Keratoprosthesis with retrocorneal fixation: preliminary results in dogs with corneal blindness

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Abstract
Objective To evaluate the use and complications of a penetrating keratoprosthesis implantation in the management of corneal opacification in dogs.
Methods A retrospective clinical study describes the indications for the surgical technique utilized and the outcomes of this procedure in 20 eyes of 19 dogs with blindness of corneal origin. A successful surgical outcome was defined as a clear keratoprosthesis optic and improvement or restoration of functional vision over a follow-up period ranging from at least 8 months to a maximum of 7 years.
Results Eyes with total corneal opacification resulting from chronic superficial keratitis (n = 11), keratoconjunctivitis sicca (n = 5), endothelial dystrophy (n = 3) and chemical burn (n = 1) were treated by unilateral (n = 18) or bilateral (n = 1) full-thickness implantation of a keratoprosthesis. Keratoprostheses were retained in 15 eyes (75%) which regained vision to the date of reporting. Among these eyes, six had uncomplicated postoperative course, five developed retroprosthetic membranes and four developed granulation tissue over the optic of the keratoprostheses. These complications were successfully removed surgically in the nine eyes. The five remaining eyes (25%) developed serious early postoperative complications, for which enucleation had to be performed.
Conclusion In keratopathies in which the corneal opacification could not be treated by standard medical or surgical procedures, this keratoprosthesis appears to be promising to restore vision in chronic superficial keratitis and deep corneal dystrophy. It appears to have a poor prognosis in keratoconjunctivitis sicca in brachycephalic dogs. The post operative complications retro-prosthetic membranes and granulomatous overgrowth could be treated well.

Key Words: cornea, corneal pigmentation, corneal surgery, dog, keratoprosthesis

INTRODUCTION

The loss of corneal transparency may be due to various pathogenic processes in the dog. The most common non-ulcerative corneal diseases which may produce corneal pigmentation and loss of vision are the chronic superficial keratitis and keratoconjunctivitis sicca. Less commonly, severe stromal edema associated with endothelial dystrophy, stromal fibrosis secondary to chemical burn or massive accumulation of metabolic infiltrates within the stroma can result in an opaque cornea with vision impairment. In such clinical settings, the long-term effect of the standard medical or surgical therapies may be limited in its action to maintain corneal transparency. In addition, neovascularization of the affected cornea can represent a contraindication to penetrating keratoplasty because it will predispose to graft rejection.

In humans, the concept of replacing severely opacified corneal tissue with a synthetic prosthesis providing a small optical window was first introduced at the end of the 18th century, but it is only during the past half-century that real progress has been achieved. Although the restoration of vision in human patients with corneal blindness is successful in a majority of cases following penetrating keratoplasty, there remains a subset of patients with a history of repeated graft failures for whom a successful outcome from further corneal transplantation would be unlikely. For such patients, an alternative mode of treatment has been the
surgical application of an artificial cornea, or keratoprosthesis, to provide a small optical window for clear vision. Over the last 20 years, Dohlman, Strampelli and Cardona keratoprosthesis have become the most familiar models used in human ophthalmology but as their surgical procedures required different stages and were associated with a significant rate of both early and late complications, recent experimental and clinical efforts have centered on improving keratoprosthesis safety and long-term efficacy through material selection and device design. As such, a keratoprosthesis made of two lightweight elements and designed to be maintained to the posterior face of the cornea by the intraocular pressure (PCL5®, Corneal S.A., Paris, France) has been conceived in an attempt to simplify the surgical procedure and increase the biocompatibility between the prosthesis and surrounding cornea. The use of this device provided satisfying results in a series of human patients with corneal blindness associated with pseudopemphigus, chemical burns, trachoma, and pseudophakic edema. With a follow-up period ranging from several months to more than 3 years, it appeared that vision was restored in 20 eyes out of the 30 operated.

The different patterns of keratoprosthesis which have previously been studied in dogs with corneal blindness were reviewed in a recent paper which described the clinical evaluation of a nonpenetrating keratoprosthesis. This device although promising for treating chronic superficial opacification is not adapted to cases in which corneal blindness is the result of a full-thickness blinding corneal disorder such as stromal edema associated with endothelial dystrophy.

A canine pilot study with the PCL5® keratoprosthesis in a few subjects with intractable and blinding corneal disorder began in 2000 (P. F. Israd, E. Lacombe, and F. Villain, unpublished data; P. F. Israd, unpublished data). As these initial results were encouraging, the investigation was extended over the last 7 years to evaluate the safety and performance of this keratoprosthesis in dogs. Reported here are the surgical procedure and clinical outcome in this series of dogs with blindness of corneal origin treated by implantation of this device.

