Characteristics and Vitreoretinal Management of Retinal Detachment in Eyes with Boston Keratoprosthesis

Short title: Retinal Detachment and K-Pro

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Synopsis

Retinal detachment in eyes with Boston keratoprosthesis seems to have specific characteristics and the visual acuity remains poor despite successful anatomical results. 23 gauge vitrectomy can be effectively performed in these patients.

Abstract

Purpose: To review the incidence and features of vitreoretinal complications of a permanent Boston keratoprosthesis and to report the use and outcomes of 23-gauge vitrectomy to manage vitreoretinal pathology.

Design: Retrospective non comparative, interventional case series.

Subject, Participants: 27 eyes of 27 patients managed with a Boston Keratoprosthesis at Moorfields Eye Hospital over a three-year period.

Methods: All eyes that underwent pars plana vitrectomy (PPV) and had at least 6 months follow-up were analysed with a specific focus on the anatomical and histological characteristics of retinal detachment and outcomes of surgery.

Main Outcomes Measures: Anatomical success and characteristics of retinal detachment over the follow-up period.

Results: 27 patients underwent Boston Keratoprosthesis implantation over the study period. Of these 6 (22%) required PPV for retinal detachment which demonstrated a specific pattern of serous elevation with subsequent severe anterior proliferative vitreoretinopathy. The mean follow up period was 9 months (range 6-14 months). At final follow-up visual acuity ranged from PL to 6/18 and 5 of 6 cases had attached retinae under the silicone oil. Histological analysis of a subretinal membrane demonstrated a predominatly glial / RPE fibrocellular tissue consistent with proliferative vitreoretinopathy (PVR).

Conclusion: The study showed that retinal detachment complicated by PVR, as demonstrated by the clinical and histological characteristics of this condition, is common in patients undergoing Boston Keratoprosthesis. We also showed that 23 gauge vitrectomy can be effectively performed in patients with a permanent prostesis. Visual acuity often remains poor despite successful anatomical results.

Introduction

Use of the Boston Type 1 keratoprosthesis has increased since its approval by the Food and Drug Administration (FDA) in 1992, and its recent CE mark. It is a viable alternative to corneal transplantation in eyes with a poor prognosis for penetrating keratoplasty including severe ocular surface disease (cicatricial pemphigoid, Stevens-Johnson syndrome, stem cell deficiency, chemical burns) or repeated corneal graft failure. [1-3] There have been continuing refinements of the anterior segment surgical techniques as well as an increasing experience in the management of complications in patients requiring Boston keratrosthesis. This has highlighted the need for vitreoretinal expertise in the management of posterior segment complications.

Vitreoretinal surgical management of posterior segment disease in eyes with Boston KPro has been previously reported, [4-6] – this has focused on the vitreoretinal techniques involved. To date, there has been a systematic report of case series which documents the incidence of posterior segment complications. [7] However, the specific clinical and immunohistological characteristics of retinal detachment in the setting of Boston Kpro have not been examined.

The purpose of this study was to review the incidence and features of vitreoretinal complications in a consecutive cohort of patients with a permanent Boston keratoprosthesis, to report clinical features of posterior segment complications and the operative management of these using 23-gauge vitrectomy and to examine the characteristics of a subretinal membrane surgically excised

from an eye complicated by PVR retina following the procedure . Additionally, the anatomical and functional outcomes are reported in relation to the presenting and secondary pathology.

Patients and Methods

Moorfields Eye Hospital Research Management Committee (RMC) approval was obtained for this study. We conducted a retrospective chart review of the patients implanted with Boston Keratoprosthesis at Moorfields Eye Hospital over a period of three years as identified from the anterior segment service database. All eyes that underwent a 23 gauge pars plana vitrectomy (PPV) and had at least 6 months follow-up were included in the analysis. Data were collected on demographic characteristics, the corneal pathology for which the eyes required keratoprosthesis implantation, the best corrected visual acuity (BCVA) pre and post keratoprosthesis, the number of previous grafts, pre-existing glaucoma or other ocular co-morbidity, and previous glaucoma surgical intervention. Data on posterior segment pathology requiring surgical intervention, the BCVA pre and post PPV and the intraoperative characteristics of posterior segment pathology and post-operative complications were also collected.

