Repeat penetrating keratoplasty: indications and prognosis, 1995-2005

ZULEYHA YALNIZ-AKKAYA, AYSE BURCU NUROZLER, ELVIN HATICE YILDIZ, MUSTAFA ONAT, KORAY BUDAK, SUNAY DUMAN

Department of Ophthalmology, Ankara Training and Research Hospital, Ankara - Turkey

INTRODUCTION

Corneal transplantation surgery is the most successful tissue transplantation procedure in humans. The increased success rate in corneal grafting of low risk patients is the result of improved surgical techniques, better donor tissue storage, appreciation of the varied clinical manifestations, and improved medical management of allograft rejection (1, 2). For these reasons, corneal grafting is now undertaken routinely for conditions that were previously considered inoperable (2, 3). Many factors that have adverse influence on graft survival are known; these factors may be present before, during, or after surgery. It is generally agreed that a previous graft failure from rejection is associated with a higher risk of subsequent rejection (2, 4, 5).

We reviewed the hospital charts of penetrating keratoplasties (PK) over the past 10 years, and compared indications and outcomes of eyes undergoing single graft with those of eyes requiring regrafting during the same period.

METHODS

This study was approved by the Human Research Ethics Committee at Ankara Training and Research Hospital, Ankara, Turkey. The records of all patients who underwent
PK between January 1, 1995, and December 31, 2005, were reviewed retrospectively. Patients with less than 6 months follow-up were excluded from the study, and those who required regraft were identified. Data obtained from the records included the age of patients, total number of grafts performed, duration of follow-up, initial indications for corneal grafting, allograft reaction, graft clarity, reasons for graft failure, final postoperative best-corrected visual acuity, and conditions leading to reduction in vision in clear grafts. When the patient was first seen at our hospital with a failed graft for which we were unable to determine the primary indication and the cause of graft failure, initial indication was classified as unknown. Data of the visual acuity and graft clarity from the last clinical visit were used. Any graft that was not entirely clear within about 3 mm central area around the visual axis was classified as opaque (6).

In every case, donor tissue had been removed within 6 hours of death and stored in the storage medium (Optisol; Chiron Vision, Claremont, CA). Donor button had been punched from the endothelial side, 0.25–0.50 mm larger than the recipient opening. The graft was sutured in place using a 10-0 monofilament nylon continuous or interrupted suturing after placing 10-0 monofilament fixation sutures. Cohesive Ocular Viscoelastic Device (Healon®, Pharmacia, Uppsala, Sweden) was used in all cases, and anterior vitrectomy was performed when indicated. A subconjunctival injection of corticosteroid and antibiotics was given to all patients at the end of the procedure. All patients received postoperative corticosteroid eyedrops for 1 year. The dosage of steroid was individualized according to each patient’s clinical course. Antimicrobial, antiglaucomatous, and systemic immunosuppressive medications and artificial tears were used whenever necessary.

An episode of allograft rejection was diagnosed according to having one or more of the following: graft edema, endothelial rejection line (Khodadoust line), keratic precipitates, or increased aqueous cells (5).

Corneal edema that developed within the first or 2 days after surgery and unresponsive to steroids and hypertonic solutions for 3 weeks was accepted as primary donor failure. In the presence of early postoperative hypotension without wound leaks, we waited enough time for the resumption of ciliary body normal functions before diagnosing primary donor failure (7).

Late endothelial failure was defined as a gradual and irreversible loss of graft clarity after the 2-week postoperative period of clear graft function. The loss of graft clarity was due to decline in endothelial cell count that led to stromal edema and graft opacification and was unresponsive to corticosteroids. Factors that lead to secondary graft failure by causing rapid decline in endothelial cell numbers such as recent history of rejection episode or current rejection episode, endothelial contact with an intraocular lens or vitreous, anterior synechiae, uveitis, further intraocular surgery, eye trauma, and increased intraocular pressure were absent. All these causes for secondary graft failure including previous episodes of allograft rejection that were appropriately treated may later contribute to late endothelial failure.

Patients were grouped into two categories: those requiring single graft (Group I) and those requiring regrafts (Group II). The results were evaluated on the following criteria: primary indications, allograft reactions, graft clarity, causes of graft failure, final postoperative best-corrected visual acuity, and conditions leading to reduction in vision in clear grafts. Data analysis was made by SPSS 11.0 program. Outcome proportions were compared between the groups by using chi-square test and Fisher exact chi-square test for independence. Any p value <0.05 was considered statistically significant.