MATERIALS AND METHODS

The material

The PCL5® keratoprosthesis consists of a transparent optical system in polymethylmethacrylate (PMMA) anchored to the cornea with a protruding retrocorneal skirt, and a watertight collar made in colonisable material (Teflon® or polytetrafluoroethylene) to allow biointegration by the recipient cornea (Fig. 1). It is implanted such that the posterior skirt and Teflon® collar sandwich the central cornea between them and is sewn in place with three retrocorneal sutures. The optical system has a 40-D refractive power and gives a visual angle of 60° in coherence with the optical features of the human cornea. The refractive power of the PCL5® keratoprosthesis is within the values of the canine cornea refractive power which range from 37.8 to 43.3 D.20,21

Animal recruitment

Dogs selected for keratoprosthesis implantation had a bilateral or unilateral corneal blindness resulting from total loss of corneal transparency. All dogs had a history of chronic, intractable corneal disorder. They all had received various topical medications without improvement of their vision. Eyes with glaucoma and external ocular infection were excluded from the study. An overview of the 19 patients in which the keratoprosthesis implantation was used is presented in Table 1.

Surgical procedure

An intravenous injection of an antibacterial agent (marbofloxacin 4 mg/kg, Marbocyl®, Vetoquinol, Lure, France) and a nonsteroidal anti-inflammatory drug (ketoprofen 2 mg/kg, Ketofen®, Merial, Lyon, France) was performed. Under general anesthesia (induced by intravenous injection of medetomidine 2 μg/kg, ketamine 5 mg/kg, followed by isoflurane gas inhalation), the eyes were prepared for aseptic surgery and draped routinely. The different steps of the surgical procedure are described in Fig. 2. In eyes with superficial corneal pigmentation, the first step consisted in a 0.2-mm depth superficial keratectomy performed in the central cornea with a 5.0-mm corneal trephine (Ophtec, Groningen, The Netherlands) (Fig. 3). Around the keratectomy site and at the same depth, the superficial cornea (pigmented corneal epithelium and anterior stromal lamella) was undermined over 360° with a crescent knife (2 mm angled bevel up, Extrem®, Corneal, Paris, France) to create an annular space in which the Teflon collar of the corneal prosthesis will further take place (Fig. 4). The dissected superficial cornea was then cut with scissors over 300–310°, 2–3 mm in front of the limbus and parallel to it (Fig. 5). In this step, the aim was to reach the deep portion of the cornea without damaging the superficial cornea. The rim of superficial cornea was then reflected to uncover the cornea on this step, the aim was to reach the deep portion of the cornea which the keratoprosthesis was placed to determine the position for the three retrocorneal fixations which will

Figure 1. The PCL5® keratoprosthesis, (1) optical system, (2) colonisable material, (3) suture sites.
anchor the prosthesis to the deep portion of the cornea. These retrocorneal fixation sites were identified with a corneal marking pen (Oasis, EDC Lamy, Carvin, France). A complete penetrating keratectomy of the central cornea was then performed with the 5-mm trephine, and the full-thickness corneal button removed with Katzin scissors (Fig. 6). The anterior chamber was filled with a viscoelastic material (Healon GV®, Pharmacia, Stockholm, Sweden). The setting of the cornea after this step justified the identification of the retrocorneal fixation sites before the penetrating keratectomy.

The keratectomy was enlarged with a 2–3 mm full-thickness radial incision made along the 6 o’clock meridian. This allowed the keratoprosthesis to be implanted, with its posterior skirt inserted into the anterior chamber and its Teflon® collar fitted into the trephined opening (Fig. 7). The device was then anchored to the cornea by passing three U-shaped sutures of 9-0 nylon (Premilene®, B.Braun, Melsungen, Germany) through the retrocorneal fixation sites (Fig. 8). The corneal radial incision was closed with a simple interrupted suture of the same suture material. The viscoelastic substance was withdrawn by aspiration through a separate corneal incision. At that stage, the rim of superficial cornea was repositioned to cover the Teflon® collar (Fig. 9), and fit the edge of the keratoprosthesis optic (Fig. 10). Thereafter, the 300–310° opening was closed with 6-0 absorbable material (Safil®, B. Braun, Melsungen, Germany) using either simple interrupted or continuous suture patterns (Fig. 11).

