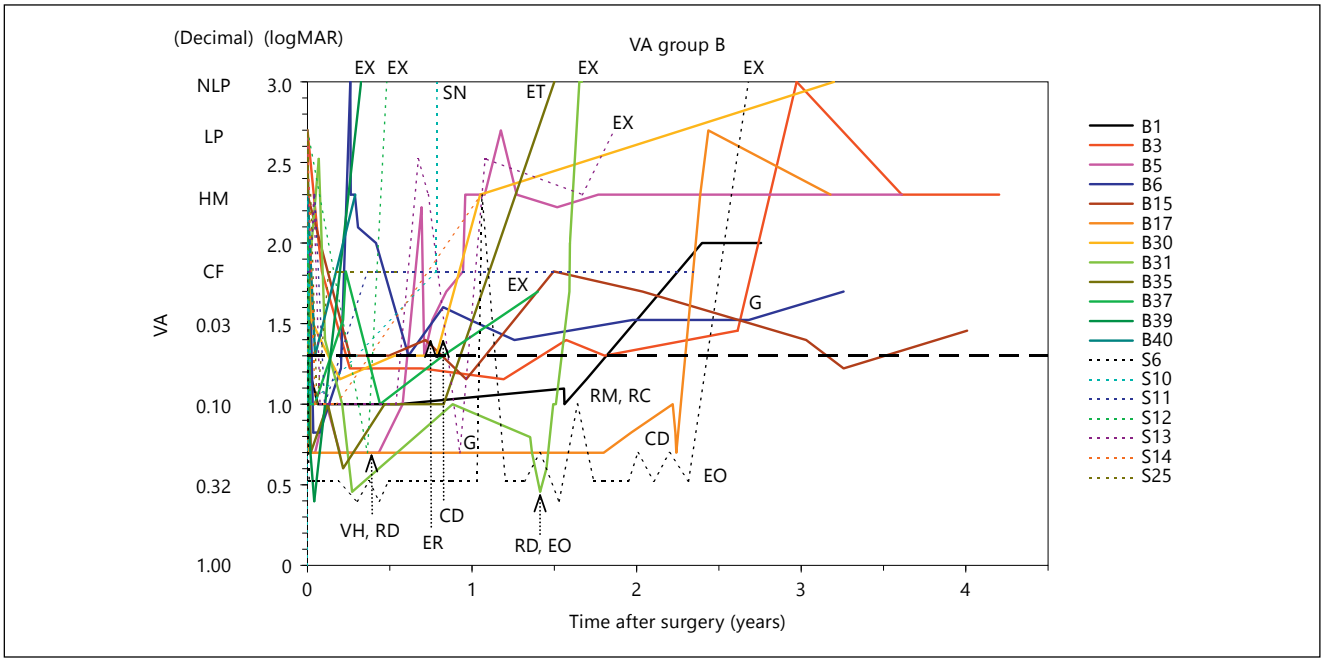

Fig. 2. Evolution of VA for all cases with improvement that reached 0.05 at least once during follow-up but later worsened. Complications at the time of unresolved major worsening of VA are specified: EO = endophthalmitis (S6, B31); ET = extrusion (B35); ER = epiretinal membrane (B5); EX = Kpro exchange (B31, B37, B39, S6, S12, S13); CD = choroidal detachment (B30, B17); G = glaucoma (S13, B3); RD = retinal detachment (S12, B31); RM = retroprosthetic membrane (B1); SN = stromal necrosis (S10); VH = vitreous haemorrhage (S12).

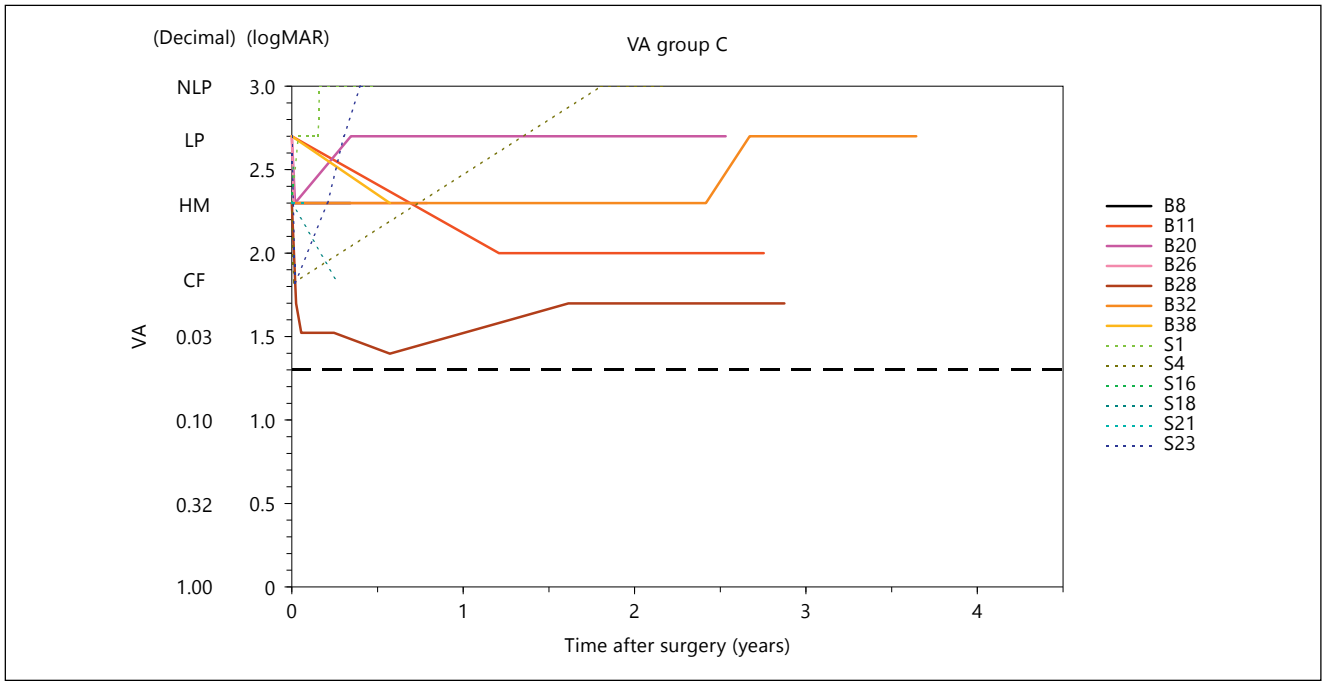

Fig. 3. Evolution of VA for all cases that did not demonstrate improvement or never reached better than 0.05.

