Endothelial Cell Loss Rate Following Penetrating Keratoplasty: Optical versus Therapeutic Grafts

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Research Article

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Abstract

Purpose: To compare the rate of endothelial cell loss (ECL) following penetrating keratoplasty (PKP) for optical and therapeutic indications and to state whether therapeutic PKP is inferior to optical PKP or not.

Methods: This is a Prospective, observational, comparative study that included patients who sought medical advice at the Cornea Outpatient Clinic of Ain Shams University Hospitals. The study enrolled two groups; group 1 included 30 corneas of 30 patients who performed optical PKP for various purposes, while group 2 comprised 30 corneas of 30 patients who were planned for performing therapeutic PKP for unhealed, resistant corneal infections. Specular microscopy was done to all the patients at the 3-, 6- and 12-months visits using Nidek CEM-530 (NIDEK Co., Ltd. Japan) specular microscope.

Results: There were no statistically significant differences between both groups as regards to the timing of the graft clarity following surgery or the rate of ECL at the 3- and 6- months intervals, yet the rate of ECL was significantly higher in group 2 compared to group 1 at the 12 months interval (P-value <0.05), though the statistical difference was narrow from a clinical point of view. There was also no statistically significant difference between both groups regarding the rate of graft rejection.

Conclusion: Therapeutic PKP can be considered non-inferior to optical PKP regarding the graft viability, the rate of ECL, and the rate of graft rejection along a follow up interval of one year.

Introduction

The corneal diseases are the second major cause of blindness worldwide after cataract. They comprise a wide range of ectatic, infectious, and inflammatory disorders, where the prevalence of such diseases is variable across different countries and populations depending on the availability and the general standards of eye care [1].

The mainstay of treatment for infectious keratitis is the frequent application of topical antimicrobial agents. Although this modality of treatment commonly eliminates the infectious agent, there is an uprising incidence of resistance to the antimicrobial agents [2,3]. Accordingly, other modalities for proper management should ensue, including mainly keratoplasty as a presumably effective surgical intervention. Therapeutic keratoplasty may be needed in a significant portion of corneas with resilient infectious keratitis. There are also other indications for surgical intervention in corneal infections (other than the resistance to antimicrobial agents), which are progressive corneal thinning, descemetocele, and perforated corneal ulcers [4].

Besides therapeutic keratoplasty, optical keratoplasty is another common indication for performing corneal transplantations in cases of significant corneal scars following Keratoconus (KC) or healed corneal infections. It can help the patient to restore the corneal clarity and thus to attain a good visual performance [5].

Following penetrating keratoplasty (PKP), either for therapeutic or optical purposes, both the postoperative visual acuity and the graft clarity are related to many complex physiological and immunological conditions, as restoring the anatomical integrity of the globe cannot on its own guarantee the improvement of vision [6]. Previous studies have demonstrated the importance of both the endothelial cell density (ECD) and the rate of endothelial cell loss (ECL) as major physiological determinants for maintaining the graft clarity and survival after performing the PKP [7].

The ECD of the donor's graft is an unstable parameter that is amenable to change with time. In the transplanted corneal graft, a progressive ECL can occur in many instances. The underlying reasons for this observed ECL, even years after the PKP, are poorly understood. Some factors in the donor's graft have been shown to play a major role, including the donor's age, the pre-operative ECD, the death-to-preservation time, and the storage media used for preserving the graft. Other factors in the recipient have been reported to affect the rate of ECL, including mainly significant surgical traumas, the development of up-shoots of intraocular pressure "IOP", and/or attacks of graft rejection [8].

To date, no studies have compared the rate of ECL between optical and therapeutic corneal grafts. Hence, the aim of the present study was to evaluate the survival rate of optical and therapeutic PKPs, and to compare the rate of ECL between both types of corneal grafts.

Patients And Methods

This is a prospective, observational, comparative study that included patients who sought medical advice at the Cornea Outpatient Clinic of Ain Shams University Hospitals, Cairo, Egypt. All the enrolled subjects attended the clinic in the period from July 2019 to June 2020.The study abided by the ethical standards of the Ethical Committee of Ain Shams University. All the participants were informed about the nature of the study and informed consents were signed before their participation.

The study included patients with an age range of 17 to 76 years. We excluded candidates with any clinically detected posterior segment pathology, and any corneas having factors that would possibly alter the postoperative rate of ECL, including mainly preoperative glaucoma, the occurrence of any intraoperative complications that would compromise the corneal endothelium, any postoperative increase of the intra-ocular pressure (IOP), steroid responders, and any detected postoperative attacks of endothelial graft rejection.