In cases of chronic stromal edema, the surgical procedure was adapted at two points. Firstly, the initial step consisted of a total removal of the corneal epithelium prior to performing the 5-mm full-thickness trephination in the central cornea. Secondly, at the end of surgery the corneal surface was covered with a conjunctival flap except for the central optical system of the keratoprosthesis.

At the completion of surgery, 2 mg of betamethasone phosphate was subconjunctivally injected (Celestene®, Schering-Plough, Levallois-Perret, France). During the first week following surgery, oral therapy included 2 mg/kg marbofloxacin once a day (Marbocyl®, Vetoquinol, Lure, France), 1 mg/kg prednisolone (Megasolone®, Merial, Lyon, France) once a day and 2 mg/kg ranitidine (Azantac®, GlaxoSmithKline, Marly-le-Roi, France) twice a day. Topical administration of an antibiotic-corticosteroid combination (Maxidrol®, Alcon, Rueil-Malmaison, France) was prescribed for 3 months. An Elizabethan Collar was used for 15 days following the surgical procedure.

**Follow-up**

Postoperatively, the dogs were re-evaluated at 8 days, 15 days, and then monthly for 6 months. After this period, follow-up examinations were planned every 6 months when possible. A complete ophthalmic examination was performed and a successful surgical outcome was defined as a clear visual axis and improvement or restoration of functional vision, assessed by response to menacing gesture, ability to follow thrown cotton balls, and ability to navigate an obstacle course. Follow-up examination period ranged from a few weeks to a maximum of 7 years.

If a retroprosthetic membrane developed as a postoperative complication, it was surgically removed under general
anesthesia. In these eyes, the anterior chamber was entered through the peripheral cornea using a 15° corneal knife and was filled with a viscoelastic material. Then, the membrane was removed by gentle dissection with a cystotome until total clearing of the visual axis was obtained. Thereafter, dexamethasone alcohol (Maxidex®, Alcon, Rueil-Malmaison, France) was topically applied twice a day for 1 month. If the optical portion of the prosthesis was postoperatively covered with a growing corneal granulation tissue (Fig. 12), removal of this inflammatory tissue was performed by slight dissection with Castroviejo scissors (Fig. 13) under topical anesthesia. The following day and under general anesthesia, the margins of the optical portion of the keratoprosthesis were frozen with nitrous oxide using a 2-mm retinal cryo-probe (Cryomedics MC1000, Bridgeport, Connecticut, USA) and a double freeze-thaw technique. The extent of the cryosurgery was determined visually to include only the superficial cornea around the prosthesis (approximately 15 seconds). Topical dexamethasone alcohol was prescribed as in the aforementioned procedure.

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Figure 3. The 0.2-mm depth/5 mm diameter superficial keratectomy.

Figure 4. The corneal dissection with a crescent knife.

Figure 5. The peripheral corneal incision.

Figure 6. The 5 mm diameter penetrating keratectomy in the central cornea.

Figure 7. The PCL5® keratoprosthesis implementation.

Figure 8. The PCL5® keratoprosthesis anchoring.

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RESULTS

A series of nineteen dogs (20 eyes) which had received the PCL5® keratoprosthesis from 2001 to 2007 was included in this study. The median age of affected dogs was 8.42 years (range, 4–13 years). Nine different breeds of dogs were represented, with the German Shepherd (10/19 = 53%) being the most common. There were 13 males and 6 females. Corneal blindness resulted from chronic superficial keratitis in 10 cases, keratoconjunctivitis sicca in five cases, chronic corneal edema presumably due to endothelial dystrophy in three cases, and corneal fibrosis secondary to chemical burn in one case. The keratoprosthesis was implanted in the right cornea for seven cases, in the left cornea for 11 cases, and in both eyes for one case (case 15). An overview of the 19 patients in which the keratoprosthesis implantation was used is presented in Table 1.
There were no complications during the surgical procedure for any of the different kinds of corneal opacification which were operated. The curvature of the prosthesis did not create any problems of adaptation to that of the canine cornea and its size appeared to be suitable for the dog. The follow-up periods as well as specific and overall results are presented in Tables 1 and 2, respectively.

A successful outcome of keratoprosthesis implantation with uncomplicated postoperative course was observed in six eyes (6/20 = 30%), including five eyes (cases 1, 6, 10, 14 and 15) of CSK (5/11 = 45%) and one eye (case 17) of chronic stromal edema due to endothelial dystrophy (1/3 = 33%). For these patients, the complete postoperative follow-up period was at least 8 months, extending to a maximum of 7 years for case 1. Five of these results were associated with unilateral prosthesis implantation, and in case 15 which has had a bilateral implantation occurred in the right eye. According to the owners all these dogs regained vision and the visual tests were normal at each ophthalmic examination performed during the follow-up period. In these patients, the keratoprosthesis was well included in the cornea, without inflammatory reaction around it and with a clear optic (Figs 14,15). Intraocular pressure and Schirmer tear test values remained within the normal data range for canine eyes throughout the observation period.

