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REPEAT CORNEAL TRANSPLANTATION: OUR EXPERIENCE

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KEYWORDS

INTRODUCTION

Corneal blindness is a debilitating condition and is the fourth most common cause of blindness all over the world accounting for over 5% of the total blind population.[1] It presents a significant public health problem, especially in the developing world.[2] In India, it is estimated that there are approximately 6.8 million people who have vision less than 6/60 in at least one eye due to corneal disease, of these about a million have bilateral involvement.[3]

Corneal blindness encompasses a range of eye conditions that alter the transparency of the cornea, leading to corneal scarring and, eventually, blindness. As most of the corneal blindness is amenable to prevention, prevention of the causes that lead to corneal blindness would be a preferred approach for this problem in the long run. However, the overwhelming magnitude of this problem poses a certain challenge to blindness prevention efforts in India. Visual rehabilitation with corneal transplantation or corneal grafting, at present, remains the best hope for curing corneal blindness.[4]

Transplantation of cornea has the distinction of having achieved a success unequaled by other organ or tissue transplants.[5]The success of corneal grafting in visual rehabilitation of the corneal blind, however, depends largely on survival of the corneal graft. Corneal grafts may fail for a number of reasons including rejection, infection, and displacement of corneal graft, trauma and recurrence of original disease.[6]In many of these cases re-grafting is indicated to restore vision. In any large unit, therefore, repeat corneal transplantation continues to be an important and increasingly common indication for keratoplasty.[7]

While the risk factors for corneal transplantation and the outcomes of surgery have been well studied in India, there is a paucity of literature on the outcomes after corneal re-grafting. In order to assess the role that repeat corneal transplantation could play in visual rehabilitation of the corneal blind with failed primary corneal grafts, data on the survival rates and outcomes of corneal re-grafting are required.

The present study is a retrospective case series analyzing the survival and visual outcomes of repeat corneal transplantation in those eyes with primary corneal graft failure.

Methodology

This study is a retrospective analysis of the records of 31 patients who underwent repeat corneal grafting at two apex armed forces institute in India over a period of 63 months from July 2015 to October 2020. All patients undergoing repeat corneal graft in this institute during the study period were included in the study. Patients who underwent more than one corneal re-graft were also included. Patients for whom data were missing were excluded from the study. All the patients included in the study were operated by a single experienced anterior segment surgeon.

Patient parameters that were evaluated included age and gender, ophthalmic co-morbidity, indication for primary corneal transplantation, the preoperative uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA), type of corneal re-graft surgery performed and associated procedures, failure of corneal re-graft and the reasons for failure. Post-operative complications, if any, were also recorded. The patients were followed up at regular intervals after corneal transplantation but the follow up visits included in the study are from 1, 3, 6 and 12-months post operatively. At each follow up visit the UCVA and the BCVA were assessed and slit lamp findings documented. The duration from the day of re-graft surgery till the day the re-graft failure was diagnosed was taken as the graft survival time. The corneal graft was considered to have failed if it did not retain optical clarity and therapeutic attempts to improve this had no impact. The duration of follow-up was taken as the time between the last re-graft and the final follow-up. Visual outcomes were assessed based on the visual acuity on the last follow up. More than one corneal re-graft was considered as a multiple re-graft. Details of previous grafts in cases of multiple re-grafts were also collected from old records.

Statistical Analysis

Categorical variables were presented as percentages and as frequency distribution and compared by Chi- square tests. Continuous variables were inclusive of age and survival time of corneal re-grafts and was presented as median and interquartile ranges. Kaplan Meier Survival curve was plotted for overall survival of the corneal re-grafts wherein the primary end was graft failure. Cox proportional hazards regression was done to determine factors associated with the risk of corneal re-graft failure. A p value of <0.05 was considered significant at a confidence interval of 95%.

RESULTS

A total of 33 patients underwent repeat corneal graft in the institute from July 2015 to October 2020. Two patients had missing data and were excluded from analysis. Ten (32.3%) patients were female and 21 (67.7%) patients were male. Median (Interquartile range, IQR) age of patients was 60 (26) years. Maximum patients (10, 32.3%) belonged to the 60-70 years' age group. Of a total of 31 eyes, 27 eyes had one corneal re-graft and 4 had multiple corneal regrafts.

