Review of endophthalmitis following Boston keratoprosthesis type 1

Marie-Claude Robert, Krystel Moussally, Mona Harissi-Dagher

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Department of Ophthalmology, Centre Hospitalier de l'Université de Montréal (CHUM), Hôpital Notre-Dame, Montréal, Québec, Canada

Correspondence to
Dr Mona Harissi-Dagher, Department of Ophthalmology, Notre-Dame Hospital, 1560, rue Sherbrooke Est, Montréal, Québec H2L 4M1, Canada; monadagher@hotmail.com

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ABSTRACT

Endophthalmitis remains one of the most damaging and challenging complications following Boston keratoprosthesis type 1 (KPro) surgery. The authors reviewed the literature from 2001 onward to identify cases of endophthalmitis following KPro surgery and present an additional case of endophthalmitis in a patient with Stevens Johnson syndrome. The prevalence of endophthalmitis between 2001 and 2011 was 5.4%. Gram-positive bacteria are the most common agents responsible for endophthalmitis in this patient population while gram-negative bacteria and fungi are emerging pathogens. Risk factors for endophthalmitis include preoperative diagnosis of cicatricial disease and postoperative infectious keratitis, glaucoma drainage device erosion and non-compliance with antibiotic prophylaxis. Additional studies on the prevention and treatment of endophthalmitis are required to improve the overall prognosis of these patients.

INTRODUCTION

The Boston keratoprosthesis type I (KPro) is gaining recognition as an excellent alternative for patients with severe corneal disease and poor probability of success with traditional penetrating keratoplasty. The KPro design, the procedure itself, and the postoperative management of patients continue to evolve.[1–3] Such advances have improved outcomes for these patients and thus, allowed the indications for KPro surgery to expand.

While a KPro readily allows for restoration of visual axis clarity, complications following surgery can compromise the initial improvement of visual acuity (VA). In recent case series, glaucoma was shown to be the most prevalent vision-threatening complication.[4 5] However, the most severe and feared complication remains endophthalmitis as this can be both sight and globe-threatening. While the incidence of postoperative endophthalmitis was tremendously reduced after the implantation of routine prophylactic antibiotics post-KPro surgery, new cases are still emerging.[6]

The purpose of this review is to summarise the current knowledge on endophthalmitis in patients with a Boston KPro. We will critically evaluate the literature on this subject to determine what future studies are needed to improve patient outcomes. In addition, a new case of endophthalmitis will be reported.

MATERIALS AND METHODS

A review of the literature from January 2001 to September 2011 was performed using Pubmed and the search term 'Boston Keratoprosthesis'. Cases of endophthalmitis following KPro surgery were identified by review of the title and abstracts of the search results. Twelve retrospective case series and two case reports were identified. The average prevalence of endophthalmitis was calculated using pooled data. Studies were grouped by the year of publication to calculate yearly rates. We present an additional case of endophthalmitis in a patient with Stevens Johnson syndrome.

RESULTS

Review of the literature

Definition of endophthalmitis

Endophthalmitis is an infectious inflammatory reaction affecting the anterior and posterior segments of the eye.[7] Its aetiology can be exogenous or endogenous. Exogenous endophthalmitis results when an external pathogen is introduced directly into the eye by either surgery or trauma. Endogenous endophthalmitis results from the haematogenous spread of infectious organisms from a distant site. The most common form of endophthalmitis is postoperative exogenous endophthalmitis, and accounts for 55–70% of cases.[8–10] There is a risk of contracting endophthalmitis after any type of surgical procedure, either acutely or in a delayed fashion.