Table 1. Pre-operative, best and final VA corresponding to VA group

VA	All cases	Group A	Group B	Group C
Pre-operative	HM (LP–0.10)	HM (LP–0.10)	HM (LP–0.08)	HM (LP–HM)
Best	0.15 (HM–1.00)	0.30 (0.05–1.00)	0.10 (0.05–0.40)	HM (HM–0.04)
Final	0.02 (NLP–0.85)	0.20 (0.05–0.85)	HM (NLP–0.04)	HM (NLP–0.02)

Median and range of VA. Calculated with logMAR data and retransformed to decimal or descriptive values. NLP was defined as 0.001 in the decimal VA scale (3.00 logMAR), LP as 0.002 in the decimal VA scale (2.70 logMAR) and HM as 0.005 in the decimal VA scale (2.30 logMAR).

Patients with retroprosthetic membrane – the most common post-operative complication – fell mostly into group A (50%) and group B (40%). In total, 23 eyes (39%) presented with posterior segment complications, most of them in group B or C (21 eyes). Retinoschisis cases were all in group B. Choroidal detachment cases were found in groups A and B. Cases of vitreous haemorrhage were distributed over all three VA groups. The only case of epiretinal membrane appeared in group B. Retinal detachment cases were evenly distributed between groups B and C. Non-infectious vitreitis, central artery occlusion and retinal necrosis cases were all in group C (table 3).

Endophthalmitis, keratitis and stromal necrosis, which presented in 25% of our cases (15 eyes), were predominantly found in group B, with only 1 case in group C. Only 4 of the patients recovered VA after this complication and remained in group A. New or worsened glaucoma was most frequently found in group A (60%). We had 2 cases of successful Kpro exchange (B39 final VA 0.40 and S6 final VA 0.20), included in group B because of the failure of the first implant.

A post-operative period free of complications does not necessarily correlate with good visual outcome. There were 12 eyes without documented complications, 7 of

Table 2. Case assignment for primary diagnosis, pre-existing glaucoma and graft failure before Kpro to their corresponding VA group

Primary diagnosis	Group A 'stable VA improvement'	Group B 'lost VA improvement'	Group C 'no significant VA improvement'	Group A, %	Group B, %	Group C, %
Chemical burn and radiation injury	B10, B25, S2, S3, S8, S9, S20	S6, S12, S13	S1, S21	58	25	17
Immunotactoid keratopathy	B13, B14			100		
Calcic keratopathy	B18			100		
Congenital glaucoma	S7			100		
Autoimmune diseases (Lyell, SJS, OCP)	B36, S22, S24, S26	B30, B35, B39	S16, S18, S23	40	30	30
Bullous keratopathy	B4, B16, B21	S10	B11, B32	50	17	33
Aniridia keratopathy	B7, S17, B12		B20, B28	60		40
Trauma	B22	S11	B26, S4	25	25	50
Post-keratitis leucoma	B23, B27, S5	B5, B15, S14	B8	43	43	14
Congenital opacity	B24	B31	B38	33	33	33
Corneal ectasia	B2	B3, B40		33	67	
Corneal dystrophy and degeneration		B6, S25			100	
Limbal deficiency after contact lens		B17			100	
Neurotrophic keratopathy		B1			100	
Trachoma		B37			100	
Glaucoma, pre-existing	B4, B12, B16, B18, B22, B23, B25, B27, S2, S3, S5, S7, S8, S17, S20, S26	B1, B5, B6, B37, S6, S11, S12, S13, S14	B28, B32, S4, S18, S21, S23	50	30	20
Graft failure before Kpro implantation						
No previous graft	B18, S20, S26	B35, B39, S12, S13, S14	B38, S1	30	50	20
1	B10, B13, B14, S3, S7, S24	B30, B37, S25	B8, B11, B26, B32	46	23	31
2	B4, B7, B12, B22, B36, S2, S8, S9, S22	B40, S10	B20, S16, S23	64	14	21
3 or more	B2, B16, B21, B23, B24, B25, B27, S5, S17	B1, B3, B5, B6, B15, B17, B31, S6, S11	B28, S4, S18, S21	41	41	18

Table includes 2 bilateral cases, B2 and B3, as well as B13 and B14. SJS = Stevens-Johnson syndrome; OCP = ocular cicatricial pemphigoid.

Table 3. Case assignment for post-operative complications to their corresponding VA group

Complication	Group A 'stable VA improvement'	Group B 'lost VA improvement'	Group C 'no significant VA improvement'	Group A, %	Group B, %	Group C, %
Retroprosthetic membrane	B4, B10, B14, B18, B22, B23, B24, B25, S8, S26	B1, B6, B15, B17, B31, B35, B37, S13	B28, B38	50	40	10
Posterior segment complications						
Retinoschisis		B1, B39			100	
Choroidal detachment	B24	B6, B17, B30		25	75	
Vitreous haemorrhage	S7	S6, S12	S16	25	50	25
Epiretinal membrane		B5			100	
Retinal detachment		B31, B40, S12, S25	B20, B26, B32, S21		50	50
Non-infectious vitreitis			B38			100
Central artery occlusion			S23			100
Retinal necrosis			B32, B38			100
Infection-associated pathologies						
Endophthalmitis	B24, S3	B6, B15, B17, B31, S6	S18	25	63	13
Keratitis		B15, B30, B37			100	
Stromal necrosis	B2	B31, S10, S13		25	75	
Glaucoma (new, worsened)	B7, B22, B27, B36, S2, S3, S8, S9, S26	B35, S13, S14	B32, S1, S18	57	21	21
Anatomical failure						
Extrusion		B35, B39			100	
Kpro exchange		B31, B37, B39, S6, S12, S13			100	
Kpro explant		S10, S12	S18		67	33
Enucleation			S1			100
No complications	B12, B13, B16, B21, S5, S20, S22	B3, S11	B8, B11, S4	58	17	25

Table includes 2 bilateral cases, B2 and B3, as well as B13 and B14.

them were in group A and 2 in group B (B3 and S11). Patient S11 had a history of trauma due to explosives with glaucoma and retinal detachment as well as 5 keratoplasties prior to Boston Kpro. We attribute the visual loss to optic nerve atrophy. Patient B3 had originally high myopia and visual field examination confirmed central scotoma due to myopic maculopathy, which probably worsened. Furthermore, the post-operative gain in VA was never superior to 0.07.

