VOLUME - 13, ISSUE - 10, OCTOBER - 2024 • PRINT ISSN No. 2277 - 8160 • DOI : 10.36106/gjra

Original Research Paper

Ophthalmology

PREDICTORS OF GRAFT REJECTION FOLLOWING FULL THICKNESS PENETRATING KERATOPLASTY - A PROSPECTIVE ,ANALYTICAL HOSPITAL BASED STUDY

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ABSTRACT This study analysed the influence of various risk factors on graft rejection and emphasized the importance of its early recognition and management. **Materials & Methods:** Prospective, Analytical, Hospital-based study, the study population consisted of 84 eyes of 80 patients who underwent full-thickness penetrating keratoplasty from September 2014 to May 2016. All transplant surgeries were performed by a single surgeon. Patients were examined on the first postoperative day and followed up periodically. During each visit, the graft was assessed and findings documented. **Results:** Rejection rate was 34.52% (29 out of 84 eyes). Young recipient age, presence of corneal vascularisation and peripheral anterior synechiae were associated with a significantly higher risk of rejection. **Conclusion:** Identification of high risk patients preoperatively helps the surgeon to plan for aggressive therapy and follow up of these patients.

KEYWORDS : Cornea, penetrating keratoplasty, rejection

INTRODUCTION

Visual impairment due to corneal disease is a significant public Health problem in the developing world. Visual rehabilitation with corneal transplantation is the only option possible in many of these cases.

Recent advances in corneal graft technology including donor tissue retrieval, storage and surgical techniques, have greatly improved the clinical outcome of corneal grafts. Despite these advances, immune-mediated corneal graft rejection remains the most important cause of corneal graft failure. This study was done to analyze the influence of various risk factors on graft rejection and to emphasize the importance of its early recognition and management.

AIM OF THE STUDY

To evaluate the risk factors for graft rejection following full-thickness penetrating keratoplasty and to emphasize the importance of early management of Rejection.

MATERIALS AND METHODS

This was a prospective hospital-based study where the study population consisted of 84 eyes of 80 patients who underwent full thickness penetrating keratoplasty from September 2014 to May 2016.

Inclusion Criteria:

1. Patients in all age groups who required penetrating keratoplasty for various indications like Aphakic and Pseudophakic bullous keratopathies, Adherent leucoma, corneal opacity, previous graft failure, Fuch's Endothelial Dystrophy, Iridocorneal Endothelial syndrome, keratoconus, spheroidal degeneration and Atheromatous ulcer.
2. Good Patient compliance

Exclusion Criteria:

1. Transplant done in cases of active infectious keratitis
2. Primary graft failure
3. Non compliant patients

Protocols Followed:

1. Approval for research from institution
2. Informed consent from the patient
3. Pre-operative assessment

A detailed history regarding symptoms, onset of visual disturbance, prior ocular conditions, previous ocular surgeries, use of any topical medications, general medical history were obtained.

Visual acuity was determined with Snellen's chart. A gross ocular examination to rule out lid abnormalities and ocular surface disorders was done.

A detailed slit lamp examination was done to study the type of corneal disorder, extent of corneal involvement, peripheral anterior synechiae, anterior chamber depth, lens status, any vascularisation of the cornea, shape and size of the pupil, positioning of intra ocular lens in pseudophakic eyes, posterior synechiae, presence of vitreous in the anterior chamber in aphakic eyes, co-existent cataract ete. In case of vascularised corneas, the extent and depth of vascularisation was noted.

Intraocular pressure was checked with an Goldman Applanation Tonometer. Recipients with uncontrolled glaucoma were treated and the intraocular pressure decreased to below 20 mmHg before transplantation.

Fundus examination and ultrasonography was done to rule out posterior segment pathology.

An anterior segment photograph was taken for documentation.

4. Preparation of donor cornea:

Donor eyes enucleated aseptically , Sclerocorneal rims were made and the buttons were preserved in McCarey and Kaufman medium at 4°C.