Serious complications leading eventually to enucleation were observed in 5 eyes (5/20 = 25%) between one and 8 weeks postoperatively. These included two eyes (cases 8 and 19) with CSK (2/11 = 18%) in which the prosthesis extruded as a result of self-inflicted ocular traumas, and three eyes (cases 4, 9, and 16) with KCS (3/5 = 60%) in which bacterial endophthalmitis developed because of keratoprosthesis extrusion. The bacteria isolated were *Staphylococcus intermedius* and *Staphylococcus epidermidis*.

A retroprosthetic membrane developed in five eyes (5/20 = 25%) within the first 30 days following surgery. It occurred in three eyes (cases 2, 11, and 15) with CSK (3/11 = 36%) and in two eyes (cases 5 and 13) with endothelial dystrophy (2/3 = 66%). As a result, all these eyes had vision impairment and required surgical excision of the retroprosthetic membrane as previously described. No bleeding was observed during the discission of the retro-prosthetic tissue. In case 15, the membrane regrew 4 weeks after its removal, requiring a second surgical treatment. All these eyes recovered vision after removal of the retro-prosthetic tissue, and the visual function was maintained throughout the follow-up period which ranged from at least 13–16 months for cases 5, 11, and 15 to a maximum of 2.5–3 years for cases 2 and 13 respectively (Table 1).

In four eyes (4/20 = 20%), an overgrowth of granulation tissue progressively covered the optic of the keratoprosthesis within the first 4 (cases 7 and 12) to 8–12 weeks (cases 3 and 18) following the surgical procedure (Fig. 13). This was observed in two eyes (cases 3 and 7) with KCS (2/5 = 40%), in one eye (case 18) with CSK (1/11 = 9%) and in the eye with the corneal fibrosis due to the chemical burn (case 12). In all these eyes, the development of granulation tissue over the visual axis led to vision loss, requiring surgical excision and cryoapplication as previously described. In case 18, topical 1% 5-fluorouracil prepared in sterile saline (Fluoro-Uracile ICN, ICN Pharmaceuticals, Orsay, France) was prescribed two times a day for 1 month, in addition to the topical corticotherapy, in order to obtain a synergistic antagonistic effect on the inflammatory reaction which was particularly marked in this eye. No recurrence was observed in any of these eyes during the follow-up period and vision was considered normal after the procedure based on owner reports and ophthalmic examinations. For these eyes, the follow-up period ranged from a minimum of 8–12 months for cases 7 and 12 to a maximum of 16–18 months for cases 3 and 18, respectively (Table 1).

**DISCUSSION**

Blindness can be the end result of chronic superficial keratitis, keratoconjunctivitis sicca, and chronic corneal edema in the dog, and this long-term complication cannot always be prevented or reversed by the classical medical therapies. In such cases, corneal transplantation (penetrating keratoplasty) may be a treatment option to restore a clear central axis, but it is known that there is a clear relationship between the incidence of allograft rejection and pre-existing vascularisation of the host cornea, as observed in chronic superficial keratitis and keratoconjunctivitis sicca. Keratoprosthesis

**Table 2. Surgical outcomes of PCL5 implantation in 19 canine eyes with corneal blindness in relation to the initial corneal condition**

<table>
<thead>
<tr>
<th>Initial corneal condition</th>
<th>Total Number of eyes</th>
<th>Eyes with no postoperative complications</th>
<th>Eyes with postoperative retroprosthetic membrane</th>
<th>Eyes with postoperative covering of the optic by granulation tissue</th>
<th>Eyes with severe postoperative complications leading to enucleation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic Superficial keratitis</td>
<td>11</td>
<td>5</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Keratoconjunctivitis sicca</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Endothelial Dystrophy</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Corneal fibrosis due to chemical burn</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Overall</td>
<td>20</td>
<td>6</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