Surgical Technique

Pars Plana Vitrectomy was performed in all cases using 23 gauge valved trocars placed as anteriorly as possible (i.e at the limpus) using 4-mm infusion cannulae. The binocular indirect ophthalmo-microscope (BIOM) was used as a viewing system. As a default, the wide field BIOM lens was used and on some occasions the 90 diopters (0.4) BIOM lens was used if needed (see results and discussion section). Perflouro-n-Octane (perlfruoron, Alcon Laboratories, Watchmore Park, Riverside Way, Camberley GU15 3YL, UK), silicone oil (1300 centistokes, Bausch & Lomb U.K., Ltd, Surrey KT2 6TN, England) and membrane blue-dual® (D.O.R.C, 3214 VN Zuidland, The Netherlands) for epiretinal membrane staining were used where appropriate.

Histological examination of subretinal membrane

A subretinal membrane excised during vitrectomy (patient 5, Table 1,2) was fixed in 4% paraformaldehyde in Phosphate-bufferred saline (PBS, pH 7.2), cryoprotected in 30% sucrose and embedded in OCT (Optimum Cutting Temperature compound) prior to cryostat sectioning. Sections 12µm thickness were immunostained using our publishedprotocols. [8] Briefly, sections were

incubated overnight at 4°C with primary antibodies, following by three 10 min washes in Tris-buffered saline (TBS, pH 7.5). Specific binding of primary antibodies was detected using donkey anti-IgG labelled with AlexaFluor 448 or AlexaFluor 555 (Molecular Probes, Invitrogen) reacting the species in which the primary antibody was raised, for 2 h at room temperature. Slides were then washed three times as above, counterstained with 4_,6_-diamino-2-phenylindole (DAPI) for 1 minute and covered with glass coverslips using Vectashield mounting medium (Vector Laboratories, Burlingame, CA). Fluorescent images were recorded using a confocal microscope (LSM 710; Carl Zeiss, Oberkochen, Germany) operating in multitrack mode for Alexa 488, 555 and DAPI fluorochromes. Primary antibodies used in the study included antibodies to i) the intermediate filament protein glial fibrillary acid protein (GFAP, a marker of reactive gliosis) (DAKO, UK; 1:50 dilution), ii) Cellular retinaldehyde binding protein (CRALBP, a Müller glia and RPE cell marker) (Santa Cruz, USA; 1:200 dilution), iii) Cytokeratin 8/18 (RPE cell marker) (Dako, UK). Isolectin B4 (a microglia and endothelial cell marker) (Life technologies, UK; 1:200 dilution) and CD68 (a macrophage and RPE cell surface marker) (DAKO, UK; 1:50 dilution).

Results

Overall, 27 patients underwent Boston Keratoprosthesis implantation over a period of three years. Of these, 6 required pars plana vitrectomy (22.2%), **Table 1**. The mean age of the patients who underwent PPV was 63.8 years with a male to female ratio of 5:1,

respectively. The mean follow up period was 9 months (range, 6-14 months).. The baseline (prior to vitrectomy) best-corrected visual acuity ranged between perception of light (PL) to 6/36.

In the majority of patients (5 out of 6 cases) the posterior segment pathology that required vitrectomy followed a specific pattern. Anterior proliferation was observed from the KPro to the ciliary body/anterior retina causing anterior (retro-prosthesis) membrane formation and contraction. Hypotony was noted in these cases although the exact intraocular pressure and the time course of the hypotony was difficult to assess with the KPro in situ. These features were combined with extensive serous/tractional anterior retinal detachment with co-existent aggressive subretinal and epiretinal proliferation. Intraoperatively, no pre-existing retinal breaks were identified in these patients. One patient (case 4) required vitreoretinal intervention for the management of a blocked Baerveldt tube (posteriorly placed).

In four cases, silicone oil was used (case 1,2,5 and 6). In one case the retina failed to re-attach intraoperatively after extensive membrane peeling due to extensive PVR with epiretinal and subretinal PVR membranes (case 3). Perluoro-N-octane was used and it exchanged wih silicone oil.One case required three vitreoretinal procedures (including inferior retinectomy, endolaser and silicon oil injection during the last procedure) for retinal re-attachment due to recurrent PVR (epiretinal and subretinal membranes) 7 months following the initial vitreoretinal intervention (case 2). In all procedures extensive peeling of the pre and sub-retinal PVR membranes and bands was performed. Notably in one case the BIOM widefield lens failed to provide

adequate focus on the posterior pole and the 90 diopters BIOM lens had to be used for the entire length of the vitreoretinal procedure (case 3).