5. Surgical Technique:

All transplant surgeries were performed by a single surgeon.

Surgery was done under peribulbar anaesthesia. In younger age groups a general anaesthesia was given.

At the time of surgery, donor corneal buttons were punched out of the endothelial side using disposable punch trephines. A superior rectus bridle suture was applied A Flieringa scleral fixation ring was used in patients with high myopia, keratoconus and in paediatric age group.

The geometric centre of the host cornea was located using calipers and marked using a surgical marking pen.

Trephination of host cornea was done using Barron trephines. The size of the trephine depended on the extent of the corneal disease. The size of the graft ranged from 7.5mm to 8.5mm. A graft-host disparity of 0.5mm was maintained.

Additional procedures like anterior vitrectomy, extracapsular cataract extraction, intraocular lens implantation, trabeculectomy, iridoplasty, limbal stem cell transplantation were done in relevant cases.

The donor cornea was placed on the recipient bed and secured with sutures. Interrupted sutures with 10-0 nylon were used in most of the cases.

6. Patient Follow-Up

Patients were examined on the first postoperative day and followed up weekly for one month, every 2 weeks during the second month and monthly for one year.

There after patients were followed every 3 months. All patients were treated with topical steroids after surgery. 1% Prednisolone acetate eye drops was given every 2 hours for the first week followed by 6 times a day for 2 weeks and slowly tapered to once daily .

Patients who had a rise in intraocular pressure and those with preoperative glaucoma were treated with topical antiglaucoma medications. Oral Azathioprine was prescribed in 3 patients who underwent penetrating keratoplasty with limbal stem cell transplantation for corneal opacity following chemical injury.

During each visit, the following examination was done.

1. Visual acuity
2. Retinoscopy
3. Slit lamp examination
4. Intra ocular pressure by Goldman Applanation tonometry
5. Fundoscopy - when required

Management Of Rejection

Patients in whom signs of epithelial rejection developed were treated with subconjunctival Dexamethasone injection, hourly prednisolone acetate eye drops.

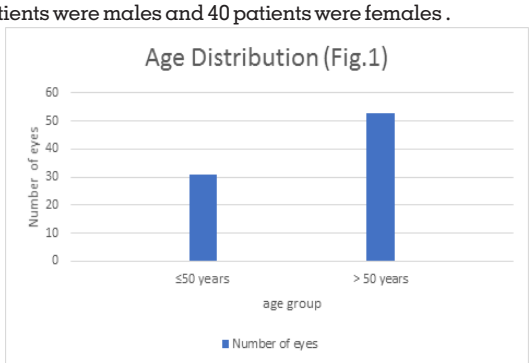
Patients with mild endothelial rejection were treated with a more intensive immunosuppressive regimen beginning with subconjunctival Dexamethasone injection, hourly prednisolone acetate eye drops and oral steroids 1mg/kg body weight in tapering doses.

Patients with signs of severe endothelial rejection immediately received 500mg methylprednisolone sodium succinate intravenously, followed by prednisolone 1 mg/Kg orally which was slowly tapered.

Statistical analysis for the various risk factors associated with rejection was done with chi-square test and analysis of variance.

RESULTS

This prospective study was conducted over a period of 2 years. A total number of 84 eyes of 80 patients who underwent penetrating keratoplasty were included in the study. 40 patients were males and 40 patients were females .



Age Distribution (Fig.1)

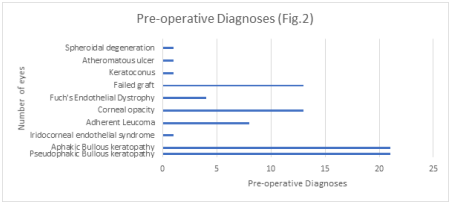
The age group ranged from 7 years to 84 years. The mean age of patients was 52.39 years.

According to age, patients were divided into 2 categories.