For all participants, a full ophthalmological examination was performed before and after the surgical intervention, including Unaided Distance Visual Acuity (UDVA), Corrected Distance Visual Acuity (CDVA), complete slit lamp examination, and fundus examination using fundus biomicroscopy. Investigations like B-scan in cases with blurred or no fundus view and electrophysiological tests to determine the postoperative visual potential were also done when required.

The study enrolled two groups; group 1 included 30 corneas of 30 patients who performed optical PKP for various purposes, while group 2 comprised 30 corneas of 30 patients who were planned for

performing therapeutic PKP for unhealed, resistant corneal infections.

For all the chosen participants, the PKP was performed by using corneal grafts with a viability of no more than the 11th day post-preservation. Besides, all the enrolled donors' grafts were sutured to the recipients' beds using a fixed number of sutures (16 sutures for all cases), and all the included cases were performed by the same surgeon (M.O.Y.).

Post-operatively, all the patients were examined at the 3rd day, 10th day, and then at 1-, 3-, 6-, 9- and 12-months visits. Standard post-operative treatment was prescribed for patients in both groups (prednisolone acetate 1% 6 times daily with gradual withdrawal combined with topical Moxifloxacin 3 times daily for 10 days or until full epithelization of the graft). As regards to the therapeutic PKP group, twelve cases were categorized as high-risk cases for reinfection, based on the peripheral location of the infection preoperatively. These cases received intense antimicrobials postoperatively for 2 to 3 weeks till reassuring that no re-infection occurred in the graft bed. This was in the form of fortified vancomycin (25mg/ml) together with fortified ceftazidime (50mg/ml). For fungal infections, topical fluconazole (2mg/ml) was added following the same regimen of anti-microbials.

In the enrolled participants, the grafts were considered clear postoperatively when there were not any detected Descemet's or stromal folds on slit lamp examination in comparison with the other normal patients' eyes.

Specular microscopy was done to all the patients at the 3-, 6- and 12-months visits using Nidek CEM-530 (NIDEK Co., Ltd. Japan) Specular Microscope. The images were captured according to the respective guidelines of the device user manual. Subjects were seated and properly positioned. Then they were asked to fixate on the internal target within the device, followed by a rapid complete blink to ensure a smooth spread of the tear film. The corneal endothelium was evaluated at the central area using the auto-analysis mode. The ECD was then recorded and analyzed.

Statistical analysis

Data were collected, revised, coded and entered to the Statistical Package for Social Science (IBM SPSS) version 23. The quantitative data were presented as mean, standard deviations and ranges (being parametric), and qualitative variables were presented as numbers and percentages. The comparison between groups with qualitative data was done by using Chi-square test. The comparison between the two groups with quantitative data and parametric distribution were done by using Independent t-test. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant if < 0.05.

Results

The study started with 60 eyes of 60 patients (30 eyes in each group), however we excluded 5 eyes from group 1 (2 eyes which developed attacks of graft rejection, and another 3 eyes which developed

postoperative up-shoots of IOP), and we also excluded 10 eyes from group 2 (6 eyes with attacks of graft rejection, 2 eyes which developed up-shoots of IOP, and 2 cases who had re-infection on top of the therapeutic graft). Thus, our statistical analysis was performed on 25 patients in group 1 and 20 patients in group 2.

The mean patients' age in group 1 and 2 was 43.70 ± 14.79 and 47.27 ± 14.51 years, respectively. The female to male ratio for group 1 was 1:1.33 and for group 2 was 1:1.42, and the percentage of right to left eyes was 44.9% to 55.1% for group 1 and 54.3% to 45.7% for group 2. There were no statistically significant differences between the two groups regarding any of these demographic parameters. Moreover, the IOP measurements, fundus biomicroscopy, and B-scan or electrophysiological studies that were performed were all unremarkable.

The details of the indications for the PKP, the donor's age, the time interval from death to graft preservation, the preservation time of the graft, and the initial ECD of the donor's graft for both groups are all detailed in table 1. The results declared the absence of statistically significant differences between both groups regarding any of the aforementioned factors, except for the ECD of the donor's graft, which was significantly less in group 2 compared to group 1 (P-value<0.01).

As regards to the graft clarity, 90.4% and 77.2% of the grafts of groups 1 and 2, respectively, gained clarity at the 10th post-operative day, with no statistically significant difference between both groups. The graft clarity reached 100% for both groups by the 1-month follow up visit.