In two cases (3 and 5) with total retinal detachment and retroprosthetic membrane, although the trocars had been anteriorly placed at the limbus, pre-operative anterior displacement of the retina resulted in sclerotomies passing initially subretinally and then through retinal tissue to the vitreous cavity. The BCVA at the last follow-up ranged from NPL to 6/60 and apart from case 3, all cases demonstrated attached retinae under the silicon oil at the last follow-up visit. All data and additional comments are summarized in **Table 1** and **Table 2**.

Table 1. Presenting Characteristics of patients with Boston K-Pro who underwent vitreoretinal surgery for retinal detachment.

N	Age	Sex	Pre-Kpro Diagnosis	Pre Kpro VA	Number of previous grafts	Glaucoma Sx	Ocular co-morbitity	Post K-Pro VA
1	47	M	SJS	CF	7	None	None	6/12
2	64	M	Chemical injury	HM	1	None	None	6/6
3	85	M	Aniridia+post ICCE aphakia	HM	2	Tube	chronic CMO	6/6
4	25	M	KC	HM	2	None	None	6/9
5	80	M	Penetrating trauma	HM	4	Tube	glaucoma/BRVO	1/60
6	82	F	Failed grafts	PL	6	Tube	TRD	6/60

SJO=Sjogren syndrome, ICCE=intracapsular cataract extraction, KC=Keratoconjunctivitis Sisca, CF=Counting Fingers, HM=Hand Movement
PL=Perception of Light, CMO=cystoid macular oedema, BRVO=Branch retinal Vein Occlusion, TRD=Tractional Retinal Detachment

Table 2. Posterior segment pathology, Surgical Management and Outcomes

N	Posterior segment complication	Pre VR VA	KPro to VR (m)	VR procedure	End VA	FU (m)
1	TRD	CF	4	V/ILM+ERM peel/L/C/SO	6/60	9
2	ERM/TRD and High IOP	HM	8 months then second PPV/PEEL 6months LATER then third PPV/RETINECTOMY/OIL	V/peel/L/posterior tube	CF	24
3	RP membrane/open funnel RD+epi and subretinal PVR	HM	6 weeks later then 8	tube removal/ V/ 360 retinectomy/ SRB removal	PL	7
4	High IOP/required Baerveld tube posterior+Vitrectomy	6/36	1 month then second PPV/cryo/gas 4 months later and third PPV/RETINECTOMY/OIL 3 months later(MULTIPLE GLAUCOMA PROCEDURES FOR MALIGNANT GLAUCOMA)	Vitrectomy/Baervelt tube insertion	NPL	14
5	RPM membrane/hypotony/choroidal effusion/TRD	HM	6	Vitrectomy/L/silicon oil	HM	8
	TRD+RRD	PL	9	combined KPro/V/retinectomy/L/SO	HM	13

VR=Vitreoretinal

Immunohistochemical features of the subretinal membrane

Immunohistochemical analysis of the subretinal membrane examined showed that this had the distinctive characteristics of a PVR membrane. This was demonstrated by its intense staining for GFAP and CRALBP, indicative of retinal glial cells.. In addition, a dense infiltration of RPE cells was also observed, as judged by the strong staining for cytokeratin 8/18 staining. Intense staining for Isolectin B4 and CD68 was was also observed, indicating severe microglia and macrophage infiltration of the subretinal membrane. (**Fig 1**). These observations are consistent with previous reports of PVR subretinal membranes [9,10]

Discussion

The worldwide clinical experience of the use of Boston Keratosprosthesis has increased and several modifications of the device have resulted in better retention and lower complication rate. [11] There are, however, a number of significant complications occurring in eyes which have undergone Boston KPro implantation including retroprosthetic membrane (RPM), [1,7,11] vitritis, [12] endophthalmitis, [7,12] prosthetic failure, [1] epiretinal membrane, [7] vitreous haemorrhage, [7] choroidal detachment, [7] and retinal detachment. [4-7]. In our series, a significant incidence (22.2%) of posterior segment pathology (retinal detachment) requiring surgical management was noted. In the majority of patients (5 out of 6 cases) we observed a specific pattern of very

severe retinal detachment which resulted in profound vision loss. We noted that the eyes were hypotonous with characteristic anterior proliferation causing traction to the ciliary body and anterior retina. This resulted in extensive and significant tractional retinal detachment with significant epi- and sub-retinal proliferative vitreoretinopathy (PVR) in all cases. It was notable that no retinal breaks were identified intraoperatively.