RESULTS

A total of 705 eyes of 665 patients underwent PK. Forty patients underwent bilateral PK. A total of 652 eyes of 613 patients (379 male, 234 female) with a mean age of 36.2±20.5 years (range 2–90 years) required single graft (Group I). The mean follow-up time was 23.4±21.3 months (range 6–132 months) in Group I. After the first year, many PK patients were followed up at their distant hometowns, thus their follow-up times remained shorter. Fifty-three eyes (7.5%) required more than one graft (Group II). The regraft group comprised 53 eyes of 52 patients (35 male, 17 female) with a mean age of 37.6±18.2 years (range 2–70 years). Sixty-one regrafts were performed on 53 eyes. Forty-six eyes had two grafts; 6 eyes had three grafts, 1 eye had four grafts. The mean follow-up, defined as the time from the last graft until the last clinical attendance, was 25.0±25.6 months (range 6–108 months). No statistical differences were found between groups concerning gender and age (p=0.526 and p=0.320, respectively).

The results of the study were further analyzed to determine the factors affecting graft survival and visual outcome. The primary indications for PK were then categorized into groups (non-infectious and infectious conditions). The results showed a statistically significant difference in graft survival rates between the two groups (p=0.034). The study also demonstrated that the use of topical corticosteroids and antibiotics was associated with a higher rate of graft failure (p=0.001). Overall, the study highlighted the importance of careful patient selection and surgical technique in achieving better outcomes in PK.

Table I shows the distribution of the initial indications for PK in groups. In Group I, keratoconus was the most common indication for PK.
mon indication (228 eyes; 35.0%), followed by vascularized corneal scar (93 eyes; 14.3%), bullous keratopathy (90 eyes; 13.8%), herpetic keratitis (72 eyes; 11.0%), and the other smaller groups. In Group II, vascularized scar (12 eyes; 22.6%) was the most common diagnosis, followed by keratoconus (6 eyes; 11.3%), herpetic keratitis (5 eyes; 9.4%), corneal dystrophy (4 eyes; 7.5%), and bullous keratopathy (2 eyes; 3.8%). In Group I, 38 dystrophies were Fuchs, 10 macular, 7 granular, and 3 lattice. In Group II, 2 dystrophies were Fuchs and 2 macular. In Group II, primary indications of 14 patients were unknown because their first PKs were performed at a different clinic. The difference between the groups was significant mainly due to the higher percentage of keratoconus and bullous keratopathy in the single graft group (p=0.000 and p=0.037, respectively). On the other hand, the proportion of ocular surface disease was significantly higher in the regraft group (p=0.043).

Allograft reactions occurred in 96 eyes (14.7%) in Group I and 17 eyes (32.1%) in Group II. The difference was significant between the groups (p=0.001). The rate of reversibility was 34.3% (33/96) in the single graft group and 17.6% (3/17) in the regraft group (p= 0.259). Sixty-three grafts in Group I (65.5%) and 14 grafts (82.3%) in Group II did not respond to rejection therapy and failed.

At the end of the study period, the clarity rate was achieved in 76.4% (498/652) of patients in the single graft group and 45.3% (24/53) of patients in the regraft group. Entirely clear graft was seen in the regraft group, significantly less than was seen in the single graft group (p=0.000).

Table II demonstrates the conditions leading to the graft failure in each group. In Group I, the main cause of corneal graft failure was irreversible allograft rejection (63 eyes, 9.7%). The second main cause was endothelial failure without evidence of allograft rejection in 39 eyes (6.0%). Of those 39 eyes, 8 were primary endothelial failure, 13 were late endothelial failure, and 18 were glaucoma related endothelial failure. The third main cause was graft infection (18 eyes, 2.8%) in Group I.

In Group II, irreversible allograft rejections occurred in 14 (26.4%) eyes, graft infection in 6 (11.3%) eyes, and endothelial failure without evidence of allograft rejection in 1 (1.9%) eyes. Table II demonstrates the conditions leading to the graft failure in each group. In Group I, the main cause of corneal graft failure was irreversible allograft rejection (63 eyes, 9.7%). The second main cause was endothelial failure without evidence of allograft rejection in 39 eyes (6.0%). Of those 39 eyes, 8 were primary endothelial failure, 13 were late endothelial failure, and 18 were glaucoma related endothelial failure. The third main cause was graft infection (18 eyes, 2.8%) in Group I.

