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Risk factors for the development of retroprosthetic membranes with Boston Keratoprosthesis type 1: multicenter study results

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Abstract

Objective—The purpose of this study was to identify possible risk factors for retroprosthetic membrane (RPM) development in a large multicenter cohort of patients receiving a Boston type 1 keratoprosthesis.

Design—Cohort study.

Participants—The final analysis included 265 eyes of 265 patients who underwent implantation of a Boston Keratoprosthesis Type I device between January 2003 and July 2008 by one of 19 surgeons at 18 medical centers.

Methods—Forms reporting preoperative, intraoperative, and postoperative parameters were prospectively collected and subsequently analyzed at a central data collection site.

Main Outcome Measures—The primary outcome was the presence or absence of a retroprosthetic membrane (RPM) during the follow-up period.

Results—265 Boston Type 1 keratoprosthesis surgical procedures (265 patients) from 19 surgeons at 18 surgical centers were included in the analysis. The average age of patients was 63.3±19.1 years, 48.5% of the patients were female, and 52.5% of procedures were performed on

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the right eye. The mean follow-up time was 17.8 ± 14.9 months. The majority (85.4%; $n=222$) had undergone an average of 2.2 ± 1.2 (range 1–8) penetrating keratoplasties prior to keratoprosthesis implantation, and 38 eyes (14.6%) received a primary keratoprosthesis. The overall RPM formation rate was 31.7% ($n=84$). The most significant risk factor for RPM development was infectious keratitis (as a surgical indication for keratoprosthesis surgery itself), resulting in a rate of RPM formation of 70.6%. As an independent risk factor, the hazard ratio (HR) of RPM development in these eyes was 3.20 (95% confidence interval: 1.66, 6.17). Aniridia was also an independent risk factor for RPM development (HR=3.13; 95% confidence interval: 1.10, 8.89).

Conclusions—RPM formation is a common complication of keratoprosthesis surgery, occurring in approximately one third of cases. Eyes at the highest risk of RPM development are those receiving corneal replacement for infectious keratitis and aniridia.

The Boston Keratoprosthesis, developed at the Massachusetts Eye and Ear Infirmary and approved by the US Food and Drug Administration in 1993, is used in eyes at high risk for penetrating keratoplasty (PK) failure. Over the years, the device underwent several modifications to improve retention and, subsequently, is now used by ophthalmologists worldwide. However, there are a number of significant complications that can occur in eyes that have received a keratoprosthesis, including retroprosthetic membrane (RPM),^{1–4} glaucoma,^{4–5} endophthalmitis,^{3, 6} sterile vitritis,^{4, 7} and prosthetic failure.^{1–2, 4, 8}

One of the most common complications is the development of RPM, reported to affect between 25% – 65%³ of cases. Although not every patient will require treatment for RPM, which includes neodymium:yttrium-aluminum-garnet (Nd:YAG) laser membranotomy, some will require surgical removal because the RPM can become too thick and dense to treat with laser. Zerbe et al⁴ reported an RPM incidence of 25% (35/141 eyes); 74% ($n=25$) of affected eyes were treated with ND:YAG laser, 11.4% ($n=4$) were treated surgically and 17% were simply observed.

The etiology of RPM is unknown; authors have reported that the performance of other intraocular surgery at the time of keratoprosthesis implantation,¹ increased anterior segment inflammation,^{7, 9} diabetes,¹⁰ hypertension,¹⁰ and race,¹⁰ increase the risk of RPM formation. The purpose of this study was to identify possible risk factors for RPM development in a large multicenter cohort of patients receiving a Boston type 1 keratoprosthesis.

Methods

The Boston Keratoprosthesis Multicenter Study is a large prospective case series gathering data on Boston Keratoprosthesis Type 1 implanted since January 1, 2003. At study commencement, all surgeons known to have performed multiple procedures were contacted and encouraged to participate. Data was reported via a mail-in form evaluating approximately 70 pre-, intra-, and post-operative variables. Submissions were voluntary, although all participants were encouraged to submit as complete data as was available, regardless of outcome. In compliance with Health Insurance Portability and Accountability Act regulations, patients were assigned a unique study number. Forms were sent to a central collection site, under Institutional Review Board (IRB) approval (Department of Ophthalmology, Albany Medical Center, Albany, New York). IRB approval was also obtained by participating institutions, where the surgeons report follow-up at 1 month, 6 months, 12 months, and yearly thereafter. The keratoprosthesis implantation technique has been previously described elsewhere.¹¹

The primary outcome of interest in this study was the time to development of RPM, which was defined as the time from the surgical date to development of an RPM or last follow-up, whichever was earliest. The inclusion criteria for this study included eyes undergoing their

first keratoprosthesis surgery. Some patients underwent bilateral sequential implantation of keratoprostheses; only the data from the first eye of a patient was eligible for this study. A Microsoft Excel spreadsheet was used to compile the data and SAS (version 9.2, SAS Institute Inc., Cary NC, USA) was used for all analyses. Dates were inputted from the information provided by each participating surgeon. For example, if a patient underwent keratoprosthesis implantation on 1 January 2005 and their 6 month study report indicated the development of an RPM at this visit, the date of RPM formation was recorded as 1 July 2005. RPM development was estimated using Kaplan-Meier methodology.