Although the histological features of retroprosthetic membranes have been previously reported, the characteristics of subretinal membranes excised from eyes complicated by PVR following Boston KPro implantation have not been documented. Unlike the negative staining for pan-cytokeratine observed in retroprosthetic membranes [Stacy RC et al- PMID 21402987], our study showed that the subretinal membrane examined exhibited a strong staining for cytokeratines 8/18, well known markers of RPE cells [Hiscott et al- PMID 12101446]. In addition, strong immunoreactivity for GFAP and CRALBP, which are markers of Müller glia and indicative of reactive retinal gliosis, was also seen. Microglial and macrophage infiltration, as judged by the intense immunostaining for isolectin B4 and CD68 was also demonstrated, which is again consistent with the inflammatory nature of PVR membranes [Charteris et al- PMID 8094546]. These observations are consistent with previous reports of PVR subretinal membranes [9,10] and confirm that a strong inflammatory response can be also elicited by Boston K-Pro implantation within the retina, leading to an aggressive PVR response to retinal detachment secondary to the implant procedure.

Performing posterior segment surgery in these patients can be challenging and the information regarding the type of posterior segment pathology, the intraoperative techniques and expectations, as well as the post-operative management and prognosis have been brief in previous reports . [4-6] Kiang et al, [5] reported on their experience from the use of small gauge vitrectomy (23 procedures) in 14 eyes. Of them, 7 were performed at the time of KPro placement, 1 included KPro removal and one was an exploratory endoscopy prior to KPro placement. In their series, the indication for PPV was the presence of RPMs in 7 cases and retinal detachment in 6 cases. The authors have concluded that small gauge vitrectomy can be effectively used for patients with permanent KPro. More recently, Harissi-Dagher et al, [6] reported on the outcomes from the use of 20 gauge PPV (modified technique as described by Stanescu-Segall et al, [13]) in 5 cases. Retinal detachment was the primary indication in 4 cases and suprachoroidal haemorrhage from glaucoma tube overfiltration in one case. The authors concluded that PPV through KPro is a viable approach butthe visual outcome remains poor.

In our study, 23 gauge vitrectomy with valved trocars was used in all cases. We believe that the use of valved trocars is important in these cases given the complexity of the previous history and the higher risk for intraoperative choroidal detachment/haemorrhage predisposed by intraoperative intraocular pressure fluctuations. In all cases, the trocars were placed as anteriorly as possible (ie at the limbus) to ensure that the sclerotomies were performed at the pars plana. However, in two cases

pre-operative anterior displacement of the retina resulted in sclerotomies passing through retinal tissue in order to gain access to the posterior pole. This occurrence highlights the distinct pattern of retinal detachment that was observed in our series.

All the patients in our series with retinal detachment demonstrated a variable degree of retroprosthetic membrane (RPM). It is possible that simultaneous PPV at the time of the KPro placement as suggested by Kiang et al, [5] may play a role in decreasing the incidence of anterior proliferation, nonetheless it may add a new set of possible complications to an already complex procedure. In addition, one of our cases (case 5) with significant tractional retinal detachment and anterior proliferation had previously undergone vitrectomy. As demonstrated in the results section and Table 2, the BCVA at the last follow up visit ranged from 6/60 to NPL, emphasizing the poor prognosis of patients with Boston Kpro requiring vitreoretinal intervention. In the future the use of a titanium back plate for the KPro might assist in reducing RPM occurrence. It is also notable that in our series three of the six patients with severe anterior traction and retinal detachment had previously had glaucoma drainage tube surgery. This may have contributed to ongoing anterior proliferation either through low grade inflammation and blood ocular barrier breakdown or potentially because of chronic hypotony (which may be undiagnosed because of the presence of the KPro) contributing to the observed anterior serous retinal detachment. Two patients in our series had a drainage tube placed at the time of vitreoretinal surgery.