Endophthalmitis can be caused by bacterial, fungal or viral pathogens. In postoperative exogenous endophthalmitis, the most likely pathogens vary according to the onset of symptoms and by the type of surgery performed. Following cataract surgery, coagulase-negative *Staphylococcus* spp. are the most common infecting organisms of acute endophthalmitis, while *Propionibacterium* spp. predominate in chronic endophthalmitis.[11 12] On the other hand, *Streptococcus* spp. are the predominant agents responsible for delayed-onset bleb-associated endophthalmitis.[13]

The clinical presentation of endophthalmitis comprises decreased vision, redness, lid swelling and pain.[11] Chemosis, corneal oedema, anterior chamber reaction with fibrin and hypopyon, vitreous inflammation and retinal periphlebitis are commonly found on slit-lamp examination. Endophthalmitis should be diagnosed and treated as soon as possible to avoid complete and permanent loss of vision. Up to 30% of patients with endophthalmitis will develop severe visual impairment following the infection.[14]

The differential diagnosis of postoperative endophthalmitis includes sterile vitritis. This entity seems more frequent following KPro surgery when compared with other intraocular procedures. In fact, the pathogenesis of sterile vitritis may relate to an immune reaction to antigens released

following tissue necrosis and melt, both of which are more common following KPro surgery.[15] Causes of sterile endophthalmitis described with other types of intraocular surgery include toxicity from residual matter found on surgical instruments or other chemical compounds, inflammation from retained lens material and mechanical irritation of the uvea from intraocular implants.[16] Patients with sterile vitritis following KPro typically do not present with erythema or pain. Vision usually recovers to previous levels following treatment with topical corticosteroids. The diagnosis of sterile vitritis remains one of exclusion as some patients with culture-proven endophthalmitis have presented with ocular inflammation but minimal discomfort.[17]

Endophthalmitis following KPro surgery

While the prognosis of patients with KPro has improved significantly in the last decade, endophthalmitis remains a major concern. Table 1 (see online supplementary file) summarises and describes previously reported cases of endophthalmitis after KPro surgery based on a review of articles published between 2001 and 2011.[4–6 15 17–26] In these studies, the prevalence of endophthalmitis ranges from 0% to 12.5%. Using pooled data, we calculated an endophthalmitis prevalence of 5.4% over the last 10 years. We did not include the case series by Bradley *et al*[22] in our calculations as the study by Greiner *et al*[5] reported longer follow-ups of the same patients. Unfortunately, we could not control for the possibility of patient overlap among the other studies.

The rate of endophthalmitis dropped from 12% in 2001,[15] to a pooled rate of 2.3% in 2007.[18 19] To our knowledge, no studies showing the prevalence of endophthalmitis following KPro surgery were published between 2002 and 2005. The pooled prevalence of endophthalmitis post-KPro surgery increased to 6.8% in studies published between 2009 and 2010,[6 17 22–26] while studies published in 2011 showed a rate of 5.7%.[4 5] The follow-up period between the date of the surgery and the diagnosis of endophthalmitis is specified in only five studies where it ranged from 1.5 months to 46 months postoperatively.[6 18 15 23 25] In the four studies with no cases of endophthalmitis post-KPro, the mean follow-up period was of 8.5, 10, 17 and 17.3 months.[4 19 21 26] As cases of endophthalmitis occur months to years after KPro surgery, the follow-up in these studies may have been insufficient to observe endophthalmitis.

To our knowledge, a total of 59 cases of endophthalmitis have been described or cited in the literature between 2001 and 2011.[5 6 15 17 18 20–25 26] This includes all the cases found in table 1 in addition to a patient described by Tsui *et al* with *Nocardia farcinica* endophthalmitis and Baerveldt implant infection following KPro.[20] Microbial culture results were described in 53 of these endophthalmitis cases. When a culture was obtained, 32 (60%) were caused by gram-positive bacteria, 5 (9%) were caused by a gram-negative bacteria, 5 were fungal (9%), 7 (13%) showed negative cultures and 2 (4%) showed a mixed gram-positive and gram-negative culture (table 2). In the majority of gram-positive endophthalmitis, patients were not using vancomycin as a prophylaxis treatment, or had stopped its use before the diagnosis of the infection.