A priori predictors of RPM development, such as surgical indication,^{4, 7–8} concurrent intraocular surgery, diabetes mellitus and intraocular inflammation were recorded. Other surgical parameters, such as the number of prior PK performed, keratoprosthesis type (phakic or pseudophakic), host trephine size, donor button size and surgical time were all considered for their effect on RPM development. Backplate type was not included as a covariate because the vast majority of patients received the same type (PMMA). Data regarding the use of intracameral steroids was included because of their possible confounding effect on the development of fibrous tissue as a result of intraocular inflammation. The relationship between RPM development and categorical covariates was analyzed using Kaplan-Meier curves with 95% Hall-Welner Bands¹² and the log-rank test. For continuous variables, a simple Cox proportional hazards model was utilized. For categorical analyses in which time was not a factor, Fisher's exact test was calculated. Similarly, for continuous data in which time was not a factor, t-tests were used.

Multivariate analysis utilized a Cox proportional hazards model to determine the hazard ratio (HR); a priori predictors, as well as covariates that demonstrated a significance level of <10% on univariate analyses, were included. However, because some survey respondents did not respond to all queried covariates, variables were only eligible for inclusion in the model if the data were more than 90% complete.

Results

Between January 2003 and July 2008, information on 321 Boston Keratoprosthesis Type I implants in 303 patients by 19 surgeons at 18 medical centers was received. Of these, 32 eyes underwent implantation of an alternate keratoprosthesis prior to their inclusion in the multicenter study; these eyes were excluded. Seven patients underwent sequential bilateral keratoprosthesis implantation; the second eyes of these patients were excluded. The data was incomplete for 17 eyes and did not include information regarding complications; these eyes were excluded. The final analysis included 265 eyes of 265 patients.

The mean age at the time of implantation was 63.3 ± 19.1 years (range 10.5 – 96.7 years) and 48.5% were female. The procedure was performed in the right eye for 52.5% of the cases. Eyes that developed an RPM were followed for a longer time (23.6 ± 16.5 months) than those that did not develop RPM (15.1 ± 13.3 ; $p < 0.0001$). Overall, 146 eyes (55.1%) had at least 1 year of follow-up and 87 eyes (32.8%) had at least 2 years of follow up.

The majority of eyes (85.4%) had experienced a failed PK prior to keratoprosthesis implantation; these eyes ($n=222$) had undergone an average of 2.2 ± 1.2 prior cornea transplants (range 1 – 8). There was no difference in the rate of RPM development in eyes that underwent prior PK ($p=0.708$) nor was there a relationship between RPM development and increasing number of prior penetrating keratoplasties (Mantel-Haenszel chi-square test, $p=0.555$). Thirty-eight eyes (14.6%) were considered high-risk for PK failure and therefore underwent primary keratoprosthesis implantation; there was no difference in RPM

development between primary operations and eyes that underwent PK prior to keratoprosthesis ($p=0.708$).

The observed proportion of patients who developed an RPM was 31.7% ($n=84$). More RPM's developed in eyes that eventually failed (50.0%) versus those that retained the keratoprosthesis (30.0%) but this difference wasn't statistically significant ($p=0.091$). The mean time to development of RPM was 216.7 days post-operatively, although there was considerable variability, with a range of 7 days – 4 years (Figure 1).

None of the a priori predictors^{7, 9–10} of RPM development demonstrated statistically significant impact on time to development of RPM (table 1). However, patients who had a history of infectious keratitis (table 2) were more than twice as likely to develop an RPM ($p=0.002$; Fisher's Exact Test) and also developed them faster in comparison to patients with other surgical indications ($p=0.0002$; log-rank test). This association was confirmed with multivariate analysis ($HR=3.20$; $p=0.0005$).

Interestingly, those with a chemical injury demonstrated the opposite relationship; chemical injury was protective against RPM development, with less than a third of eyes developing an RPM ($p=0.022$; Fisher's Exact Test) and taking longer for it to be evident ($p=0.045$; log-rank test). While the hazard ratio on cox regression analysis suggests a protective effect of chemical injury eyes ($HR=0.441$), this was not a statistically significant association ($p=0.174$) after controlling for other possible predictors of RPM development.