In our series, all vitreoretinal maneuvers were performed without difficulty through the 23 gauge valved system with the use of BIOM as a viewing system. It is interesting that in one case we failed to achieve a good focus of the retina using the wide-field

lens and the surgeon had to use the 90 diopters BIOM lens for the full length of the procedure. In this case all surgical steps including fluid-air exchange, use of PFCL, retinectomy, membrane removal and dissection, cryotherapy/endolaser retinopexy and injection of silicon oil were performed using the 90 diopter lens.

Our study has limitations due to its retrospective nature and the relatively small number of cases with retinal detachment. Nevertheless we have identified a typical pattern of severe retinal detachment in eyes with a permanent Boston KPro, with anterior proliferative vitreoretinopathy extending from the Krpo and we have demonstrated the results of the histological examination of a subretinal membrane in one of our patients. . We also report our experience in managing vitreoretinal complications in this group of patients.

In conclusion, 23 gauge vitrectomy can be effectively performed in patients with permanent Boston KPro. Retinal detachment in these cases seems to have specific characteristics and the visual acuity remains poor despite successful anatomical results. Further studies are needed to explore ways of reducing and better treating post KPro retinal detachment.

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Contributorship Statement

PP and DGC contributed to the conception and design of the work, the acquisition, analysis or interpretation of data. Also, they contributed to drafting the work for important intellectual content.

PJB, MW, MS, KE and GAL contributed to the acquisition, analysis or interpretation of data. Also, they contributed to revising the manuscript critically for important intellectual content.

All authors are responsible for the final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Legend to Figure

Confocal microscopy images of subretinal membrane showing immuno-positivity for the reactive glial marker GFAP **(A),** the Müller cell marker CRALBP **(B),** cytokeratin 8/18, a marker of RPE cells **(C),** isolectin B4, a marker of endothelium and reactive microglia **(D)** and the macrophage/microglia marker CD68 **(E).** Cell nuclei stained with DAPI (blue). Images on the left show the corresponding section stained with H&E. Scale bars: 50μm (images A,B and C) and 100μm (images D and E).

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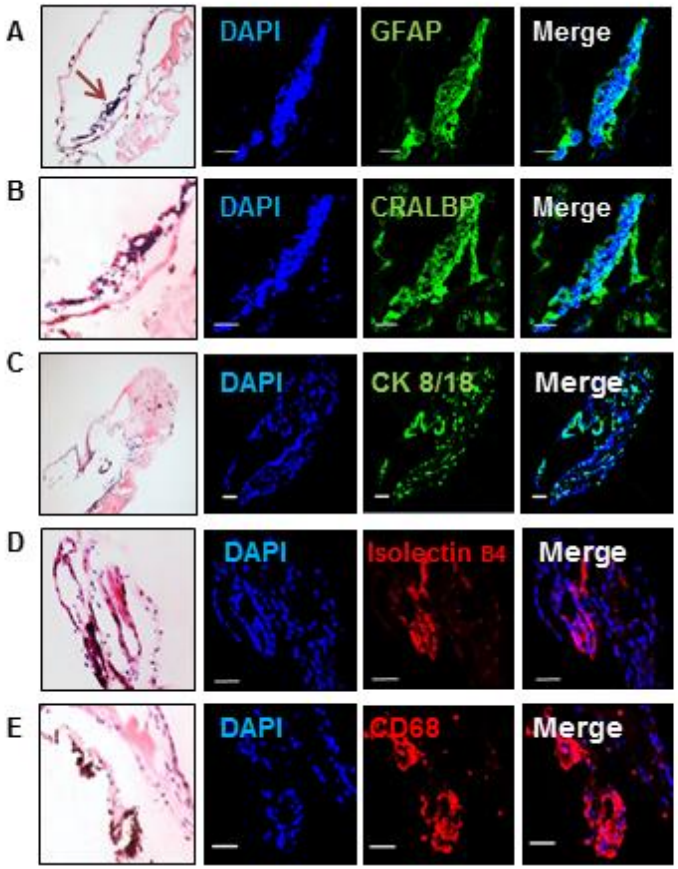
Figure



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