The clinical indications for the primary corneal graft are listed in table 1. Most number of patients (9 out of 31 eyes, 29%) who received repeat corneal graft had pseudophakic (PBK)or aphakic bullous keratopathy (ABK) as the indication for original corneal graft, followed by adherent leucoma post perforated corneal ulcer (6 out of 31 eyes, 19.4%). Both perforated corneal ulcer and fungal keratitis were the indication for original corneal graft each in 4 (12.9%) out of 31 eyes. Other indications for primary corneal graft included post traumatic keratitis (3 out of 31 eyes, 9.7%), viral keratitis (2 out of 31 eyes, 6.5%) and corneal scar (2 out of 31 eyes, 6.5%). Only 1 patient underwent corneal graft for keratoconus.

Table 1: Indications for Primary Corneal Graft

Indication		Frequency	Percent
	Perforated corneal ulcer	4	12.9
	Keratoconus	1	3.2
	Fungal keratitis	4	12.9
	PBK/ABK	9	29.0
	Viral keratitis	2	6.5
	Post traumatic	3	9.7
	Adherent leucoma post perforated corneal ulcer	6	19.4
	Corneal scar	2	6.5
	Total	31	93.9
Missing		2	6.1
Total		33	100.0

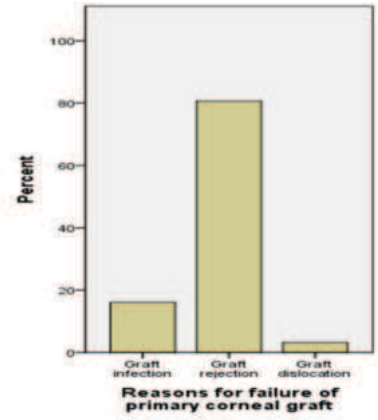

Figure 1: Reasons for Failure of Primary Graft

The commonest cause for failure of primary corneal graft in the patients who underwent repeat corneal graft was graft rejection which occurred in 22 (71%) patients. Infected graft accounted for 8 (25.8%) patients. One patient underwent repeat corneal graft for displacement of primary graft (figure 1).

Failure of re-graft was observed in 12 out of the 31 eyes (38.7%). The median survival of corneal re-grafts was 365 days (95%CI 305-425) (Figure 2). The reasons of failure in these eyes were attributable to graft rejection in 10 out of 12 eyes (83.3%). Two corneal re-grafts failed due to infection (Figure 3). The frequency of graft rejection in these eyes was not statistically different from that of the primary graft.

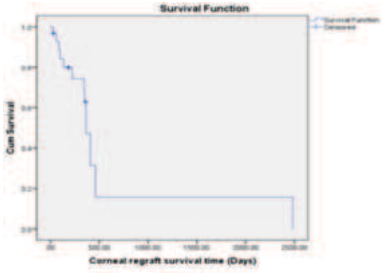

Figure 2: Corneal Regraft Survival

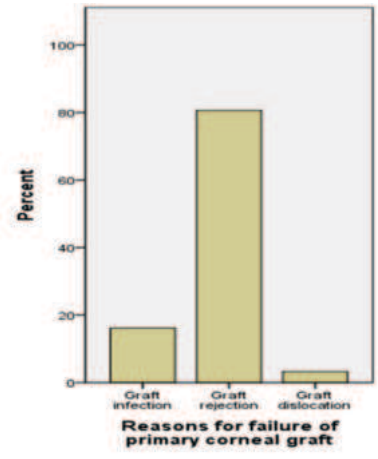

Figure 3: Reasons for Failure of Corneal Regraft

Kaplan Meier analysis done for the failure rates of corneal re-grafts between the types of re-graft surgeries that is, PK and DSEK showed that the difference was not statistically significant. (Table 2, Figure 4)

Table 2: Kaplan Meier Survival Analysis to Find Out Graft Survival Rate and to Compare it Between Type of Repeat Surgery

Type of repeat surgery			PK	DESK
Total N			18	13
N of Events			11	5
Censored	N		7	8
	Percent		38.89%	61.54%
Graft survival at the end of 3 months			82.64%	91.67%
Graft survival at the end of 6 months			63.57%	68.75%
Graft survival at the end of the study			31.78%	45.83%
Mean	Estimate		9.18216	9.875
	Standard Error		0.99946	1.15491
	95% Confidence Interval	Lower Bound	7.22322	7.61137
		Upper Bound	11.1411	12.1386
P value			0.465	