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represents an alternative to penetrating keratoplasty in the cases of corneal blindness for which this procedure is at high risk for graft failure. The surgical procedure for keratoprostheses insertion does not present more technical difficulties than penetrating keratoplasty for surgeons accustomed to corneal surgery and it might be most commonly used if keratoprostheses become more readily available for use in dogs. A recent paper is a good example of this trend. In that study, a prototype of non penetrating keraprosthesis was implanted in dogs with chronic superficial keratitis and endothelial disease. The overall findings in the 20 eyes with corneal blindness of the current study indicate that 15 eyes (75%) were visual at the time of reporting, and they suggest that surgical outcome of keratoprosthesis insertion seems to depend on the primary corneal condition as shown previously in human patients. In humans, the most favorable pre-operative condition is represented by allograft rejection in non cicatrizing conditions, whereas Stevens-Johnson syndrome seems the worst. In our dogs, postoperative complications included bacterial endophthalmitis, retroprosthetic membrane, and granulation tissue overgrowth. Only bacterial endophthalmitis, observed in 25% of our operated eyes, led to postoperative vision loss. The rate of this complication in humans who underwent keratoprosthesis implantation is very high in patients with Stevens-Johnson syndrome and ocular cicatricial pemphigoid, moderate in those with chemical burns, and low in subjects with non cicatrizing corneal disease. In the current study, panophthalmitis was observed in three out of the five eyes with KCS (60%) and in two out of the 11 (18%) that suffered from CSK. Suture related problems (loose/broken sutures), defect in biointegration of the keratoprosthesis into the stroma and ocular surface infection might have been the predisposing or precipitating factors in the development of panophthalmitis in our study. From our clinical experience, it seems that corneal opacification due to KCS in brachycephalic dogs (two French Bulldogs and one Cavalier King Charles in our study) carries a high risk for surgical failure. In addition, the naturally exophthalmic eyes and oversized palpebral fissures of these dogs are predisposing factors to excessive trauma to the keratoprosthesis. The most frequent bacteria isolated were Staphylococcus intermedius and Staphylococcus epidermidis, which are both ubiquitous bacterium of the conjunctival fornix. In humans, almost all the bacteria isolated after panophthalmitis following keratoprosthesis implantation are Gram positive (Streptococcus pneumoniae, other streptococci, Staphylococcus aureus and Staphylococcus epidermidis). The development of a retroprosthetic membrane is often observed after keratoprosthesis implantation in humans. This membrane develops gradually and can cover the inner face of the prosthesis. Its precise origin remains unclear but it was said to correspond to fibrous metaplasia of the endothelium after a penetrating corneal wound or iatrogenic modification of the endothelium. In humans, the incidence of development of a
retroprosthetic membrane depends on the type of keratoprostheses used.\textsuperscript{10,11,28–31} Arterial systemic hypertension and diabetes mellitus were shown to be risk factors in the development of retroprosthetic membrane in humans.\textsuperscript{28} It was showed that perioperative management may also play a significant role in this complication. Pre- and postoperative therapy with corticosteroids, non-steroidal anti-inflammatory, heparin or tPA should be considered in cases identified as at greater risk for membrane formation.\textsuperscript{28} In our study, no such risk factors were highlighted. Surgical removal of retroprosthetic membranes in humans is carried out using Nd:Yag laser.\textsuperscript{10} The surgical technique used in our study was acceptably safe and consisted of gentle dilaceration and aspiration. Four eyes with retroprosthetic membrane were treated once and one eye twice. Vision was not impaired after the correcting procedure. Unfortunately, histopathologic examination of the membranes could not be performed because they disintegrated during the discussion.

Covering of the optic by excessive wound healing tissue seems related to factors such as an overzealous healing activity of the epithelium, the conjunctival flap, or poor adaptation of the flap of the upper covering to the rim of the implant. Surgical removal, followed by cryosurgery the day after, appeared sufficient to cure this problem in three cases. As for the retro-prosthetic membrane, the link between the covering of the implant by a granulation tissue and the underlying corneal condition was not obvious. To the authors’ knowledge, this complication has not been described in humans who underwent keratoprosthesis implantation. Complication rate associated with different types of keratoprostheses used in humans are reported in Table 3.

The majority of the cases that had no complications were CSK. Regarding the success rate, CSK turns out to be a good indication for the artificial cornea implantation, if all initial medical therapies are insufficient to restore vision. Similarly, the success rate of the keratoprosthesis implantation in eyes with endothelial dystrophy seems very promising to change the prognosis of this keratopathy because this procedure may yield better optical results that those presently obtained with the current medical (topical osmotic compounds) or surgical (thermokeratoplasty) therapies.

In summary, this study shows that blindness of corneal origin can sometimes be treated by implantation of a penetrating keratoprosthesis. A thorough understanding of its surgical procedure, its potential complications and the strategies to manage them is essential for surgeons who will perform it, and will help in improving surgical outcomes.

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