“FACTORS AFFECTING THE OUTCOME OF CORNEAL REGRAFT”

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ABSTRACT
A prospective case series study to analyze the various factors affecting the outcome of corneal regrafts performed during the period from November 2011-may 2013, at Minto Ophthalmic Hospital and Regional Institute, Attached to Bangalore Medical College & Research Institute, Bangalore, in 25 eyes of 24 patients met our inclusion and exclusion criteria. The following inferences are obtained, We found a equal gender ratio in patients undergoing regraft, with mean age group of about 44years. Cataract and glaucoma were found to be the most common co morbidities in our patients. Almost 92% of our patients had only one previous keratoplasty. Most of the regrafts had a duration ranging from one to three years from the previous graft. Infective corneal ulcers leading to vascularised corneal scars are the most common primary indication, followed by dystrophies. Almost 92% of regrafts are optical compared to 8% of tectonic regrafts. so most of the cases undergoing regrafts in our hospital are for visual purpose. The most common cause of graft failure in our scenario is allograft rejection, followed by glaucoma and graft infections. 36% of our regrafts had clear graft following a period of one and half month, in which 20% cases progressed to graft failure at the end of last follow up. With respect visual acuity only 8% cases shows VA > 6/60 at end of last visit.

KEYWORDS: Regrafts, Visual Acuity, Keratoplasty & Corneal

INTRODUCTION
The main purpose of the majority of corneal grafts is to improve vision, but other benefits for patients include pain relief or even simply saving an eye. With some notable exceptions, many analyses of the outcome of corneal grafting have focused primarily on graft survival and immunological rejection, which still remains the most common cause of early graft failure and the continuing subject of both laboratory and clinical follow up studies. Since many of the factors influencing visual outcome remain uncertain. The emphasis of the study is on visual outcome with the purpose of providing evidence to support or to change current practice in patient selection and the management of grafts. In many reports, the end point for follow up is only 1 year. However, healing after corneal grafting is an extended process and procedures such as suture removal and refractive surgery are most likely to occur after 1 year. We therefore decided to study or analyze the various factors affecting the outcome of corneal regrafts

MATERIALS AND METHODS
Corneal regrafts were attempted in Minto Ophthalmic Hospital and Regional Institute, Attached to Bangalore Medical College & Research Institute. Bangalore, in 25 eyes of 24 patients from November 2011-may 2013.

Inclusion Criteria: Patients giving written informed consent, all graft failure with good prospective
visual outcome. Regrafting of previous therapeutic and tectonic keratoplasty for optical purpose.

**Exclusion Criteria:** Failed grafts with, severe neovascularisation, Secondary glaucoma, Posterior segment pathology & perception of light - negative.

**METHODOLOGY**

Inpatients of Minto Ophthalmic Hospital with failed graft included in study were asked about their history of diminution of vision and its duration and any other associated symptoms. The patients underwent a detailed preoperative examination including visual acuity measurement with snellen’s chart, retinoscopy, and subjective correction, slit lamp examination. Patients were subjected to a detailed examination to rule out any ocular surface disorder or tear film instability with schirmer’s test. Intra ocular pressure was recorded with ton open or digital estimation which ever method was possible. Patients underwent a detailed fundus examination if possible and with hazy media in whom the fundus could not be visualized, underwent a posterior segment ultrasonography. Patients with pathology involving posterior segment and those with glaucoma would affect the final visual outcome were not included in the study. Lacrimal syringing was done to check the patency of the lacrimal system. Investigations were done to rule out systemic illness like diabetes and hypertension. Informed consent was taken from all patients. Donor eyes were obtained from the eye bank, Minto Ophthalmic Hospital and Regional Institute and were graded according to kishinchand chellaram eye bank donor corneal grading.

**RESULTS**

<table>
<thead>
<tr>
<th>Epithelium</th>
<th>Stroma</th>
<th>Endothelium</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Clear and intact</td>
<td>A. Crystal clear</td>
<td>A. No defects</td>
</tr>
<tr>
<td>B. Bedewing, edema+</td>
<td>B. Striate lines SLE</td>
<td>B. Defects+</td>
</tr>
<tr>
<td>C. Defects, edema+</td>
<td>C. Obvious striae</td>
<td>C. Defects++</td>
</tr>
<tr>
<td>D. Extensive defects and</td>
<td>D. Heavy striae</td>
<td>D. Pre existing Disease</td>
</tr>
</tbody>
</table>

The donor eyes were stored in moist chamber at 4°C and where the surgery was deferred for more than 24 hrs after procurement, it was stored in M-K medium and used within 72 hrs.