Discussion

Our study demonstrated substantial VA improvement after Boston type 1 Kpro implantation in most eyes (78% of cases, groups A and B). Using the same VA criterion (0.05), Verdejo-Gomez et al. [16] found a success rate of 83% (n = 12). Using 0.10 VA, but with different follow-up times, Greiner et al. [14] had success in 89% (n = 36 at 1 year), Bradley et al. [4] in 77% (n = 30), Aldave et al. [17] in 68% (n = 27 at 1 year), Goldman et al. [18] in 63% (n = 107), Zerbe et al. [12] in 57% (n = 141) and Patel et al. [19] in 43% (n = 50) of cases. This shows that our VA success rate is consistent with previous reports. Regardless, we included some patients with poor pre-operative visual prognosis and some with non-standard indications for Kpro implantation. These included, for instance, patients with severe sicca syndrome and limbal deficiency, 2 in group C (S18, S23) and 1 with successful outcome in group A (S22). In recent publications, indications for Kpro have been extended to herpetic keratitis, aniridia and paediatric patients to prevent amblyopia [9]. Most patients in group C had pre-operative posterior segment comorbidities and underwent Kpro implantation as a final option to improve vision and quality of life.

Except for relatively good VA outcome after chemical/thermal burn, there seems to be no relationship between primary diagnosis and good or poor VA outcome, as is shown by the mixed distribution across all VA groups (table 2).

The number of graft failures before Kpro implantation does not seem to influence VA outcome. Even after three or more graft failures, 41% of these cases were found in group A. As long as there is no dry eye, symblepharon or inflammation, Kpro can be successful. On the other hand, Kpro implantation as primary procedure (with no prior keratoplasty) can be a good alternative in patients with poor prognosis for primary penetrating keratoplasty [20].

As shown in other studies [21–23], most of our patients (53%) presented with pre-operative glaucoma. When considering only central VA, patients with pre-existing glaucoma have outcomes closely similar to all other cases. Moreover, new or worsened glaucoma as post-operative complication was more often found in group A (57%) than in group B (30%) or C (20%). However, visual field is often severely affected, which should be evaluated in future studies.

In 10 eyes, the prosthesis had to be explanted, was extruded or the eye had to be enucleated, which represents an anatomical loss of 17%. Anatomical failure was always associated with other complications, most commonly multiple complications: 6 patients with infection and stromal necrosis, 4 with glaucoma, 4 with retroprosthetic membrane and 3 with posterior segment complications. However, in two of these eyes a successful exchange of the implant with good final VA was possible. Other severe complications were endophthalmitis in 8 eyes (14%) and keratitis or stromal necrosis in another 7 eyes (12%).

For AlphaCor, another Kpro designed for the wet, blinking eye, the anatomical loss was 34% in a series of 322 eyes after a mean follow-up of 16 months [24]. Stromal melting was the most important complication with AlphaCor, from 26% [24] or up to 50 or 60% in two other studies with less patients [25, 26]. Endophthalmitis was less frequent with AlphaCor, ranging between 1 and 7%, according to these publications.

As expected, most patients with retroprosthetic membrane, which most publications indicate is the most common and reversible complication, were in group A. The cases in group B all included other complications, such as choroidal detachment, retinoschisis, pseudopapilloedema or infections, which may explain the loss of VA at the end of follow-up. Cases of vitreous haemorrhage were distributed across all three VA groups.

Poor VA outcomes were confirmed after most posterior segment complications, such as retinal detachment, non-infectious vitreitis, central artery occlusion and retinal necrosis, as reported by Goldman et al. [18]. Only 1 case with choroidal detachment and vitreous haemorrhage had good VA outcome. Infections and associated pathologies (stromal necrosis, keratitis and endophthalmitis) led mostly to lost VA improvement, but 25% of patients with endophthalmitis ultimately had good VA outcomes. In these cases, early detection of endophthalmitis was successfully treated with intravitreal tap and injection of fortified antibiotics/antifungals.

Conclusion

The Boston type 1 Kpro provides visual improvement in most patients with corneal blindness and poor prognosis for penetrating keratoplasty. Pre-operative clinical diagnosis does not appear to affect the final visual outcome. The type of complication encountered in the post-operative period seems to affect final visual prognosis. Among the post-operative complications found, retroprosthetic membrane and glaucoma least affect final visual outcome. Infectious complications, such as endophthalmitis, keratitis and stromal necrosis, may lead to eventual loss in the initial improvement of vision. Posterior segment complications appear to be the most visually devastating complication, leading to no significant improvement in affected eyes compared with pre-operative visual status. These patients must be monitored, and complications should be prevented and carefully treated.

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8.3 Paper 3

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Pronóstico visual y complicaciones posquirúrgicas en queratoprótesis de Boston tipo 1.

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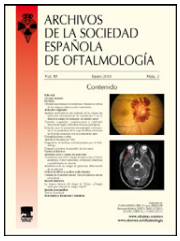

Artículo original

Pronóstico visual y complicaciones posquirúrgicas en queratoprótesis de Boston tipo 1

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RESUMEN

Objetivo: Describir el resultado visual de los pacientes intervenidos de queratoprótesis de Boston tipo 1 (QB1), así como las complicaciones postoperatorias graves que afecten a la visión en estos pacientes.

Métodos: Se realizó un análisis de los expedientes clínicos de todos los pacientes que recibieron QB1 en nuestra institución de mayo de 2006 hasta febrero de 2011.