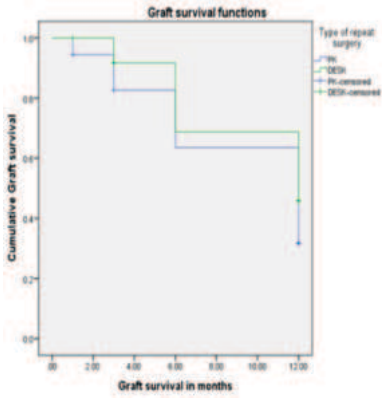

Figure 4: Kaplan Meier Survival Analysis to Find Out Graft Survival Rate and to Compare it Between Type of Repeat Surgery

Cox proportional hazards regression was used to determine whether preoperative factors have a significant association with the risk of failure of re-graft. Age of the patient (aHR 1.1 per year increase in age, 95%CI 1.003-1.227), and fungal keratitis as the indication for primary graft (aHR 0.024, 95% CI 0.001-1.005) showed statistical significance (Table 3).

A comparison of the final visual acuity with the visual acuity at the time of diagnosis of corneal disease was done. Preoperatively (before the primary corneal graft) the best corrected visual acuity (BCVA) ranged from perception of light (PL) to 6/60. Twenty-seven (86.2%) of the 31 eyes had a BCVA of less than 1/60 while 4 (13.8%) of the 31 eyes had a BCVA between 1/60 and 6/60. In none of the eyes BCVA was better than 6/60(Figure 4). In comparison, the final BCVA at the end of the follow up period in the 19 eyes with a surviving corneal re-graft showed a significant improvement in vision. Eight (42.1%) out of the 19 eyes with surviving re-grafts had a BCVA of better than 6/60 whereas 7 (36.8%) out of these 19eyeshad a BCVA ranging between 6/60 and 1/60(Table 3). Among the patients with a surviving corneal re-graft, only 4 (21.1%) eyes had a BCVA of less than 1/60 (Figure 5). Improvement in visual outcome was observed in 15 (78.9%) out of the 19 of the eyes with surviving corneal re-grafts. In the eyes with failed regraft, 8 (66.7%) of the 12 eyes had a BCVA of less than 1/60 while the remaining 4 (33.3%) of the 12 eyes had a BCVA ranging from 6/60 to 1/60. None of the eyes had a visual acuity of better than 6/60.

Table 3: Unadjusted and Adjusted Hazard Ratio for Risk of Failure of Corneal Regraft

Variables		Unadjusted hazard ratio (HR)	sig	Adjsuted hazard ratio (aHR)	Sig.	95.0% CI for aHR	
						Lower	Upper
Baseline data	Age (Per 1 year increment)	1.027	0.196	1.068	.042	1.002	1.138
	Sex (Female)	1.844	0.404	5.795	.130	.594	56.492
Primary corneal pathology	Perforated corneal ulcer		.601		.418		
	Keratoconus	.000	.990	.000	.995	.000	.
	Fungal keratitis	1.018	.986	2.909	.398	.244	34.697
	PBK/ABK	.194	.158	.052	.049	.002	1.103
	Viral keratitis	.950	.967	.405	.523	.025	6.470
	Post traumatic	.121	.139	.162	.201	.010	2.644

	Adherent leucoma post perforated corneal ulcer	.144	.139	.100	.088	.007	1.409
	Corneal scar	1.317	.825	.909	.963	.015	54.124
Reason for failure of primary corneal graft	Graft infection		.697		.616		
	Graft rejection	.494	.395	4.205	.325	.240	73.578
	Graft dislocation	.000	.989	.000	.993	.000	.

Table 4: Comparison of BCVA Preoperatively and Following Primary Regrafting in the 19 Eyes with Surviving Corneal Re-graft

Group		BCVA			Total	p
		<1/60	1/60-6/60	>6/60		
	Pre-operative BCVA(for all patiens undergoing re-graft)	27	4	0	31	<0.05
	Final BCVA	4	7	8	19	
Total		29	11	8	50	