**Pre Operative Preparation**

The patients were started on oral ciprofloxacin 500 mg BD on the day of surgery in optical cases and existing medications were continued in tectonic cases.

**Anesthesia**

Analgesia and anesthesia were obtained with a mixture of 2% lignocaine with 1:100000 adrenaline with hyaluronidase with facial and peri/ retrobulbar block.

**Surgical Procedure**

Once adequate anesthesia and analgesia was obtained, bridle sutures were passed through the superior rectus muscle lid sutures were placed in few cases. Adequate exposure was obtained with a wire speculum.

**Recipient Bed Preparation**

Recipient bed was prepared first in all cases. The recipient bed was marked with a disposable free hand trephine.
the size ranging from a minimum of 7mm to a maximum of 8mm depending on the case. The trephine was advanced to mark only the superficial stroma. Anterior chamber is entered with the #11 blade at trephined site, viscoelastics were injected then trephination is continued along the marking using corneal scissor taking care margins are well circumscribed and curvilinear. It is performed in all 360°, diseased corneal button is taken out.

Lens Management

Among 25 eyes, 12 were normal phakic eyes, 7 were pseudophakic and 6 were cataractous lens. Those with cataractous lens underwent lens extraction with PCIOL implantation. Rest were kept status quo. Peripheral iridectomy done if not done during the first grafting.

Donor Button Preparation

Donor cornea was obtained from whole globe or MK medium. The donor button was placed in the punch with the trephine of desirable size attached to it. The donor button was placed endothelium up on the Teflon block and a visco placed over it. The donor button was punched with one attempt, the punched out button carefully held with a Hoskins forceps and placed over recipient bed.

Suturing

10-0 ethilon monofilament sutures was used in all cases except two cases where 9-0 was used. In all cases 16 interrupted sutures were placed and knots were buried.

Subconjunctival Injection

A Subconjunctival injection of Gentamicin 20 mg in 0.5ml with 0.5 cc dexamethasone was given in all cases.

POST OPERATIVE MANAGEMENT

Immediate

All patients were started with antibiotic steroid combination eye drops(gatifloxacin and prednisolone). These drops were instilled hourly for initial two weeks and then tapered gradually over a period of three months. Lubricating drops included carboxymethylcellulose 1% or polyvinyl alcohol 1.4% at an hourly dosage and then tapered and maintained at 4-6 times a day. Anti glaucoma medication - Timolol eye drops 0.5% twice daily. Atropine 1% eye ointment thrice daily. Oral prednisolone 1mg/kg body weight was given to required cases (inflammation and rejection). Once the inflammation and rejection signs were came down dose was tapered at 3 days interval. In cases of epithelial defect topical antibiotic steroid was withheld and oculose patchand bandage was done till the defect healed. Systemic antibiotics were continued for 5 days postoperatively in all cases.

The Post Operative Follow Up

All patients were followed up every day for first postoperative week and then second, third, fourth and sixth week for a period of minimum of one and half month to a maximum of one year. In each visit visual acuity, slit lamp examination with special consideration for graft host junction, clarity of the graft, loose sutures, suture infiltrates, vascularisations, signs of graft rejections, infections, and scar noted. Intra ocular pressure was recorded in each visit. Retinoscopy was done at the end of one month if possible. Dilated fundus evaluation done at an interval of one month. Graft outcome was defined in terms of the clarity of the graft over a period of time till the last follow up or graft failure, whichever was earlier.
Table 2: Slit Lamp Grading of Cornea

<table>
<thead>
<tr>
<th>Clear</th>
<th>All Details of Iris Clear and Visible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clear</td>
<td>All Details of Iris Clear and Visible</td>
</tr>
<tr>
<td>Hazy</td>
<td>Corneal haziness that partially obscures</td>
</tr>
<tr>
<td>Opaque</td>
<td>White, totally edematous cornea with or without vascularisation, with or without scarring</td>
</tr>
</tbody>
</table>

Allograft rejection was diagnosed by the presence of endothelial or epithelial rejection line or both and corneal edema with anterior chamber reaction. Corneal graft failure was diagnosed when irreversible graft edema was present with or without vascularisation or scarring of the graft. Intraocular pressure greater than 25 mmHg on two separate occasions was taken as secondary glaucoma with associated slit lamp findings of peripheral anterior synechiae, posterior synechiae and glaucomatous disc changes. As our study was an observational case study, statistical methods for comparison were not applied.