Resultados: Encontramos 41 ojos de 37 pacientes, 22 (59,45%) masculinos y 15 (40,54%) femeninos. La edad media fue de 56,44 años (rango 2-90). Los diagnósticos más frecuentes fueron la queratopatía ampollosa, enfermedades autoinmunes como el síndrome de Stevens-Johnson (SSJ)/síndrome de Lyell (SL) y queratopatía anirídica. El promedio de queratoplastias (QP) previas fue de 2,36 (rango 0-8) y el de cirugías oculares previas que no eran QP fue de 1,58 (rango 0-9). La media de seguimiento fue de 22,17 meses (rango 3-46). El promedio de la mejor agudeza visual corregida (MAVC) en escala de logMAR antes de la cirugía fue de 2,05 (rango 1,10-2,52) y la MAVC conseguida después de la cirugía fue de 1,16 (rango 0,08-2,70). La complicación más frecuente fue la formación de membrana retroprotésica (MRP), la cual apareció en 22 (53,65%) ojos. De estas, 6 (27,27%) fueron posteriores a otra cirugía. Requirieron tratamiento 14 (63,63%) MRP, un promedio de 1,71 (rango 1-4) aplicaciones de láser YAG y en tres pacientes membranectomía quirúrgica. En 11 (26,82%) ojos se presentaron problemas de adherencia coriorretinianos, seis (14,63%) de los cuales sucedieron después de otra cirugía posterior a la QB1. Complicaciones infecciosas se presentaron en siete (17,07%) casos, dos (4,87%) pacientes presentaron queratitis infecciosas y cinco (12,19%), endoftalmitis.

Conclusiones: La función visual mejoró en la mayoría de pacientes. Aquellos con múltiples cirugías oculares previas y alteraciones de la inmunidad sistémica como SSJ, SL o diabetes mellitus (DM) presentan un mayor riesgo de presentar complicaciones graves que afecten a la visión, como MRP, desprendimientos coriorretinianos e infecciones. A pesar de todo, consideramos que es una alternativa efectiva en pacientes con enfermedad ocular múltiple e inminente riesgo de rechazo de una nueva QP.

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Post-surgical visual outcome and complications in Boston type 1 keratoprosthesis

Keywords:
Boston keratoprosthesis
Outcomes
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Retroprosthetic membrane
Retinal detachment

A B S T R A C T

Objective: To describe the visual outcome of patients who underwent Boston type 1 keratoprosthesis (KPro1) implantation, and describe serious sight-threatening post-operative complications.

Methods: We performed an analysis of the clinical records of all patients who underwent Boston keratoprosthesis implantation (BKI)in our institution from May 2006 to February 2011.

Results: A total of 41 eyes of 37 patients were included in the final analysis, of whom 22 (59.45%) were male and 15 were (40.54%) female. The mean age was 56.44 years (range 2-90). The most frequent diagnoses were bullous keratopathy, autoimmune diseases, such as Stevens-Johnson syndrome (SJS)/Lyell syndrome (LS), and aniridic keratopathy. The mean number of previous keratoplasties (PK) was 2.36 (range 0-8), the mean number of previous non-PK surgeries was 1.58 (range 0-9). The mean follow-up time was 22.17 months (range 3-46). The mean best corrected visual acuity (BCVA) logMAR before surgery was 2.05 (range 1.10-2.52), and the mean best corrected visual acuity achieved after surgery was 1.16 (range 0.08- 2.70). The most frequent complication was the formation of retroprosthetic membrane (RPM) which appeared in 22 (53.65%) eyes. Of these, 6 (27.27%) appeared after another surgery. Fourteen (63.63%) RPM required treatment, an average of 1.71 (range 1-4) laser YAG applications were performed, and surgical membranectomy was performed in 3 patients. Eleven (26.82%) eyes showed chorioretinal adhesion problems, 6 (14.63%) of which occurred after follow-up of BKI surgery. Infectious complications occurred in 7 (17.07%) cases; 2 (4.87%) patients had infectious keratitis and 5 (12.19%) endophthalmitis.

Conclusions: Visual function improved in most patients. Those with prior multiple ocular surgeries and alterations of systemic immunity such as SJS, LS, and diabetes mellitus are at increased risk for serious sight-threatening complications, such as RPM, chorioretinal detachment and infection. Nevertheless, we consider KPro as an effective alternative in patients with multiple ocular pathology and imminent risk of rejection of a new KP.

Introducción

Desde que el oftalmólogo francés Pellier de Quengsy propusiera por primera vez en 1789 sustituir la córnea por un tejido artificial[1] y, en 1853, Johann N. von Nussbaum implantara la primera queratoprótesis que tardó en extruirse 7 meses[2], no se había logrado en posteriores intentos el éxito anatómico esperado hasta la segunda mitad del siglo xx, momento en que se integran materiales sintéticos biocompatibles como el polimetilmetacrilato (PMMA)[3]. En la actualidad son varios los modelos de queratoprótesis utilizados alrededor del mundo en pacientes con alto riesgo de rechazo de una queratoplastia (QP); se dividen básicamente en pre, intra y epiendocorneales, siendo estas últimas las que mejores resultados anatómicos y fisiológicos logran. La queratoprótesis de Boston tipo 1 (QB1) se ha convertido en la actualidad, debido a sus buenos resultados, en uno de los procedimientos de elección en los pacientes que requieran una córnea artificial[4–6]. El diseño, hecho de PMMA, consiste en un plato óptico en forma de tornillo y otro posterior más amplio, con una córnea donadora entre ambos y sellada por un anillo posterior de titanio, suturada al receptor de la manera habitual que una QP penetrante[7].

Esta técnica se indica en pacientes con alteraciones de la visión, de preferencia binocular, pero que conserven una buena función palpebral y una adecuada superficie ocular[8], obteniendo buenos resultados en pacientes con enfermedades como queratopatía ampollosa, queratopatía herpética, queratopatía anirídica, traumatismo ocular, deficiencia de células limbares y opacidades corneales de diversas etiologías[4,9–13].

Las complicaciones más frecuentes que se han descrito son la formación de membranas retroprotésicas, glaucoma, endoftalmitis/vitreítis, defectos epiteliales y queratitis[4,5,10,11]. El propósito de nuestro estudio es evaluar el pronóstico visual y las complicaciones más frecuentes que afectan la visión de los pacientes que reciben QB1 en nuestro centro.