Table-1

Age	Number of eyes
≤50 years	31
> 50 years	53

Laterality: 4 patients had bilateral penetrating keratoplasty.
Follow Up: The minimum period of follow-up in patients who underwent keratoplasty was 1 year .

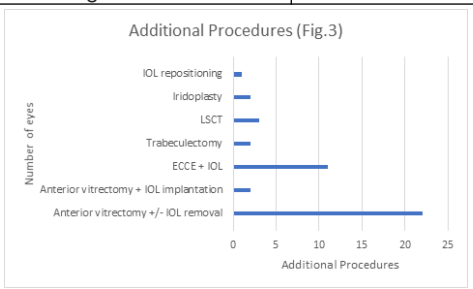


Pre operative diagnosis: (Fig. 2)

The primary pre-operative diagnoses for the 84 eyes undergoing penetrating keratoplasty were as follows:

Table – 2

Pre-operative Diagnoses	Number of eyes
Pseudophakic Bullous keratopathy	21
Aphakic Bullous keratopathy	21
Iridocorneal endothelial syndrome	1
Adherent Leucoma	8
Corneal opacity	13
Fuch's Endothelial Dystrophy	4
Failed graft	13
Keratoconus	1
Atheromatous ulcer	1
Spheroidal degeneration	1



Additional procedures (Fig. 3)

The following table gives the details of additional procedures done.

Table-3

Additional Procedures	Number of eyes
Anterior vitrectomy +/- IOL removal	22
Anterior vitrectomy + IOL	2
ECCE + IOL	11
Trabeculectomy	2
LSCT	3
Iridoplasty	2
IOL repositioning	1

Graft Size & Suturing

In 67 eyes, a graft size of 8.0 X 8.5 mm was performed, in 14 eyes, a graft size of 7.5mm X 8.0 mm was used, and in 3 eyes a graft size of 7.0 mm X7.5mm was used.

In most of the patients single interrupted suturing technique was used.

Choice of suturing technique was at the discretion of the surgeon.

Rejection Rates:

Rejection occurred in 29 eyes out of the 84 eyes (34.52%). Endothelial rejection occurred in 27 eyes, epithelial rejection in one eye and combined endothelial and epithelial rejection in one eye. (Fig. 4)

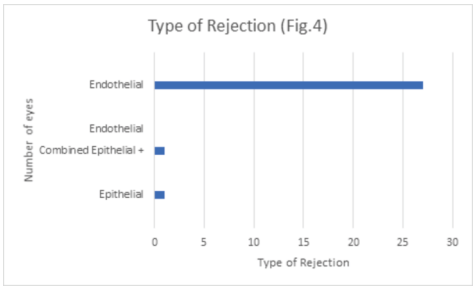


Table - 4

Type of Rejection	Number of eyes
Epithelial	1
Combined Epithelial + Endothelial	1
Endothelial	27

Pre-operative corneal vascularisation was present in 36 eyes, of which 18 eyes had rejection (50%) compared 22.91% in corneas without vascularisation which was statistically significant (P-value = 0.009)

Peripheral anterior synechiae was present in 17 eyes of which 11 eyes had rejection (64.70%) compared to 26.86% in eyes without peripheral anterior synechiae which was statistically significant (P-value 0.005)

Additional intraoperative procedures were performed in 43 eyes of which 16 eyes had rejection (37.20%) compared to 31.70% in eyes where no adl. procedure was performed which was not statistically significant (p value = 0.382)

31 eyes fell under younger age group (≤50 years) of which 14 eyes had rejection (45.16%) compared to 28.30% in older age group (>50 years) which was statistically significant (p-value 0.092)

A larger graft size (>8.5mm) was associated with a higher rejection rate of (38.80%) compared to 17.64% in graft size smaller than 8mm which was statistically significant (P-value = 0.085).