Figure 1: Gender Distribution

Of the 24 patients 12(50%) were male and 12(50%) were females, suggesting equal gender distribution among the people undergoing regrafts.

Figure 2: Age Distribution
The youngest patient was 18 years old and the oldest 70 years of age. The peak distribution was found with 36% of the patients in the age group of 41 – 50 years.

48% had their right eye operated and 52% had their left eye operated. Out of these 1 patient had both eyes operated during this period.

<table>
<thead>
<tr>
<th>Sl</th>
<th>Co Morbidities</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>GLAUCOMA</td>
<td>3</td>
</tr>
<tr>
<td>02</td>
<td>NYSTAGMUS</td>
<td>2</td>
</tr>
<tr>
<td>03</td>
<td>SQUINT</td>
<td>2</td>
</tr>
<tr>
<td>04</td>
<td>MEIBOMITIES</td>
<td>2</td>
</tr>
</tbody>
</table>

Cataract was the most common co morbidity associated, which is followed by glaucoma, squint, nystagmus, and meibomities.
Figure 5: Number of Previous Regraft

For a majority of the patients i.e. 92% it was their first regraft, whereas 8% had their second regraft.

Figure 6: Duration between Grafts

Most of the patients had their regrafs within 1-3 years of the immediate graft. The minimum interval was 20 days and the maximum time interval was 15 years.
Table 3: Primary Indications

<table>
<thead>
<tr>
<th>Primary Indications</th>
<th>Variables</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corneal ulcers</td>
<td>Fungal ulcers</td>
<td>6</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>Perforated ulcers</td>
<td>4</td>
<td>16%</td>
</tr>
<tr>
<td>Dystrophy</td>
<td>CHED</td>
<td>3</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>Macular Dystrophy</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>Degenerations</td>
<td>Fuch’s endothelial Dystrophy</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Spheroidal degeneration</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>Ectasia</td>
<td>Keratoconus</td>
<td>2</td>
<td>8%</td>
</tr>
<tr>
<td></td>
<td>Keratoglobus</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td></td>
<td>Anterior staphyloma</td>
<td>1</td>
<td>4%</td>
</tr>
<tr>
<td>Bullous keratopathy</td>
<td>pseudophakia</td>
<td>2</td>
<td>8%</td>
</tr>
<tr>
<td>Opacity</td>
<td>Adherentleucoma</td>
<td>3</td>
<td>12%</td>
</tr>
</tbody>
</table>

The most common cause in our scenario was ulcers, to be more specific fungal corneal ulcers. These patients had primarily undergone therapeutic keratoplasty to cure the disease followed by a penetrating keratoplasty to restore vision. It was followed by corneal dystrophies and degenerations which accounted for 24% of all cases. Next in the line were ectasia, PBK, and adherent leukoma. A grade cornea was used in 19 cases and B grade in 6 cases. All B grade cornea cases results in failure of graft. In our study 23 cases underwent optical and 2 tectonic keratoplasty. Within that 23 optical keratoplasty 6 were associated with lens extraction and posterior chamber IOL implantation. 36%(9) of our regrafts were successful in terms of graft clarity in the period of one and half month follow up, in that 5 cases shows signs of failure at the end of the last follow up. The number of failed graft summed up to 64%. In that first place is occupied by rejection, followed by glaucoma, primary failure, and infection. We had not taken any of the failed cases for regraft during our study period. At the end of 6 months follow up only 8% of the regrafts had a visual acuity >6/60. 28% of the regraft had visual acuity between 1/60 - 6/60. 8 cases shows graft rejection during follow up period, which was treated by using oral prednisolone 1mg/kg body wt. Secondary glaucoma was developed in 4 cases. These were treated by Timolol eye drop 0.5% BD dose, additional oral tab. Acetazolamide 250 mg TID was used in one case. One case with tectonic graft shows recurrence of infection which was responded to intravenous cefazidime 1gm and metroglyl 100ml BD dose injections. One case had a Persistent epithelial defect which was managed medically. 3 months later he developed vascularisation in 4 clock hrs. One case had intraoperative vitreous disturbance, which was managed by anterior vitrectomy followed by oral prednisolone 1mg/kg body wt.