Causative gram-positive bacteria included *Staphylococcus aureus, Staphylococcus epidermidis* and various *Streptococcus* spp. *Pseudomonas aeruginosa* was the most common cause of gram-negative endophthalmitis but *Proteus mirabilis*, *Haemophilus influenzae* and *Serratia marcescens* were also described.[6 17 22 23] Fungal endophthalmitis was mostly caused by yeasts such as *Candida parapsilosis* and *Candida glabrata.* Molds, such as *Alternaria* and *Fusarium*, were less frequently responsible for fungal endophthalmitis.[5 18] *N farcinica* and *Mycobacterium abscessus* were also identified in one (2%) endophthalmitis culture each.[6 20]

The majority of endophthalmitis cases occurred in patients with baseline diagnoses such as Stevens Johnson syndrome, ocular cicatricial pemphigoid and chemical burns. It is well recognised that patients with such cicatrising ocular surface disease belong to a poorer prognostic category for KPro surgery.[27] These patients are predisposed to severe dryness and periprosthetic corneal melting, both risk factors for infection. On the other hand, a substantial proportion of patients with endophthalmitis had preoperative diagnoses associated with a good prognosis. These included graft failure, aniridia, *Herpes simplex* keratitis, pseudophakic bullous keratopathy and anterior staphyloma. Other risk factors included the presence of infectious keratitis of the periprosthetic cornea or glaucoma drainage device erosion.[5]

As seen in the online supplementary table 1, the management of endophthalmitis always included the intravitreal injection of antibiotics and, in some cases, antifungals. In the majority of cases, a combination of vancomycin and ceftazidime was used. Vitreous aspiration was usually performed prior to the antibiotic injections to obtain culture specimens. Most patients were also treated with topical fortified antibiotics and oral antibiotics. Subconjunctival and intravenous antibiotics were used less often. Relatively few patients were treated with pars plana vitrectomy (PPV).[6 22 23 25] KPro replacement or removal was performed in a small subset of patients with coexisting infectious keratitis.[22]

New case report

A 47-year-old man presented to the ophthalmology department of the University of Montreal health centre with a history of Stevens Johnson syndrome and two previous graft failures in his right eye. He underwent KPro surgery in July 2010. Postoperative treatment included topical prednisolone acetate and moxifloxacin, but no vancomycin. VA improved from hand motion preoperatively to 20/20 at 6 weeks and 20/30 at 3 months of postoperative follow-up. Proper contact lens (CL) fit could not be achieved given the patient's irregular ocular surface and significant symblepharon formation. Lateral tarsorrhaphy was performed to improve CL retention, but was not successful in achieving this goal.

Table 2 Infective agents causing endophthalmitis following KPro surgery

Gram-positive endophthalmitis	Gram-negative endophthalmitis	Fungal endophthalmitis	Other
Coagulase-negative			
Staphylococcus spp. 16%	*Pseudomonas aeruginosa* 7%	*Candida parapsilosis* 4%	*Mycobacterium abscessus* 2%
Streptococcus spp. 33%	*Proteus mirabilis* 2%	*Candida glabrata* 2%	Culture negative 11%
Staphylococcus aureus 13%	*Haemophilus influenzae* 2%	*Fusarium* 2%	
Nocardia farcinica 2%	*Serratia marcescens* 2%	*Alternaria* 2%	

On routine examination 4 months following KPro surgery, a dellen was noted in the temporal carrier graft, adjacent to the KPro front plate. A patch graft was performed to reinforce the thinned area. Thinning recurred a month later, and an amniotic membrane graft was placed over the defect to prevent further stromal loss.

Seven months following KPro surgery, the patient presented with a gradual worsening in vision and mild pain starting the day preceding his visit. VA had decreased to hand motion. Clinical examination showed increased temporal corneal thinning, vitreous haze and vitreous haemorrhage. There was high degree of suspicion for endophthalmitis. Vitreous tap and injection of vancomycin 1 mg in 0.1 ml in addition to ceftazidime 2.25 mg in 0.1 ml and amphotericin B 0.005 mg in 0.1 ml were performed in the operating room. A corneoscleral patch graft was used to reinforce the area of thinning. The patient also received subconjunctival vancomycin (25 mg in 0.5 ml), tobramycin (20 mg in 0.5 ml) and dexamethasone. Postoperatively, the patient was given fortified vancomycin and tobramycin drops every 2 h, topical prednisolone 4 times per day and oral moxifloxacin. Gram's stain showed presence of polymorphonuclear leucocytes and gram-positive cocci in clusters. Cultures grew *S epidermidis* sensitive to vancomycin, clindamycin and moxifloxacin, but resistant to erythromycin and levofloxacin. As the infection resolved, VA recovered to 20/300. Six months later, replacement of the KPro with a new device and a new corneal graft was performed as thinning of the carrier graft had become severe. VA was maintained at 20/300 postoperatively.