In a majority of the patients, interrupted sutures were used (67 eyes) and the rejection rate in these patients was 32.83%. Continuous suturing technique used in 5 eyes had a rejection of 40%. Combined continuous and interrupted suturing technique was used in 12 eyes of which 50% had rejection which was not statistically significant. (P-value = 0.402). (Fig. 5)

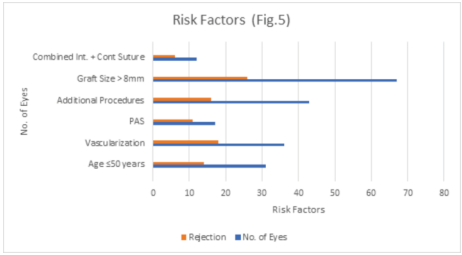


Table – 5

Risk Factors	No. of Eyes	Rejection
Age ≤50 years	31	14 (45.16%)
Vascularization	36	18 (50%)
PAS	17	11 (64.70%)
Additional Procedures	43	16 (37.20%)
Graft Size > 8mm	67	26 (38.80%)
Combined Int. + Cont Suture	12	6 (50%)

The rejection rates for various pre-operative diagnosis were as follows: (Fig.6)

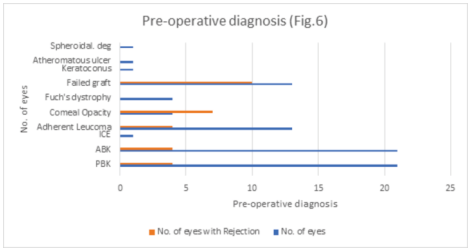


Table-6

Pre-operative diagnosis	No. of eyes	No. of eyes with Rejection
PBK	21	4 (19.04%)
ABK	21	4 (19.04%)
ICE	1	0
Adherent Leucoma	13	4 (50%)
Comeal Opacity	4	7 (53.84%)
Fuch's dystrophy	4	0
Failed graft	13	10 (76.92%)
Keratoconus	1	0
Atheromatous ulcer	1	0
Spheroidal degeneration	1	0

Late graft failure which was defined as irreversible loss of graft clarity in a graft that remained clear for atleast 2 weeks following surgery. occurred in 16 eyes. Rejection was the cause for graft failure in 8 eyes (50%)

Among the 29 eyes which had graft rejection, 8 eyes went for graft failure. (27.58%). In 21 eyes the rejection was reversed without failure by intensive steroid therapy.

DISCUSSION

Corneal transplantation remains the only option for visual rehabilitation for those who are blind from corneal diseases. One of the most important factors that affects the clinical outcome of penetrating keratoplasty is allograft rejection. The high success rate in low-risk corneal transplantation is however overshadowed by the results of corneal grafts placed in high-risk beds even with maximal local and systemic immunosuppression[14]. To establish an optimal treatment for these corneas, the first hurdle remains the definition of high-risk cornea.

Several studies[7,20,26,27,33] have shown the association between these high risk factors and increased incidence of graft rejection.

In a retrospective analysis of 457 participants in the Collaborative Corneal Transplantation Studies by Maguire et al[27], young recipient age, previous failed grafts, previous anterior segment surgery and ABO incompatibility were identified as influential risk factors for rejection.

The Collaborative Corneal Transplantation studies[33] - A randomized, Prospective clinical trial of histocompatibility in corneal transplantation was designed to evaluate the effect of donor recipient HLA matching and cross matching on the survival of corneal transplants in high-risk patients. The study was unable to detect any beneficial effect of such tissue matching on the rate of failure caused by rejection. The CCTS however did found that ABO incompatibility increased the risk of failure from rejection.

In a study done by Boisjoly et al,[7] 35% of the graft failure was preceded by severe rejection. The strongest risk factors for

rejection were presence of recipient corneal vessels, large size of the graft and HLA- incompatibility.