DISCUSSIONS

The primary purpose of this prospective study is to analyze the factors influencing the outcome of patients undergoing repeat corneal transplantation. A total of 25 eyes of 24 patients who had undergone repeat corneal transplantation between nov 2011 to may 2013 were included in this study and observations made. In our study we observed a equal gender distribution of fifty percent each. Weisbroad et al \(^1\) in their study of 116 patients in Toronto western hospital, observed a slightly greater number of women with a gender ratio of 1.27. Patel et al \(^8\) in their study too made a similar observation with women being around 54% and men 46%. The average age group in our study is 44.32 years. Most of the regrafts done between the age group of 41-50 years that is 36%, it is followed by 31 40 years group(24%). patel et al\(^8\) have observed an average of 68.2 years in their study. Weisbroad et al\(^5\) derived at an average age of 69 yrs from their study. Vanathi et al\(^4\) results were similar to our observations with a mean age of 45.2 yrs.
48% of our patients had their right eye operated and the rest 52% underwent regrafting for the left eye. 1 out of our 24 patients had both their eyes operated. Cataract is the most common co morbidity presenting in 6 of the total 25 regrafts. The cause for the cataract are prolong steroid use, inflammation leading to complicated cataracts and manipulation of lens during the first surgery. It is followed by glaucoma in 4 patients , all are secondary glaucoma’s due to inflammation, peripheral anterior synechiae formation. Other co morbidities in the list are nystagmus and squint in 2 patients, meibomitis present in 2 patients.