DISCUSSION

Based on this review, endophthalmitis cannot be considered a rare complication following KPro surgery. A mean of 5.4% of cases developed this infection in the last 10 years. It was even one of the most frequent complications observed post-KPro in some studies.[23] It may even be expected that the frequency of endophthalmitis could be higher if studies with longer follow-up periods were done. Our review suggests that the rate of endophthalmitis after KPro surgery may have increased since 2007. However, we cannot confirm that this is true given the obvious fluctuation in the reported prevalence between studies. The wide range of follow-up duration of these studies further confounds our calculated pooled prevalence.

Endophthalmitis is more frequent following KPro surgery than following other types of intraocular surgeries such as cataract, penetrating keratoplasty or glaucoma surgeries. The incidence of endophthalmitis for these surgeries has been evaluated at 0.8%, 0.18% and 0.12%, respectively.[28] Eyes with a KPro are particularly vulnerable to severe infections as the interface between the corneal graft and the polymethyl methacrylate optical cylinder of the KPro creates a potential space for communication between the ocular surface and the anterior chamber. Anterior segment optical coherence tomography has further demonstrated the presence of gaps in the KPro-donor cornea interface.[29] The risk of intraocular migration of pathogens and endophthalmitis is always present. As such, the ophthalmologist should maintain a heightened suspicion for endophthalmitis indefinitely. In contrast to cataract surgery, the risk of endophthalmitis following KPro extends well beyond the early postoperative period.

Gram-positive bacteria were the most common microorganisms isolated from eyes with endophthalmitis following KPro surgery. Because of the predominance of gram-positive bacteria causing endophthalmitis, vancomycin was introduced as part of the postoperative prophylaxis to all patients following KPro surgery starting in 2001.[15] The routine administration of vancomycin has played a primordial role in decreasing the incidence of endophthalmitis.[6] On the other hand, reports of gram-negative bacteria or fungi causing endophthalmitis seem more frequent. It has been hypothesised that the long-term and continuous use of vancomycin may predispose to gram-negative and fungal endophthalmitis.[5] Similarly, the risk of fungal endophthalmitis after KPro surgery in patients using vancomycin was reported to be higher compared with patients not using vancomycin (p=0.011).[18] This same study showed that chronic administration of vancomycin increased the incidence of fungal endophthalmitis without significantly modifying the rate of fungal colonisation. This suggests that vancomycin may alter the ocular surface flora and the epithelial barrier function sufficiently to allow the progression of fungal colonisation to infection. The predisposition to gram-negative and fungal endophthalmitis may not be solely related to the chronic use of vancomycin. For example, therapeutic CL wear was introduced in the routine management of KPro patients in 1999–2000.[6 30] This occurred at approximately the same time as vancomycin prophylaxis and may thus act as a confounder. Indeed, CL wear is a well-recognised risk factor for gram-negative bacterial and fungal keratitis.[31 32] Barnes *et al* showed that, similar to vancomycin prophylaxis, therapeutic CL use was associated with a higher rate of fungal endophthalmitis post-KPro surgery (p=0.015).[18]

Current recommendations include the use of vancomycin and fluoroquinolone prophylaxis in high-risk patients following KPro surgery. These include patients with autoimmune disease and chemical burns in addition to monophthalmic patients. A fourth-generation fluoroquinolone alone is used as prophylaxis in more standard patients, such as those with multiple graft failures. In both cases, the fluoroquinolone can be switched to polymyxin B/trimethoprim after the first postoperative month.[33] The prevention of fungal endophthalmitis may be more straightforward as visibly apparent signs of colonisation usually precede infection. Indeed, fungi form small, white, mulberry-shaped precipitates on the surface of the CL or KPro. Cleaning or replacing the CL will remove the bulk of the colonising fungi. To eradicate the fungi, a several-week course of topical amphothericin B has been recommended.[18]