While there was no difference in the rate of RPM development between eyes that received intracameral steroid ($p=0.789$) or not, the time to development (Figure 2) was much shorter in eyes that were not treated with steroid (median time = 2 versus 4 years; $p=0.041$). Again, although the hazard ratio on multivariate analysis was suggestive of a protective effect ($HR=0.696$), the association was not statistically significant ($p=0.172$). It has been suggested (Sippel KC. Techniques in permanent keratoprosthesis surgery: intraoperative dexamethasone may predispose to postoperative vitreous hemorrhage. Invest Ophthalmol Vis Sci 2007;48:E-Abstract 1897) that there is an increased rate of vitreous hemorrhage in keratoprosthesis eyes receiving intraoperative intracameral steroids, but this was not observed in this cohort; there was no difference in the proportion of eyes with a vitreous hemorrhage at the 1 week follow-up visit in steroid-treated eyes (1.1%) versus those not receiving steroids (0.9%; $p=1.000$). Similarly, after 1 month, no steroid-treated eyes developed a vitreous hemorrhage in comparison to 3.5% of those not receiving steroids ($p=0.122$). At 6 months, only 1 eye (1.2%) had a vitreous hemorrhage and it had not received intraoperative steroids; this proportion was not statistically significantly different ($p=0.460$).

Of the surgical parameters assessed in this study, eyes with longer surgical time tended to develop RPM more frequently, although this difference was not statistically significant (Table 3). Furthermore, the response rate to this covariate was low, and as such could not be included in a multivariate analysis.

Multivariate analysis (table 4) demonstrated that, in this cohort, the underlying indication for corneal surface rehabilitation is the most important predictor of RPM development. Both infectious keratitis ($HR=3.20$, 95% confidence interval: 1.66, 6.17) and aniridia ($HR=3.13$, 95% confidence interval: 1.10, 8.89) significantly and independently increased the hazard of RPM development.

Discussion

This study, on the largest sample of keratoprotheses to date, demonstrated that the etiology of RPM development may be different than previously thought, and in fact may relate more to the underlying reason for corneal replacement surgery. However, it is important to note that this study was unable to evaluate the impact of hypertension¹⁰ and race.¹⁰

The strongest risk factor for RPM development was infectious keratitis (HR=3.20; 0=0.0005), where the first quartile time to RPM development was only 30 days. To the best of our knowledge, this is the first literature report of this association.

Although not previously recognized, other keratoprosthesis investigators have observed that chemical injuries may be protective against RPM formation. Bradley et al² reported a 35.7% rate (n=10) of RPM development and, from patient data in their paper, observed a lower rate of RPM development (20.0%; n=1) in eyes with chemical injuries. Similarly, 37% of the eyes described in Yaghouti et al¹³ developed an RPM overall, whereas those with chemical injuries developed them at a lower rate (24%; n=4). Although the protective effect of chemical injuries was not statistically significant on controlled analysis (HR=0.441; p=0.136), the finding was statistically significant on univariate analysis (p=0.022), suggesting that its contribution to the development of RPM may be mitigated by other factors.

There is no definitive literature reference demonstrating the beneficial effect of intracameral steroids and one report (Sippel KC. Techniques in permanent keratoprosthesis surgery: intraoperative dexamethasone may predispose to postoperative vitreous hemorrhage. Invest Ophthalmol Vis Sci 2007;48:E-Abstract 1897) noted an increased rate of vitreous hemorrhage following its use; this association was not observed in this cohort. Some authors¹⁰ have advocated for intracameral steroids, but participants in this study were divided on whether or not to use them, with 47.4% of eyes (n=126) receiving steroid prophylaxis. The data herein do not conclusively answer the question about whether or not to use them; intracameral steroids was a statistically significant predictor on univariate survival analysis (p=0.041) but not on multivariate analysis (HR=0.696; p=0.172). The Kaplan-Meier curve in Figure 2 is illustrative of the inability of steroid to prevent RPM development; rather, they delay their formation. This finding suggests that steroids may influence RPM development but that the effect is limited because of the rapid turnover rate of anterior chamber fluid. It is possible that surgeons may use less post-operative steroids in keratoprosthesis eyes given that graft rejection is less of a concern. Therefore, it may be beneficial to investigate this association further.

RPM formation is a common complication of keratoprosthesis surgery, occurring in approximately one third of cases. Eyes at the highest risk of RPM development are those receiving corneal replacement for infectious keratitis. However, both chemical injuries and adjuvant intracameral steroids may delay the development of RPM; further research into these risk factors is warranted.