In a longitudinal non-comparative case series[26], which analyzed the factors for specific causes for initial graft failure, deep stromal vascularisation peripheral anterior synechiae, large recipient bed were found to be risk factors for rejection failure. The rate of rejection was 27.9%

Dandona et al[20] found that previous transplant failure, aphakic bullous keratopathy, adherent leucoma, lower socioeconomic status, younger age, vascularisation of the host cornea were associated with poor graft survival.

The rate of rejection in the Swedish Corneal Transplant registry[23] was 15%. In the Corneal transplant followup study[1], the rate of rejection was 12 % The various factors associated with rejection in the corneal transplant followup study were corneal vascularisation, regrafts, young recipient age and pre operative uveitis. In these studies, Keratoconus, corneal dystrophies were the major indications for Keratoplasty where the expected outcome is good. In our study the rate of rejection was 34.52% and the major indications were bullous keratopathy, previous failed grafts and vascularized corneal opacities which explains the higher rejection rate compared to other studies.

In our study, the various risk factors that were associated with high incidence of rejection were previous failed grafts, adherent leucoma, corneal opacity among the various pre-operative diagnosis for keratoplasty. Rejection occurred more frequently if vascularisation was associated with corneal opacity.

Young recipient age, presence of corneal vascularisation and peripheral anterior synechiae were associated with a significant higher risk of rejection. These factors are supported by various studies. [20, 26, 27 17]. There was no statistically significant increase in the risk of rejection between patients who underwent additional procedures during the surgery and who did not.

Larger graft size was associated with a higher risk of rejection. However an unusually small recipient bed size was associated with increased risk of rejection failure in the CCTS[27]. Interpretation of suturing technique as a risk factor is difficult because it was subject to manipulation by the surgeon. Interrupted sutures were used in a majority of the cases considering the advantage of removal to relieve high astigmatism. In the CCTS[27] , interrupted suturing technique was associated with a higher rejection rate Mild rejection alone as opposed to severe rejection were not followed by graft failure. This is in accordance with the observations reported by Musch et al[31]

In this study, rejection was the cause for 50% of the late graft failures, indicating that severe rejections result in a decrease in endothelial cell density, that exceeds expected loss. The drawbacks of this study were inadequate follow up period and relatively small sample size compared to all other studies mentioned.

The identification of risk factors for graft rejection can help surgeons determine which eyes are at increased risk, so that those eyes can be more aggressively treated. A high level of suspicion for allograft rejection should be maintained in high risk transplants so that early recognition of graft rejection episode can be made.

In the advent of graft rejection, early diagnosis and intensive treatment may prevent graft failure.

CONCLUSION

A higher risk of corneal allograft rejection is associated with certain factors like presence of corneal vascularisation, peripheral anterior synechiae, larger graft size, young recipient age and certain preoperative diagnosis like, previous failed graft and adherent leucoma.

Identification of high risk patients and recognition of the clinical risk factors predisposing to allograft rejection should be done before transplantation. This helps the surgeon to plan for aggressive therapy and follow up of these patients.

There should be clear and frequent communication with the patient to describe the symptoms of allograft rejection and to emphasize the importance of prompt evaluation and therapy.

Early diagnosis and intensive treatment of graft rejection may prevent graft failure.

APPENDIX - Abbreviations Used

ACAID -Anterior Chamber Associated Immune Deviation
APC - Antigen Presenting Cells
BCVA - Best Corrected Visual Acuity
CCTS - Collaborative Corneal Transplant Studies
ECCE - Extra Capsular Cataract Extraction
HLA - Human Leukocyte Antigen
IL - Interleukins
IOL - Intra Ocular Lens
LSCT - Limbal Stem Cell Transplantation
MHC - Major Histocompatibility Complex
MK medium - McCarey - Kaufman medium
PAS - Peripheral Anterior Synechiae
PK - Penetrating Keratoplasty

Acknowledgement

We wish to express our heartfelt gratitude to Dr Sujatha Mohan, Medical Director, Rajan Eye Care Hospital, Chennai for her guidance in this study.

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