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Research Article

Early Therapeutic Keratoplasty for *Acanthamoeba* Keratitis

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Abstract

Purpose: To describe the findings, recurrence rate and complications following therapeutic penetrating keratoplasty (PK) in eyes with Acanthamoeba keratitis (AK). **Methods:** A retrospective study comparing eyes that underwent surgery in the early stages of the disease versus eyes that had surgery delayed for more than five months of disease. **Results:** The study analyzed 23 eyes with similar demographic characteristics. Seventeen eyes (73.91%) underwent early surgical procedures within five months (Group 1), and 6 (26.08%) had the late PK after five months (Group 2). The mean clinical treatment time between the first symptoms and surgical procedure was 1.80 + 0.915 months in group 1 and 7.83 + 2.48 months in group 2 ($p < 0.001$). Patients in Group 1 achieved a final mean Best-corrected visual acuity (BSCVA) of logMar 0.61 + 1.07 versus 0.98 + 0.85 in Group 2 ($p = 0.416$). Recurrence of the AK infection occurred in 11.8% (2/17) of the early PK group and in 50% (3/6) of the eyes that underwent a late therapeutic PK ($p = 0.051$). Cornea rejection was the most reported complication following PK, and it affected 35.3% (6/17) of the eyes in Group 1 versus 66.7% (4/6) of the eyes in Group 2 ($p = 0.183$). Secondary glaucoma affected 17.6% (3/17) of patients who have undergone early PK versus 66.7% (4/6) of the eyes where surgery was delayed ($p = 0.025$). **Conclusions:** Early therapeutic PK for Acanthamoeba keratitis might have beneficial results concerning the cure of infection, fewer complications, and better visual acuity recovery than a late one.

Keywords: Keratoplasty; *Acanthamoeba* keratitis; Cornea infection.

Introduction

Acanthamoeba keratitis (AK) is a potentially sight-threatening corneal infection caused by a protozoan, whose most related risk factors are contact lens use and incorrect cleaning routine for the lenses [1]. The amoeba has two stages: the actively motile trophozoite stage - in charge of feeding and reproduction, and a cyst stage, which can survive long periods in unfavorable environmental conditions. Because of those variations in its stage, the treatment of AK is very challenging.

Conventional treatment for Acanthamoeba keratitis consists of triple antimicrobial administrations of tropical biguanide, diamidine, and chlorhexidine. The clinical treatment is often very long, despite the advances in antimicrobial therapy, because the cystic form is highly drug-resistant and may persist for months. It also might be influenced by the delay in diagnosis or previous misdiagnosis, as well as the high pharmacological resistance of the protozoan [2]. Furthermore, it often partially treats the pathology, resulting in vision-threatening sequelae, such as epithelial defects, corneal neovascularization, leukoma, limbal cell deficiency, expansion of the infiltrate to the limbus or sclera [3,4]. When clinical treatment fails, the surgical approach of a therapeutic keratoplasty might be an option. It has been shown that about 15.85% of the patients required curative surgery [5]. The PK performed for therapeutic purposes might remove the contaminated area before the amoeba spreads deeply to the tissue and anterior chamber. However, the

perfect timing for keratoplasty, if the clinical treatment has failed, is still in debate.

Some authors have shown better results when surgery is performed in the early stages of infection, whereas others defend the idea that the surgical intervention must be postponed as much as possible [2-4,6]. When surgery is performed, the area of the graft must be large enough to remove the infection and guarantee at least a 1mm rim free of disease. If earlier, it is more likely to achieve this with the donor tissue placed into a relatively undamaged and hence non-compromised recipient bed. On the other hand, when surgery is delayed, the extension of the disease might be difficult to define. In the literature, there's a suggested cut-off of 5 months to classify the surgical treatment as an early or late one, according to the time between symptoms and the surgery [4]. In our practice, it seems that patients who have undergone therapeutic keratoplasty in early stages following ineffective drug therapy had better outcomes than the ones who have had the therapeutic keratoplasty postponed. This study aims to analyze patients with AK treated with therapeutic keratoplasty in our department to study the infection cure rate, as well as visual effects and complications, and to seek any difference regarding the time-point of the surgery.