Regarding the rate of ECL at the 3-, 6- and 12-months postoperatively (table 2), no statistically significant differences were found between both groups at the 3- and 6-months intervals, yet the rate of ECL was significantly higher in group 2 compared to group 1 at the 12- months interval (P-value<0.05).

The results highlighted that for the PKP cases which were discarded from the statistical analysis, the transplanted grafts were rejected in 2 cases in group 1 and in 6 cases in group 2, which was a statistically non-significant difference (P-value:0.129). There was also no statistically significant difference in the number of steroid responders between both groups (3 cases in group 1 and 2 cases in group 2). Besides, only two grafts in group 2 were re-infected.

Discussion

This presumably novel study evaluated the graft survival and compared the rate of ECL along one year following both optical and therapeutic PKPs. The corneal grafts in both groups showed graft clarity in all cases after one month and remained clear till the end of the study period. The rate of ECL for both groups showed non statistically significant differences, except at the 12- months visit, where there was a statistically significant (yet clinically narrow) increase in the rate of ECL in group 2 compared to group 1.

In our two recruited groups, there was a significant difference between both groups regarding the initial ECD of the donor's graft, where cases of group 1 had significantly higher values of ECD compared to

group 2. This can be explained by the usual tendency towards selecting the better grafts for the cases of optical PKPs rather than the therapeutic PKPs, since the former are claimed to have a better prognosis. Also, the emergency nature of the therapeutic PKPs sometimes obliges surgeons to use the available grafts. Yet, we believe that this did not alter the credibility of our study results, as we mainly compared the grafts between the two groups regarding the rate of ECL rather than the ECD on its own.

In our study, we found that the rate of ECL in group 1 was 29.90% ± 2.19, 39.27%± 1.97, and 49.06% ± 2.83 at 3-, 6-, and 12-months intervals, respectively, while it was 30.77% ± 1.53, 39.29% ± 1.91, and 50.65% ± 1.59 in group 2. To the authors' knowledge, no previous studies explored the rate of ECL for cases of therapeutic PKP. Regarding the optical PKP cases, the rate of ECL in this study is very comparable to the study by Obata et al.[9], where the determined post-operative rate of ECL reached 10.4% at 2 weeks, 16.3% at 1 month, 33.6% at 3 months, 39.4% at 6 months, and 48.2% at 12 months. This was also found in other studies conducted by Bourne et al.[10], Nishimura et al. [11], and Patel et al. [7], in which the greatest rate of ECL after optical PKP occurred during the first postoperative year, with a collective rate of 30% to 50%. Again, these documented rates of ECL after one year of performing optical PKPs are comparable to our deduced rate.

In our study, no statistically significant difference was found between both groups as regards to the rate of graft rejection. Thus, the therapeutic corneal grafts can be considered non-inferior to the optical ones regarding the viability and the prognosis of the grafts (represented in our study by the regaining of the graft clarity, the incidence of graft rejections, and the rate of ECL).

To the best of our knowledge, very few studies explored the postoperative prognosis in cases of therapeutic PKPs. Xiao et al. [12], declared that for cases of fungal keratitis and herpes simplex keratitis, the cases that performed therapeutic PKP minimally suffered from endothelial decompensation, which gradually declined in its rate along their five years of follow up. This supports our study results in declaring the good prognosis of therapeutic PKPs overtime. However, the rate of ECL was not reported in their study.

In our studied cohort of group 2, the addition of antimicrobials for 2 to 3 weeks following therapeutic PKPs did not show any detected adverse effects on the rate of ECL postoperatively. Future studies to be conducted on larger cohorts and for even longer follow up intervals may support or contradict our study results.

We excluded some patients from the statistical analysis and from further enrollment in the study. All those excluded candidates developed factors that would possibly alter the rate of ECL. Discarding those participants gives more credibility to the present study.

In conclusion, our study results declared that therapeutic PKP can be considered non-inferior to optical PKP regarding the rate of graft rejection, the graft viability, and the rate of ECL along a follow up interval of one year. Hence, it can be considered as a safe alternative for cases with infected corneal ulcers which are resistant to the conventional medical therapies. Further long-term longitudinal studies are needed to

validate or contradict our study results and to determine whether the clinically narrow change that was detected in the rate of ECL at the 12 months interval in cases of therapeutic PKP is an ongoing process that may progressively affect the graft survival or it is a stationary loss rate.

Declarations

- **Funding Info:** Not applicable
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- **Consent to participate:** Available
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Tables

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Supplementary Files

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- Table2.pdf