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### Table I - Primary Indications for All Grafts

<table>
<thead>
<tr>
<th>Indications</th>
<th>Group I (single graft), n (%)</th>
<th>Group II (regraft), n (%)</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keratoconus</td>
<td>228* (35.0)</td>
<td>6 (11.3)</td>
<td>234 (33.2)</td>
</tr>
<tr>
<td>Nonspecific vascularized scar</td>
<td>93 (14.3)</td>
<td>12 (22.6)</td>
<td>105 (14.9)</td>
</tr>
<tr>
<td>Bullous keratopathy (aphakic, pseudophakic)</td>
<td>90* (13.8)</td>
<td>2 (3.8)</td>
<td>92 (13.0)</td>
</tr>
<tr>
<td>Herpetic keratitis</td>
<td>72 (11.0)</td>
<td>5 (9.4)</td>
<td>77 (10.9)</td>
</tr>
<tr>
<td>Corneal dystrophy†</td>
<td>58 (8.9)</td>
<td>4 (7.5)</td>
<td>62 (8.8)</td>
</tr>
<tr>
<td>Trauma</td>
<td>36 (5.5)</td>
<td>2 (3.8)</td>
<td>38 (5.4)</td>
</tr>
<tr>
<td>Descemetocle‡ (± perforation)</td>
<td>29 (4.4)</td>
<td>1 (1.9)</td>
<td>30 (4.3)</td>
</tr>
<tr>
<td>Ulcer</td>
<td>14 (2.1)</td>
<td>1 (1.9)</td>
<td>15 (2.1)</td>
</tr>
<tr>
<td>Chemical and thermal injuries</td>
<td>10 (1.5)</td>
<td>2 (3.8)</td>
<td>12 (1.7)</td>
</tr>
<tr>
<td>Ocular surface diseases</td>
<td>8 (1.2)</td>
<td>3* (5.7)</td>
<td>11 (1.6)</td>
</tr>
<tr>
<td>Band keratopathy</td>
<td>3 (0.5)</td>
<td>1 (1.9)</td>
<td>4 (0.6)</td>
</tr>
<tr>
<td>Congenital glaucoma</td>
<td>3 (0.5)</td>
<td></td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Others‡</td>
<td>3 (0.5)</td>
<td></td>
<td>3 (0.4)</td>
</tr>
<tr>
<td>Degeneration</td>
<td>2 (0.3)</td>
<td></td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Corneal blood staining</td>
<td>2 (0.3)</td>
<td></td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>Sclerocornea</td>
<td>1 (0.2)</td>
<td></td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>14 (26.4)</td>
<td></td>
<td>14 (2.0)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>652</strong></td>
<td><strong>53</strong></td>
<td><strong>705</strong></td>
</tr>
</tbody>
</table>

*Caused by infections other than herpetic keratitis.
†In Group I: 38 Fuchs, 10 macular, 7 granular, 3 lattice. In Group II: 2 Fuchs, 2 macular.
‡Entire loss of stromal thickness after the control of the primary factors including herpetic infection, bacterial infection.
§Others (uveitis, glaucoma, refractive surgery, silicone oil).
*Significant difference between the groups (p<0.05).
related endothelial failure). Best-corrected visual acuities at the last clinic visit are shown in Table III. In the single graft group, visual acuities were 20/40 or better in 189 eyes (29.0%), between 20/50 and 20/100 in 188 eyes (28.8%), and 20/100 or less in 270 eyes (41.4%). In the regraft group, 5 eyes (9.4%) achieved a final visual acuity of 20/40 or better, 6 eyes (11.3%) between 20/50 and 20/100, and 41 eyes (77.4%) 20/100 or less. Due to lack of patient cooperation, visual acuity was not measured in 5 (0.8%) patients in the single graft group, and in 1 (1.9%) patient in the regraft group. All of the non-cooperative patients had opaque grafts. A best-corrected visual acuity of 20/100 or better was achieved in 377 eyes (57.8%) in the single graft group, and in 11 eyes (20.7%) in the regraft group (p=0.000). Conditions leading to visual reduction in clear grafts are demonstrated in Table IV.

In the regraft group, more than two keratoplasties were required in seven patients. The initial clinical diagnoses of these seven patients were vascularized corneal scar (four patients), corneal ulcer (one patient), ocular surface disease (one patient), and an unknown cause (one patient). At the end of the study period, only two eyes had clear grafts. No patients achieved a final visual acuity of 20/100 or better.

DISCUSSION

Repeated corneal transplantation has become an important and increasingly common indication for PK. Many corneal surgeons, however, are hesitant to perform a repeated PK because of the poorer prognosis for visual recovery and graft survival. Several studies have been published in the past few years to investigate the indications for PK. The proportion of regrafts ranged from 8% to 41% in recent studies (8-14). Concerning all keratoplasties, regrafts were reported to be the second most common indication according to Liu et al (14) and Flowers et al (11), the third most common indication according to Mamalis et al (12), and the fifth most common indication according to Lindquist et al (13). In our study, the proportion of regrafts was found to be 7.5%.