Sujetos, material y métodos

Realizamos nuestro estudio siguiendo la Declaración de Helsinki. Se hizo un análisis retrospectivo incluyendo todos los expedientes de los pacientes en quienes hubiera sido implantada la QB1 desde mayo de 2006 hasta febrero de 2011 en nuestro centro. Todas las intervenciones quirúrgicas fueron realizadas por tres de los autores (JAT, RIB y MP). Se excluyeron aquellos expedientes que no contaran con un mínimo seguimiento de 3 meses. Basándose en estos criterios se encontraron 42 ojos de 38 pacientes.

La agudeza visual se midió en escala decimal y se realizó la conversión a escala logMAR. Utilizamos las escalas de conversión propuestas por Schulze-Bonsel et al.[14] para agudezas visuales entre los rangos de no percepción de luz (0,001) y contar dedos (0,015).

Nuestros criterios para la elección de pacientes aptos para la QB1 (Massachusetts Eye and Ear Infirmary, Boston, EE. UU.) son tener una agudeza visual a 20/200 con su mejor o peor ojo, pero que conserven una función visual aceptable, demostrada mediante toma de agudeza visual o exámenes complementarios (potenciales visuales provocados). La elección del poder refractivo de la QB1 se decide basándose en el estado del cristalino: si el paciente es fáquico, se realiza extracción de catarata y se coloca una prótesis para afaquia, y si el paciente tiene lente intraocular (LIO), se coloca una prótesis para seudofaquia.

La implantación de la QB1 fue hecha mediante la técnica recomendada, la córnea donadora fue trepanada 0,5 mm más que la receptora, con un trépano central de 3 mm, sellado el dispositivo mediante el anillo de titanio y suturada con 16 puntos de nailon 10-0. Al final se colocó una lente de contacto de gran diámetro.

El régimen terapéutico postoperatorio básico consistió en gotas de antibiótico de amplio espectro (ofloxacino [Exocin, Allergan] o tobramicina [Tobrex, Alcon]), vancomicina 14 mg/ml y acetato de prednisolona (Pred Forte, Alcon), así como lente de contacto terapéutica. Este tratamiento se sigue por tiempo indefinido. Se realizan seguimientos periódicos, semanalmente durante los primeros meses y posteriormente entre 6 y 12 semanas. Durante los últimos meses se han añadido lavados con povidona yodada al 5% en cada revisión en pacientes con alto riesgo para endoftalmitis, como aquellos con ojos únicos, enfermedades autoinmunes o antecedentes de endoftalmitis previa.

En los controles postoperatorios se toma la presión ocular digital, se determina la agudeza visual y se valora el estado del injerto y la QB1 y el polo posterior. Se interconsulta con las demás subespecialidades si es necesario y se añaden medicamentos extras a los ya descritos en caso de requerirse.

Resultados

Pacientes

Siguiendo los criterios establecidos fue excluido un paciente por no contar con seguimiento mínimo. Fueron estudiados 41 ojos de 37 pacientes, 22 (59,45%) masculinos y 15 (40,54%) femeninos. La edad media fue de 56,44 años (rango 2-90). En 4 (10,81%) pacientes se realizó el procedimiento bilateral y uno (2,70%) contaba con una osteoodontoqueratoptrótesis contralateral. Veinte (48,78%) de los ojos fueron derechos y 21 (51,21%), izquierdos, y 12 (32,43) de los pacientes fueron ojos únicos. Los diagnósticos aparecen detallados en la tabla 1. El promedio de QP previas fue de 2,36 (rango 0-8) y el de cirugías oculares previas que no eran QP fue de 1,58 (rango 0-9). Se implantaron 10 (24,39%) modelos afáquicos y 31 (75,60%) seudofáquicos. El recuento endotelial de las córneas donantes fue en promedio 2.264 cél./mm^2 (rango 920-3.077) y se realizaron un total de 16 procedimientos concomitantes en la cirugía de implantación de la QB1: ocho vitrectomías, ocho extracciones de catarata, cuatro colocaciones de LIO, tres explantes de LIO y una colocación de válvula de Ahmed. La media de seguimiento fue de 22,17 meses (rango 3-46).

Tabla 1 – Diagnóstico clínico primario de los pacientes operados de queratoprótesis de Boston tipo 1

Diagnóstico	Casos (%)
Queratopatía ampollosa	7 (18,91)
Síndromes mucosinequiantes	5 (13,51)
Queratopatía anirídica	4 (10,81)
Úlcera corneal	3 (8,10)
Causticación	2 (5,40)
Leucoma	2 (5,40)
Queratitis herpética	2 (5,40)
Traumatismo ocular	2 (5,40)
Queratocono	2 (5,40)
Queratopatía cálcica	1 (2,70)
Queratopatía inmunotactoide	1 (2,70)
Degeneración marginal de Terrien	1 (2,70)
Insuficiencia limbar secundaria a lentes de contacto	1 (2,70)
Esclerocórnea	1 (2,70)
Queratitis neurotrófica	1 (2,70)
Síndrome ectodérmico	1 (2,70)
Glaucoma congénito	1 (2,70)
Total	37 (100)

Pronóstico visual

El promedio de la mejor agudeza visual corregida (MAVC) antes de la cirugía fue de 2,05 (rango 1,10-2,52) en la escala de logMAR, y hasta el último seguimiento fue de 1,47 (rango 0,08-3). La MAVC conseguida después de la cirugía fue de 1,16 (rango 0,08-2,70) (figs. 1 y 2).