The data from our study showed that for 92% it was the first regraft, 8% had their second regraft. so the regrafts which are undergoing in our institution are first regrafts in most of the time, incidence of multiple regrafts are less because of severe neovascularisation, secondary glaucomas,patient’s non-willingness for multiple surgeries. Bersusdky et al\textsuperscript{6} in their study observed 64% underwent first regraft. 31.4% had their second, 3.5% had their 3\textsuperscript{rd} and 1.2% had their fourth. Vanathit et al\textsuperscript{3} had observed an incidence of 69.8% for the first regraft, 26.4% for the second & 3.7% for the third regraft. The average duration between the primary corneal transplantation and regraft was around 3.49 years in our study. most of the regrafts (24%) duration between the surgeries is less than 1 year. It is because in our study most common indication for first grafting is infective corneal ulcers undergoing therapeutic penetrating keratoplasty, so need of undergoing regraft is more for visual purpose. duration between surgeries is more in cases of corneal dystrophy and ectactic conditions as outcome of first graft is better than former. Patel et al\textsuperscript{8} observed the average number of years between the first and second corneal transplant varied depending on the initial diagnosis and ranged from 3.3 years for eyes with corneal ulcers to 19.8 years for the eyes with keratoconus. In their prior study from 1983 to 1988 the time interval for keratoconus was 18.5 years and 3.3 years for pseudophakic bullous keratopathy. The primary indication for repeat corneal transplantation deferred from those for single transplantation. The most common primary indication in repeat corneal transplant group was corneal ulcers most commonly fungal , producing a vascularised scar for which grafting was done or cases which undergo keratoplasty for therapeutic purposes. as our institution receives most of the bad corneal ulcers which are untreated in the periphery needs therapeutic keratoplasty. So these cases in feature undergo regraft for optical purpose. So most common primary indications in our study of regraft is fungal corneal ulcers(40%). This was followed by dystrophies(24%) like congenital hereditary endothelial dystrophy, macular dystrophy, fuch’s endothelial dystrophy, ectasia(16%) and pseudophakic bullous keratopathy(8%). Robinson\textsuperscript{43} reported that corneal dystrophies and bullous keratopathy have been the most common primary indications for repeated grafts. In their study Insler and Pechous\textsuperscript{44} reported an incidence of 17% of bullous keratopathy and herpetic keratitis for repeated grafts. Later studies reported that PBK and ABK were the most common primary indications for repeated transplantation. (39%)\textsuperscript{29,30,39} The increased proportion of PBK and ABK in repeated corneal transplantation may have been attributed in these studies to the increased frequency of cataract surgery and the use of certain IOLs\textsuperscript{30}. We found fewer cases of PBK and ABK compared with previous reports. This may reflect the trend towards using newly designed IOLs including flexible, open loops anterior and posterior IOLs, which replace the old iris clipped and rigid, closer loops anterior chamber IOLs. The number of eyes left aphakic even when cataract surgery was complicated by posterior capsular rupture has been decreased remarkably, thus the number of eyes with ABK was also decreased as an indication for keratoplasty. Patel et al\textsuperscript{8,7} too found pseudophakic bullous keratopathy contributing to 27%, 20% due to multiple regrafts followed by Fuch’s Dystrophy 11%, and aphakic bullous keratopathy 9%. Weisbroad et al\textsuperscript{5} too found pseudophakic bullous keratopathy head the list. Vascularised corneal scars may be the common outcome of ocular trauma,. Herpes simplex keratitis, trachoma, chemical burns and other causes. Corneal vascularisation causes the loss of the immune privilege of the avascular cornea and increased exposure for non self
antigens. In our study vascularised scars mostly due to infectious keratitis clearly topped the list, moreover corneal vascularisation increases the likelihood for corneal graft rejection, which is the major cause for graft failure in repeated transplantation. Vanathi et al\textsuperscript{4} inferred similar results in her study of 50 patients over a period of 3 years. In their study 66\% of the patients had vascularised corneal scars as their primary indication. Bersudsky et al\textsuperscript{6} also had similar inference from their study in which vascularised corneal scar contributed to a majority of 36\% followed by pseudophakic and aphakic bullous keratopathy at 14\% and 8\% each respectively. In our study A grade cornea was used in 76\% of cases and B grade in 24\% cases. Different success rates and visual outcomes in corneal regrafts have been reported in literature\textsuperscript{5,6,8,44}. Reported percentages of clear regrafts vary from 51\% to 74\% in the earlier studies. However in our study we observed clear grafts in only 36\% of the cases. Many studies have highlighted rejection and recurrence of dystrophies as the major cause of graft failure, but most of these studies were carried out in the developed countries. In a developing country like ours, the scenario slightly differed. We still had graft rejection as the predominant cause, secondary glaucoma, primary graft failure and graft infections were next in order. Vanathi et al\textsuperscript{4} in their study found graft infections to be the leading cause 47.2\%, recurrence of primary condition in 36\%, uncontrolled glaucoma in 20\% and 16\% due to allograft rejection. Insler and Pechous\textsuperscript{44} had 64.5\% of their grafted eyes failing due to rejection. Bersudsky\textsuperscript{6,45} observed immune rejection, raised intraocular pressures and corneal ulcer to be responsible for graft failure in decreasing order of frequency in his study. Recent studies have reported a visual acuity of 6/18 or more in only 15 to 41\% of the clear grafts. In our study out of 9 clear eyes 8\%(2 cases) had a visual acuity of 6/60 and better. Contrary to studies reporting that visual prognosis in multiple regrafts to be comparable to that in single grafts. Bersudsky et al\textsuperscript{6} had concluded that graft survival and visual outcome is inversely proportional to the number of corneal regrafts. Similarly our study also demonstrates a poorer visual outcome in eyes undergoing multiple regrafts, we had a total of 2 patients, 4 had vision less than 1/60. Owing to the poor graft survival, permanent keratoprosthesis may be a suitable alternative.8 patients were documented to have rejection. All are endothelial rejection with 2 eyes having associated epithelial rejection. The clinical symptoms associated are pain, diminution of vision, and redness. All cases are treated with oral steroid, in spite treatment all cases end up with graft failure. The peak time of rejection is around 5 weeks. Another inference is also made from our study, 2 patients had episodes of primary graft failure. The major drawbacks of our study is small sample size and short post operative follow up period.

CONCLUSIONS

It has been well established that grafts for certain indications fail and often do so repeatedly. The study demonstrates that visual prognosis for multiple corneal grafting is suboptimal, owing to high chance of rejection, secondary glaucoma’s and graft infections. It also highlights the changing trends in the indications of repeat keratoplasty towards vascularised corneal scars. However repeat penetrating keratoplasty should be considered when required depending on patient’s need and motivation and in the absence of contraindication.

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APPENDICES

Colour Plate 1: Primary Indications
- Fungal Corneal Ulcers
- Macular Dystrophy

Colour Plate 2: Preparation of Corneal Button
Colour Plate 3: Failed Grafts

Colour Plate 4: Keratoplasty Procedure
Colour Plate 5: Post Op Day 1

Post Op – 6 Weeks

Colour Plate 6: Complications Graft Rejection
Graft Failure with Secondary Glaucoma