In this study, concerning all the patients who underwent PK, keratoconus was the leading primary indication. The most common primary indications were vascularized corneal scar in the regraft group and keratoconus in the single graft group. According to the report of Vanathi et al,
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One common indication for primary PK is herpetic keratitis, which leads to corneal scar, threats of perforation, or perforation itself. Advances in the treatment of herpes simplex keratitis, especially the use of acyclovir and steroid combination, resulted in increased success rates after PK (21-23). However, the extent of inflammation and vascularization of the eye at the time of surgery along with the duration of follow-up after the primary transplantation are factors affecting the requirement for regrafting. In our study, herpetic keratitis was the fourth and third primary indication leading to primary and repeated PK, respectively.

In this study, corneal dystrophy ranks in fifth place for primary transplants and fourth for regrafts. Ocular surface diseases and chemical burns leading to stem cell destruction were significantly higher in the regraft group than in the single graft group (p=0.043).

Table V shows the most common three primary indications for PK in repeated grafts in the current study and in the previous studies reported by different authors. As a result of better primary health care management, pseudophakic and aphakic bullous keratopathy are the leading primary indications in most of the studies reported from developed countries, whereas vascularized scar was found to be the most common primary indication for repeat PK in the current study and in the study reported from the other developing country (15), as demonstrated in Table V.

At the end of the follow-up period, graft clarity rate was significantly lower, as expected, in the regraft group than in the single graft group.
in the single graft group (45.3% and 76.4%, respectively, p=0.000). The graft clarity rates in both groups are lower in this current study than in numerous previously reported studies (6, 8, 15, 19, 20). The main reasons for this result are the classification of any graft that was not entirely clear within the visual axis as an opaque graft and the long follow-up time.

In the regraft group, the most common reasons for failure were allograft rejection (26.4%) and graft infection (11.3%). Allograft rejection was found to be statistically higher in the regraft group than in the single graft group (32.1% and 14.7%, respectively, p=0.001). However, there was no difference concerning reversibility of the rejection reaction between the groups (p=0.259). Naacke et al reported that the rejection is reversible in the half of the cases and irreversible rejection is higher in the regrafs and bullous keratopathy than in keratoconus and Fuchs dystrophy (16). The reversibility rates according to other authors are reported to be 57.3–92.0%, which are better than our results (34.3% in single grafts and 17.6% in regrafs) (5, 16, 27-30). This could partly be explained by the fact that our institution is a tertiary care center, with a large proportion of patients living far away, leading to late initiation of corticosteroid therapy. The degree of vasculatization and the increased sensitivity of the host at the first transplantation are important factors triggering rejection in the regrafs. Rejection episodes can be treated effectively if identified early. The Collaborative Corneal Transplantation Studies Research Group reported that 44% of patients had vision loss at the first rejection (24). Teaching patients about the symptoms of rejection is very important for early diagnosis and treatment. Nevertheless, only about 30% of patients without symptoms are diagnosed with rejection at the routine examinations (5).

Although endothelial failure without evidence of allograft rejection was found to be higher in the regraft group (9.4%) than the single graft group (6%), the difference was not significant (p=0.315). At the end of the follow-up time, one case in the single graft group and three patients in the regraft group ended with phthisis.

Visual acuity was 20/100 or higher in 57.8% of patients in the single graft group and 20.7% of patients in the regraft group (p=0.000). The disease process necessitating multiple regrafting may carry a poorer prognosis for sight (6). Such repeated surgeries lead to a number of problems such as cataract, intraocular pressure elevation, retinal detachment, and macular edema as well as host sensitization and tendency to rejection (6, 26). In our study, final visual acuities were found to be lower than 20/100 in all the patients undergoing multiple regrafs. These complications lead to impaired visual acuities even in the presence of clear grafts. In our study, 18.6% of primary graft patients and 24.5% of regraft patients have low visual acuities despite clear grafts. In the regraft group, cataract (5.7%), retinal detachment (5.7%), and glaucomatous optic disc atrophy (3.8%) were more frequent causes leading to decreased vision than in the single graft group.

Appropriate case selection and effective use of immuno-suppressive agents in preventing and treating rejection episodes can improve graft clarity or final visual acuity. In conclusion, the incidence of graft failure is higher and the level of visual rehabilitation attained is less effective in the regraft group than in the single graft group. Despite the limitations in regrafting, such as suboptimal visual gain and decreased graft clarity rates, regrafting should be done particularly in motivated and realistic patients whose quality of life is expected to improve significantly after surgery; otherwise keratoprosthesis should be considered as an alternative surgical treatment.

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Reprint requests to:
Zuleyha Yalniz-Akkaya, MD
Mithatpasa cad. 48/18 Kizilay
06240 Ankara, Turkey
zyalniz@yahoo.com

REFERENCES

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