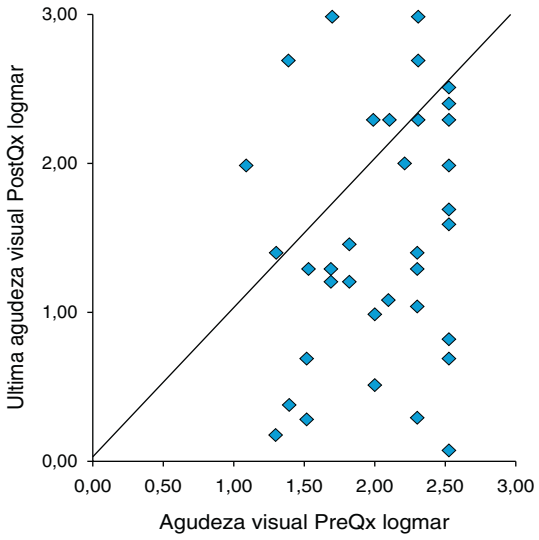

Figura 1 – Gráfico de dispersión comparando la agudeza visual prequirúrgica con la agudeza visual hasta su último seguimiento. Hubo una mejoría significativa en la mayoría de los pacientes.

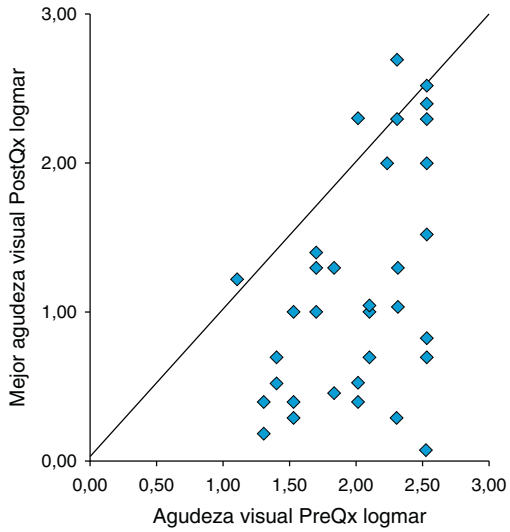

Figura 2 – Gráfico de dispersión comparando la agudeza visual prequirúrgica con la mejor agudeza visual conseguida en el postoperatorio. Se logró mejorar la visión en todos los pacientes.

Complicaciones postoperatorias

No fueron consideradas para el presente estudio todas aquellas complicaciones extraoculares y que no afectan a la visión (por ejemplo, ptosis palpebral) y no sean secundarias a la QB1. El glaucoma tampoco consideramos que sea una complicación inherente a la QB1, ya que estos pacientes, debido al número de cirugías previas, cambios anatómicos en segmento anterior y períodos largos de tratamientos con esteroides, en su mayoría presentan glaucoma de origen multifactorial que puede estar presente hasta en más de dos tercios de estos[4,10,15]. Un total de 32 (86,8%) pacientes habían recibido previamente tratamiento quirúrgico o se encontraban con tratamiento médico antiglaucomatoso.

Tabla 2 – Complicaciones presentadas por los pacientes tras la queratoprótesis de Boston tipo 1

Complicación	Número
MRP	22
DR/DC/retinosquisis	11
Infecciones	7
Necrosis estromal	2
Extrusión	2
Crisis hipertensivas	2
Vasculopatía oclusiva	2
Crisis hipertensivas	2
Vitreítis no infecciosa	1
Membrana prerretiniana	1
Hemorragia vítrea	1
Hipotonía/seudopapiledema	1
Total	53

DC: desprendimiento coroideo; DR: desprendimiento de retina; MRP: membrana retroprotésica.

Tabla 3 – Procedimientos realizados en los pacientes operados de queratoprótesis de Boston tipo 1

Procedimiento	Número
Vitrectomías	14
Láser YAG	14
Sustituciones de injerto	5
Membranectomía quirúrgica	3
CFCTE	2
Enucleación	1
Lavado CA	1
Total	40

La complicación más frecuente fue la formación de membrana retroprotésica (MRP) (tabla 2) en 22 (53,65%) ojos. De estas, seis (27,27%) fueron secundarias a procedimientos quirúrgicos realizados después de la colocación de la QB1. Un total de ocho (36,36%) membranas no requirieron tratamiento y en las 14 (63,63%) restantes se realizaron 24 aplicaciones de láser YAG (tabla 3), un promedio de 1,71 (rango 1-4), y en tres pacientes (13,63%) se requirió una membranectomía quirúrgica adicional (fig. 3).

En 11 (26,82%) ojos se presentaron problemas de adherencia coriorretinianos: desprendimiento de retina (DR) y/o desprendimiento coroideo (DC), en seis (14,63%) de los cuales sucedió después de otra cirugía posterior a la implantación de la QB1: vitrectomía o ciclofotocoagulación transescleral (CFCTE). Se realizó vitrectomía en cinco de estos pacientes.

Presentaron complicaciones infecciosas siete (17,07%) casos (tabla 4), dos pacientes tuvieron queratitis infecciosas

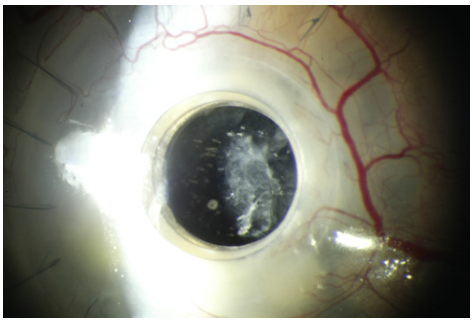

Figura 3 – Membrana retroprotésica densa que requirió tratamiento quirúrgico. Nótense los impactos del láser YAG en la lente.

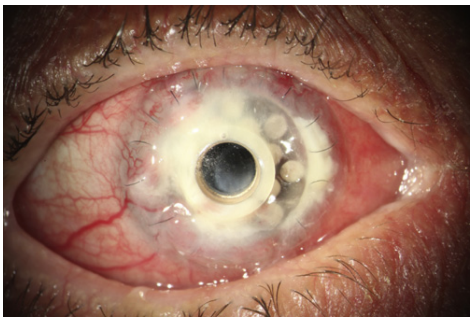

Figura 4 – Queratitis micótica. Se observan las suturas flojas y el avance de la infiltración en el botón donante y la conjuntiva adyacente.