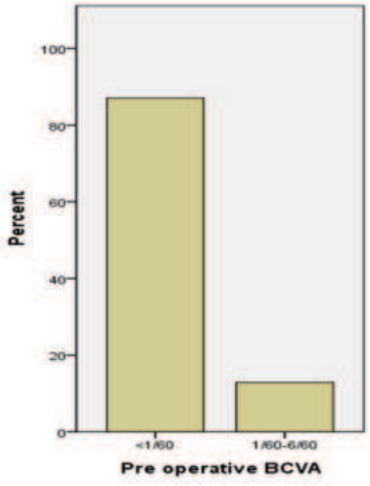

Figure 5: Pre-operative BCVA (Before Primary Corneal Graft)

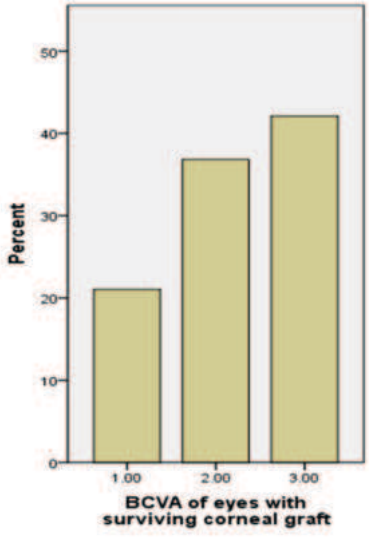

Figure 6: BCVA of the 19 Eyes with Surviving Corneal Regraft at End of the Follow-up Period

Only 4 out of the 12 patients with failed corneal re-graft underwent a second regraft. Out of these 4 eyes, 2 (50%) eyes at the end of follow up period had a BCVA of better than 6/60. The visual outcome in these patients did not differ significantly in comparison with those eyes with a surviving regraft.

DISCUSSION

Recent advances in corneal graft technology have greatly improved the clinical outcome of corneal graft, have allowed for faster restoration of vision and have enabled greater number of corneal transplantations to be performed.[8] Long term follow-up studies of patients undergoing corneal transplantation have yielded a success rate of corneal transplantation as high as 90%.[9,10] Despite the advances, graft failure still remains a daunting issue, being reported in 3-30% of the eyes undergoing corneal transplantation.[11-13] With a high proportion of these patients eventually undergoing corneal re-grafting, the frequency of repeat corneal transplantation has become one of the leading indications for corneal transplantation. The rise in the frequency of corneal regrafting parallels the increasing number of corneal transplantations being performed, and in absolute numbers, entails a drain on the existing resources.

Graft failure and vision remain the two major outcome indicators for most corneal transplantation procedures. The present series deals with a cohort of patients undergoing repeat transplantation for primary corneal graft failure. The outcomes of corneal re-grafting in these eyes have been described in terms of re-graft failure and visual outcomes following the re-grafting procedure. Additionally, the profile of patients undergoing the re-grafting procedure including the primary corneal pathology and reasons for re-graft failure has been described.

A total of 31 eyes were included in the series that underwent repeat corneal transplantation in two apex institutes in India over a period of 63 months from July 2015 to October 2020. A high incidence of corneal regraft failure was observed in the present study, failure of the regraft occurring in 38.7% of the eyes. Few studies have reported corneal regraft failure as an outcome indicator for repeat corneal transplantation. In a study by Vanathi, et al, at a tertiary centre in Northern India, the success of repeat penetrating keratoplasty in terms of graft clarity was reported to be 52.8%.[14] Other studies have reported the success of corneal re-grafting in terms of re-graft survival time. Daniel J Weisbrod, in a recent study reported an overall survival of repeat corneal transplantation as 63.9 % at the end of two years.[15]In another study, Kirkness, et al, reported a 50 % failure rate of corneal re-grafts at 4.5 years.[16]The study by Vanathi et al in India reported a median survival time of corneal re-grafts ranging between 20-30 months. In comparison, a much lower overall survival of the corneal re-grafts was observed in the present study, with the median survival of corneal re-graft being 365 days (95%CI 305-425). These observations indicate that the survival of corneal re-grafts in India were much lower in comparison with that reported in western literature.

Even though graft survival is affected by a variety of factors, allograft rejection has been implicated as a major cause of corneal graft failure. Recent studies from developed countries have reported graft rejection as the most common cause.[5,17] The reason for re-graft failure in the present study was attributable to graft rejection in more than 80% of the eyes, concurrent with observations from studies in the developed countries. The study by Vanathi, et al in India reported graft infection and recurrence of previous infection as the most common cause of regraft failure.[14]In comparison, infection as the cause of regraft failure in the present study was observed in only 2 out of the 12 eyes. Recurrence of previous infection was not observed in any of the eyes.