Acknowledgments

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Figure 1. Kaplan-Meier curve of time to development of retroprosthetic membrane (RPM) in patients undergoing implantation of a Boston keratoprosthesis type 1.

Figure 2.

Kaplan-Meier curves of time to development of retroprosthetic membrane (RPM) comparing eyes treated with intracameral steroid intra-operatively (red) compared to those not receiving steroid (blue). The time to development of RPM is faster in eyes that did not receive intracameral steroids ($p=0.041$).

Table 1

The relationship between a priori predictors and retroprosthetic membrane development.

Predictor	RPM (n=84)			No RPM (n=181)	p-value *
	RPM rate (%)	n	quartile time (d)		
Diabetes Mellitus	21.4	3	1460	11	0.233
History of Uveitis	16.7	1	-	5	0.309
Iridectomy	30.3	10	183	23	0.870
Iridoplasty	42.9	6	30	8	0.082
Iridocorneal synechiolysis	20.0	3	183	12	0.534
Vitrectomy	34.0	18	183	35	0.957
Cataract Extraction	30.8	16	365	36	0.869
Intraocular Lens Removal	20.7	6	183	23	0.465
Glaucoma Surgery	31.3	5	183	11	0.772
Intracameral Steroid	31.2	39	365	86	0.041

* Log-KanK Test.

RPM: retroprosthetic membrane

Table 2

Development of retroprosthetic membrane by surgical indication.

Surgical Indication	RPM (n=84)			No RPM (n=181)	p-value
	RPM rate (%)	n	quartile time (d)	n	
Ocular Cicatricial Pemphigoid	23.5	4	183	13	0.561
Herpes Simplex Keratitis	31.6	6	183	13	0.475
Bullous Keratopathy	31.7	13	365	28	0.347
Chemical Injury	12.5	3	730	21	0.045
Fuchs Dystrophy	28.6	2	365	5	0.739
Keratoconus	20.0	2	-	8	0.306
Infectious Keratitis	70.6	12	30	5	0.0002
Stevens-Johnson Syndrome	27.3	3	183	8	0.829
Trauma	25.0	3	365	9	0.418
Aniridia	66.7	4	183	2	0.069
Neurotrophic Keratitis	50.0	2	30	2	0.136
Limbal Stem Cell Deficiency	50.0	4	107	4	0.221
Miscellaneous	36.6	15	365	26	0.953

* Log-Rank Test

RPM: retroprosthetic membrane

Table 3

Comparison of surgical parameters in patients who developed retroprosthetic membrane versus those who did not.

Variable	RPM (n=84)	NoRPM(n=181)	Data Completeness	p-value
Aphakic KPro	34.0%	66.0%	96.2%	0.648 [*]
Pseudophakic KPro	30.3%	69.7%	96.2%	0.648 [*]
Surgical Time (minutes)	134.9 ± 43.5	122.0 ± 37.8	51.7%	0.056 [†]
Host Trephine Size (mm)	8.2 ± 0.4	8.3 ± 0.6	95.5%	0.428 [†]
Donor Button Size (mm)	8.6 ± 0.4	8.8 ± 0.7	94.7%	0.127 [†]

^{*} Log-Rank Test

[†] Cox Proportional Hazards Univariate Model

RPM: retroprosthetic membrane

Table 4
Cox multivariate analysis of possible risk factors for retroprosthetic membrane development.

Variable	HR	95% CI	Parameter Estimate	SE	χ^2	p-value
Diabetes Mellitus	0.584	0.179 – 1.905	–0.538	0.603	0.795	0.373
History of Uveitis	0.493	0.066 – 3.711	–0.706	1.029	0.471	0.493
Iridocorneal synechiolysis	0.714	0.097 – 5.235	–0.337	1.017	0.110	0.740
Iridectomy	0.892	0.427 – 1.862	–0.144	0.376	0.093	0.761
Iridoplasty	2.667	0.935 – 7.606	0.981	0.535	3.365	0.067
Intracameral Steroid	0.696	0.414 – 1.170	–0.363	0.265	1.868	0.172
Chemical Injury	0.441	0.136 – 1.434	–0.819	0.602	1.852	0.174
Infectious Keratitis	3.199	1.660 – 6.166	1.163	0.335	12.070	0.0005
Aniridia	3.126	1.098 – 8.894	1.140	0.533	4.563	0.033

HR = hazard ratio

CI = confidence interval

SE = standard error

χ^2 = chi-square product

RPM: retroprosthetic membrane