Tabla 4 – Tabla que muestra el listado de pacientes con complicaciones infecciosas, diagnósticos previos, microorganismo causante y datos clínicos relevantes

	Infección	Tiempo de QB1 a infección	Diagnósticos	Microorganismo	Comentarios
1	Queratitis/endoftalmitis	19 meses	Síndrome de ectrodactilia-displasia ectodérmica-hendidura	*Brachinebacterium conglomeratum*	Distriquiasis/4 QP y una esclerectomía previas/Panoftalmitis/Enucleación
2	Queratitis/endoftalmitis	4 meses	Insuficiencia limbar secundaria a LC	*Candida* spp.	DM e HTA/4 QP previas
3	Queratitis/endoftalmitis	12 meses	Queratitis herpética	*Candida* spp.	DM/distriquiasis/3 QP previas/mala higiene de LC
4	Queratitis/endoftalmitis	27 meses	Degeneración marginal de Terrien	Ninguno	Dacriocistitis crónica/2 vitrectomías, una CFCTE y 4 QP previas
5	Endoftalmitis	2 meses	Glaucoma congénito	*Streptococcus viridans*	EC, una vitrectomía y 3 QP previas
6	Queratitis	18 meses	Síndrome mucosinequiante	*Candida* spp.	DM e IRC/EC y una QP previas
7	Queratitis	13 meses	Pénfigo ocular cicatricial	*Candida* spp.	Leucemia Mieloide/EC, 2 homoinjertos de limbo, una vitrectomía y una QP previas

CFCTE: ciclofotocoagulación transescleral; DM: diabetes mellitus; EC: extracción de catarata; HTA: hipertensión arterial; IRC: insuficiencia renal crónica; LC: lentes de contacto; QP: queratoplastia.

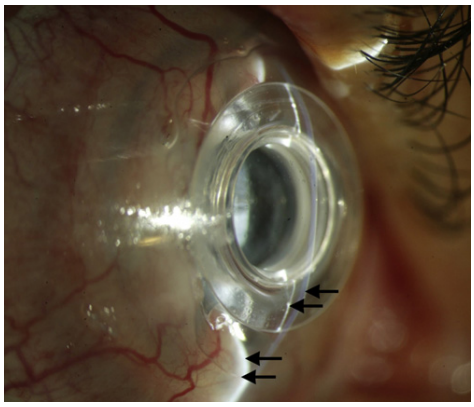

Figura 5 – Extrusión de la prótesis. El primer reflejo (flecha) corresponde al lente de contacto, el segundo reflejo (punta de flecha) a la queratoprótesis, y el tercero (flecha doble) al contorno ocular, observándose el hueco que ha dejado la necrosis estromal.

y los otros cinco, endoftalmitis, de los cuales cuatro comenzaron previamente como una queratitis que finalmente invadió el globo ocular (fig. 4). En cuatro pacientes se aislaron especies de *Candida*, en un caso *Staphylococcus viridans*, en un caso *Brachinebacterium paraconglomeratum* y en otro caso no se logró aislar ningún microorganismo (el día previo había recibido antibióticos y antifúngicos intravítreos). Hubo que realizar sustitución del injerto corneal en tres pacientes (en uno de ellos en dos ocasiones) y en todos se realizó vitrectomía (a dos pacientes en dos ocasiones) + cultivo + inyección intravítrea de vancomicina y anfotericina B + tratamiento antimicrobiano tópico. Además, otros dos pacientes con vitreítis se diagnosticaron después de vitrecomía como vasculopatía oclusiva periférica.

Hubo necrosis estromal en 2 (4,87%) casos, los mismos en los que se extruyó posteriormente la prótesis (fig. 5), con una tasa de retención del 95,12%. Dos (4,87%) pacientes presentaron episodios de glaucoma agudo que se trataron con CFCTE, lográndose un adecuado control de la presión intraocular (PIO).

Discusión

Las queratoprótesis actualmente son una alternativa efectiva en aquellos pacientes en quienes una nueva QP representa un alto riesgo de fracaso. En nuestro centro comenzamos hace más de 30 años colocando queratoprótesis biológicas (osteoodontoqueratoprótesis y tibiaqueratoprótesis) con buenos resultados[16–18]. Consideramos, concordando con la literatura médica existente, que la QB1 no es la opción más adecuada en pacientes con enfermedades autoinmunes, aunque conserven una superficie ocular adecuada[9,19,20], ya que de los cinco casos en los cuales colocamos la QB1 en estos pacientes, cuatro de ellos presentaron complicaciones graves (extrusión, endoftalmitis, queratitis fúngica y glaucoma agudo), por lo que en nuestro centro el protocolo de elección en estos pacientes siguen siendo las queratoprótesis biológicas.

Agudeza visual

Aunque la QB1 logra restaurar la visión satisfactoriamente, los resultados funcionales van a estar condicionados por el estado previo del globo ocular[11,19,21]. La visión mejoró en la mayoría de los pacientes y no se logró solo en aquellos que desarrollaron complicaciones graves después de la QB1. Es significativamente notable el hecho de que 34 (82,92%) pacientes conservaran una mejora de su visión hasta el último seguimiento.

Membrana retroprotésica

Al igual que en las diferentes series publicadas, que comunican entre un 25 y un 65%[10,11,14,19,22], nosotros encontramos que la complicación posquirúrgica más común es la formación de MRP, con una incidencia del 53,65%. Entre las hipótesis que se han sugerido para explicar la formación de la membrana es que se trata de una reacción inflamatoria al PMMA o quizá de una activación de fibroblastos debido al raspado mecánico torsional del endotelio corneal por la queratoprótesis[10]. El riesgo de formación de MRP es más elevado en pacientes con historia de enfermedad vascular, enfermedades autoinmunes y cirugías oculares previas[10,22]. Nuestro estudio confirma la hipótesis de que cualquier factor que favorezca la inflamación ocular local aumentará la incidencia de MRP, ya que una cuarta parte de las membranas retroprotésicas se produjeron en pacientes con cirugía intraocular posterior a la QB1 y 14 de las 16 restantes se presentaron en pacientes con LIO preexistente o en quienes fueron realizados procedimientos concomitantes con la QB1 (válvula, vitrectomía o LIO). La aplicación de láser YAG es un método rápido y no invasivo para remover las membranas con buenos resultados en los pacientes en los que la membrana no desapareció con el uso de esteroides[23]. Es importante una detección precoz, ya que la membranectomía con láser YAG realizada en estadios iniciales, y antes de la vascularización, facilita su completa remoción y en aquellos casos en los cuales no se logre la eliminación con láser se procede a una membranectomía quirúrgica por vía limbar o *pars plana*. En nuestro caso tuvimos que recurrir a la cirugía para la remoción de la membrana en 3 de 22 pacientes (con 1, 3 y 4 capsulotomías YAG previas, respectivamente) logrando buenos resultados y sin recurrencia de la misma.