Patient adherence is another important factor in the prevention of postoperative endophthalmitis. There are several reports of gram-positive bacterial endophthalmitis occurring after patients had stopped the use of vancomycin.[17 23] Compliance with vancomycin prophylaxis may be improved by using a lower concentration such as 14 mg/ml. This decreases the ocular pain that occurs upon instillation of a drop.[23] Since most endophthalmitis cases occurred months to years after the initial KPro surgery, long-term daily antibiotic prophylaxis, and continuous and regular follow up, is required. At each patient visit, the surgeon should reassess adherence to antibiotic therapy. Patients should also be regularly reminded of the risks of poor compliance. This is especially important in patients with high-risk preoperative diagnoses, such as Stevens Johnson syndrome or ocular cicatricial pemphigoid. In these patients, a closer follow up, and more frequent applications of broad-spectrum antibiotics, can be considered.

The treatment approach to endophthalmitis following KPro surgery deserves further evaluation. Because of the intrinsic differences between cataract surgery and KPro surgery, the results of the Endophthalmitis Vitrectomy Study (EVS) do not

apply. PPV may be warranted at VA levels different than those advised by the EVS. While vitreous tap was the most frequent means of obtaining a specimen for culture, this technique causes unwanted traction to the retina and may result in retinal detachment. Patients with KPro already have a high risk of posterior segment complications.[4] PPV prevents this traction by cutting instead of pulling on the vitreous. This approach provides a better specimen for microbiological evaluation, reduces the load of pathogens and toxins and removes tractional vitreous membranes.[10] For all these reasons, PPV may allow for better visual outcomes following endophthalmitis.[25] Finally, contrary to the EVS findings, it may be prudent to use systemic antibiotics given the safety and improved ocular bioavailability of fourth-generation fluoroquinolones. A systemic antifungal is necessary for the treatment of fungal endophthalmitis.[33]

Future directions

First, efforts should strive to decrease the incidence rate of endophthalmitis. The effect of vancomycin on the rate of gram-negative bacterial and fungal endophthalmitis merits further study. The addition of an antibiotic with better gram-negative coverage could help decrease the risk of postoperative bacterial endophthalmitis. Similarly, topical povidone-iodine is a potent antiseptic against bacteria and fungi that could be used intermittently to disinfect the ocular surface.[34] Such regimens should be evaluated in larger randomised studies before their implementation as a part of the routine prophylaxis post-KPro.

The emergence of pathogens resistant to antibiotics should also be addressed. Methicillin-resistant and fluoroquinolone-resistant coagulase negative staphylococci were responsible for half of the four cases of bacterial endophthalmitis reported by Chew *et al*.[23] Indeed, resistance to fluoroquinolones has been increasing: up to 85% of methicillin-resistant *S. aureus* ocular isolates are equally resistant to newer-generation fluoroquinolones.[35] These include moxifloxacin and gatifloxacin, agents currently used as first-intention antibiotics for anterior segment infections. Therapeutic dosing of topical antibiotics, rather than the chronic low-dose prophylaxis currently used after KPro surgery, may prevent the development of resistant organisms. This hypothesis should be studied by a proper clinical trial.

The management of endophthalmitis following KPro should also be further investigated. 25 g PPV shows promising results. The role of KPro exchange should also be considered as the device itself may harbour bacteria and support biofilm formation. The coating of KPro with N,N-hexyl, methyl-polyethylenimine has been shown to inhibit biofilm formation.[36] This technology holds promise to reduce endophthalmitis rates in the future.

CONCLUSION

There have been significant advances in the management of patients with KPro in the last decade. While our understanding of endophthalmitis following KPro surgery has improved, several challenges remain. Endophthalmitis remains a devastating complication that can dramatically threaten the patient's visual rehabilitation after KPro surgery. Despite the addition of vancomycin prophylaxis, the rate of endophthalmitis post-KPro exceeds that of other intraocular surgeries. Future studies focusing on the prevention and the best treatment modalities of such infections are needed.

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