These observations pose questions on how in our clinical practice can we reduce the risk of corneal graft rejection for this group of patients. In order to answer these questions, a comparison of various preoperative factors was undertaken with corneal re-graft failure as the primary outcome. These comparisons were based on previous observations indicating the primary corneal pathology and the type of surgery having a bearing on regraft survival. Cox proportional hazards regression was employed to determine if these factors had a significant association with the risk of failure of re-graft. It was observed that the age of the patient (aHR 1.1 per year increase in age, 95%CI 1.003-1.227) and fungal keratitis as an indication for primary graft (aHR 0.024, 95% CI 0.001-1.005) were statistically significant, implying a lower age at surgery and fungal keratitis as the primary corneal pathology conferring a significantly lower risk of corneal regraft failure. This is in comparison with a study by Eghtedari, et al in Iran wherein it was concluded that the recurrence rate in infective cases, especially fungal keratitis was very high in these patients and had a considerable role in failure of the corneal re-grafts.[18]

These variations may be explained on the basis of differences in the

profile of the populations being compared. Additionally, there exist considerable differences in the incidences of the primary corneal pathologies. The most common primary indication for repeated corneal transplantation was bullous keratopathy (pseudophakic/ aphakic) which accounted for 29.0 % of the eyes undergoing repeat corneal transplantation. This is similar to that observed by Eghtedari et al in their study. The relatively higher incidence of bullous keratopathy in patients undergoing repeat corneal transplantation has been reported in other studies as well.[19,20] Infectious causes (fungal and viral keratitis) as primary corneal pathologies, accounting for 19.4% of the eyes and being the second most common indication for primary corneal graft, were relatively less common compared to the study by Eghtedari et al, wherein its incidence was more than 30%. Adherent leucoma post perforated corneal ulcer showed an incidence similar to that of infective etiologies (19.4 %) in the present study.

The reasons for corneal re-graft failure are more likely to be multi-factorial. Factors such as socioeconomic status, treatment adherence, self-care, regular follow up and access to a transplant centre are potential determinants, especially in Armed Forces where only few centers have the facility for corneal transplantation. Detail study of these aspects is needed but has not been included as they are beyond the purview of the present study. The present study is grounds for further large scale studies in India accounting for these factors.

Visual acuity is another outcome indicator which was assessed. Overall, the results in those eyes with a surviving corneal regraft are encouraging in terms of visual outcome following repeat corneal transplantation. Preoperatively (before the primary corneal graft), among the 31 eyes, 86.2% of the eyes had BCVA of worse than 1/60, 13.8 % had a BCVA between 1/60 – 6/60. None of the eyes, preoperatively, had a BCVA better than 6/60. In comparison, the final BCVA at the end of the follow up period of the 19 eyes with a surviving re-graft showed significant improvement ($p<0.05$) in vision. It was observed that 42.1% of these eyes had a BCVA of better than 6/60, 36.8% had a BCVA between 6/60 and 1/60 while only 21.1 % of the eyes had a BCVA of less than 1/60. Studies done in recent past have also reported improvement in visual acuity of those eyes with surviving re-grafts wherein a visual acuity of 6/18 or better was observed[21,22,23] In the present study,5 (62.5 %) out of those 8 eyes with a BCVA of more than 6/60, had visual acuity of 6/18 or better. Few studies have also documented the visual outcome following re-grafting to be comparable to that after single graft.[21,22,24]The retrospective nature of the present study limited the data available to make such comparisons. Furthermore, studies have reported poorer visual prognosis in eyes undergoing more than one corneal regraft[24]. Number of eyes that underwent more than one re-graft were few in this study, so no particular trend could be established.

The present study provides recent evidences on the failure of corneal regrafts and the factors associated with their failure. Overall, the visual outcome following corneal regrafting for failed primary corneal graft is promising in terms of visual outcomes. However, it is rather disconcerting that the rate of regraft failure is high and their survival time is comparatively low. It can be discerned from the present study that rejection of corneal regraft is a major factor implicated in corneal regraft failure. It is hence imperative to identify factors associated with corneal regraft failure, especially those concerning corneal regraft rejection. These findings can help guide management of failed corneal graft. Long term and larger studies are warranted which may help in wide scale application of these results.

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