Adherencia coriorretiniana

En nuestro estudio hemos incluido desprendimientos de retina y desprendimientos coroideos como parte de una misma entidad. En los trabajos previos hay datos discrepantes sobre desprendimientos de retina, que varían de un 0 a un 12%[10,11,19,24]. Nosotros hemos encontrado una incidencia significativamente más alta, el 26,82% de los pacientes presentaron esta complicación, sin asociarla claramente a ningún proceso patológico como las enfermedades autoinmunes[25]. En 6 pacientes fue consecuencia de una cirugía posterior a la QB1 (5 operados de vitrectomía y uno de CFCTE) y en los otros 5 sucedió después de la colocación de la QB1. Analizando su historia clínica, 2 de ellos ya habían tenido desprendimientos de retina previos, otros 2 tenían antecedente de al menos una vitrectomía y un paciente tenía el antecedente de múltiples cirugías de glaucoma. Publicaciones previas indican que los pacientes con intervenciones quirúrgicas previas, sobre todo QP, extracción de catarata y vitrectomía, presentan un riesgo acumulativo de presentar desprendimientos de retina[26,27]. Si a esto añadimos la inflamación crónica, en conjunto pueden explicar la causa de la alta prevalencia en nuestros pacientes. El pronóstico visual continúa siendo pobre en estos pacientes, a pesar de lograr buenos resultados anatómicos con la intervención quirúrgica[28].

Infecciones

Estas continúan siendo un problema grave que afecta severamente al pronóstico del globo ocular, tanto funcional como anatómico. Aunque la adición tópica sistemática de antibióticos de amplio espectro ha reducido sustancialmente la tasa de infecciones bacterianas[4,29], las series recogidas por Chew et al.[10], Nouri et al.[30], Georgalas et al.[31] y Fintelmann et al.[32] muestran que la incidencia de endoftalmitis sigue siendo elevada y, sobre todo, de pronósticos devastadores, pero con datos poco concluyentes acerca de los agentes causales más frecuentes. Se han asociado las infecciones bacterianas a enfermedades autoinmunes y contaminación del humor acuoso[30] y la colonización fúngica al uso prolongado de antibióticos de amplio espectro, lentes de contacto y esteroides[31,33], asimismo se ha demostrado que especies de *Candida*, especialmente *C. parapsilosis*, muestran grandes propiedades de adherencia a los dispositivos plásticos[33], lo cual explicaría la alta incidencia en estos pacientes, aunque ninguna otra serie muestra un claro predominio de infecciones fúngicas como la nuestra. Asociamos en nuestro estudio como posibles factores de riesgo para presentar infecciones la inmunosupresión sistémica (diabetes/leucemia mieloide), enfermedades autoinmunes, trastornos locales que puedan alterar la superficie (distriquiasis, dacriocistitis, mal uso de lentes de contacto) y antecedente de múltiples cirugías previas. Solo un paciente había suspendido la medicación tópica antibiótica, por lo que la alteración de la flora externa podría ser un factor primordial para desarrollar infecciones fúngicas. El cuadro inicial de vitreítis, ojo rojo y disminución de la visión puede presentar problemas diagnósticos, por lo que se debe establecer el diagnóstico diferencial entre un cuadro infeccioso y otro inflamatorio[34]. Dos de nuestros pacientes fueron diagnosticados de vasculitis oclusiva periférica, ya que los cultivos no resultaron positivos y en el momento de la intervención quirúrgica se observó isquemia en prácticamente la totalidad de la retina. Creemos que este trabajo es el primero en describir esta complicación en pacientes con QB1.

Retención

De vital importancia en el pronóstico de la prótesis resulta la viabilidad del injerto, la cual se va a determinar por dos razones principales: el adecuado recuento endotelial y su nutrición, suministrada por la glucosa que proviene del humor acuoso y el oxígeno atmosférico que se difunde a través de la lágrima, para lo cual es imprescindible el uso de la lente de contacto[35]. Nosotros elegimos córneas saludables y con recuentos endoteliales adecuados, por encima de 2.000

células, y las complicaciones de necrosis estromal y extrusiones han sido bajas. Los 2 casos de extrusión se presentaron en pacientes con diagnóstico de síndrome de Lyell, lo que concuerda con las observaciones hechas por otros autores[9,19,20].

Otras complicaciones

Entre el 2 y 28% de pacientes desarrollarán glaucoma *de novo* después de una queratoprótesis[36], sobre todo por alteraciones de drenaje en el ángulo camerular. Frecuentemente resulta difícil determinar su incidencia y evaluar su progresión en estos pacientes por la imposibilidad de lograr una medida objetiva de la PIO. Tanto los dispositivos de drenaje como la CFCTE han demostrado eficacia en el control de glaucoma en estos pacientes[36,37], además de que esta última tiene la ventaja de ser menos invasiva y sin riesgos colaterales graves como la endoftalmitis. Aunque no se comunican en las demás series casos similares, 2 pacientes presentaron cuadros de glaucoma agudo, que se resolvieron con la aplicación de CFCTE, manteniéndose controlada la PIO, sin embargo uno de estos pacientes presentó desprendimiento coroideo posterior a la cirugía.

Nosotros consideramos que la QB1 es una buena alternativa en pacientes sin otras posibilidades de recuperación visual. Con un seguimiento suficientemente largo en nuestro estudio, una media mayor de 22 meses, hemos visto cómo la mayoría de estos ojos tienen diversas enfermedades y han recibido múltiples cirugías y tratamientos tópicos prolongados, motivo por el cual consideramos que se debe hacer una selección cuidadosa de los candidatos a QB1, sobre todo en aquellos con historia de múltiples cirugías previas, ya que el riesgo de complicaciones como MRP, e incluso otras con consecuencias fatales como desprendimientos coriorretinianos y endoftalmitis, es mayor en este grupo de pacientes.

Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

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