Methods

A retrospective cohort to analyze the patients with AK who underwent penetrating keratoplasty (PK) for therapeutic reasons. It included patients from the public system of Hospital de Clinicas de Porto Alegre and a private clinic Oftalmocentro, Porto Alegre, Brazil, between January 1998 and December 2022. The criteria for patients eligible for PK following AK was a failed clinical treatment in patients with a positive corneal scraping or biopsy for *Acanthamoeba* keratitis. The failure of clinical treatment was defined as the absence of clinical response or progression of the disease despite topical treatment, including at least, but not limited to, topical biguanide, propamidine and chlorhexidine. Patients with previous ocular infections of other causes, pregnant women, and patients with follow-ups shorter than six months were excluded.

Patients were divided into two groups according to the time, in months, from symptoms to PK. Group 1 included patients undergoing PK within five months of symptoms' onset. Group 2 includes patients who had symptoms for more than 5 months before the PK. This study was carried out in accordance with the principles of the Helsinki Declaration after receiving approval from the Health Research and Ethics Committee of the Hospital de Clinicas de Porto Alegre (GPPG-HCPA 2023-0352). All patients provided written informed consent before the procedure.

Surgical Technique

The surgery was performed either by a trained surgeon (S.K and D.M.) or by an in-training surgeon supervised by the trained ones, under peribulbar blockage or general anaesthesia in the Operation Room (OR). The trephination size was defined intraoperatively, targeting 1mm without corneal infiltration. The diameter of the donor graft was 0.5 mm larger than the recipient trephination size, and it was fixed with 16 interrupted 10-0 nylon sutures. During the postoperative period, patients kept the anti-amoeba treatment associated with topical medications: 3 mg/mL gatifloxacin (Zymar®, Allergan, Brazil) eye drops, and 10 mg/mL prednisolone (Pred-Fort®, Allergan, Brazil) QID for seven days, which was tapered off thereafter, and 0.5 mg/mL carboxymethylcellulose (Fresh-Tears®, Allergan, Brazil) as needed.

Preoperative and Postoperative Evaluations

The primary outcome was the success rate in treating the AK without recurrence in the postoperative evaluation. Clinical manifestations of postoperative recurrence include greyish-white infiltration of the recipient or donor bed with or without stroma's ring infiltration, anterior chamber inflammation, graft edema, and keratic precipitate. The secondary outcomes, which were evaluated at every postoperative visit, included the following:

a) Secondary glaucoma: defined as intraocular pressure above 21 mmHg, and/or glaucomatous visual field loss, and/or progression of cup/disc ratio;

b) Corneal endothelial rejection: defined as cornea edema and Descemet folds, associated with keratic precipitate and/or Khodadoust line in the absence of recurrence signs;

c) Best spectacle-corrected visual acuity (BSCVA): evaluated in the pre-operative and the last postoperative visit;

d) Demographic data.

Statistical Analysis

The data were entered into Excel and exported into SPSS v. 29.0 (SPSS / IBM, Inc., Chicago, IL, USA). BSCVA was converted to the logarithm of the minimum angle of resolution (logMAR) units for the statistical analyses. Frequencies and percentages described categorical variables, and quantitative variables were described by means and standard deviations. Kolmogorov-Smirnov test was used to evaluate the normality of the variables. An Independent T-test was used to compare the preoperative and postoperative measurements and the change differences between the two groups, and the Spearman's rho correlation was used to analyze the variables involved in the recurrence rates. The level of statistical significance was set at $P < 0.05$.

Results

Twenty-three patients met the inclusion criteria. The study analyzed 23 eyes in a population of 13 female (56.5%) and ten male (43.5%) subjects. There were 17 eyes (73.91%) that underwent early surgical procedures within five months (Group 1), and 6 (26.08%) in the late PK group (after five months) (Group 2). The mean age was 40.24 + 10.59 years in group 1 and 31.83 + 14.47 years in group 2 ($p = 0.072$), and there were no differences in the demographic characteristics between groups (Table 1).

	Group 1 PK within 5 months (n=17)	Group 2 PK after 5 months (n=6)	P value
Gender, female	9 (52.9%)	4 (66.7%)	0.560[1]
Eye, right	9 (52.9%)	3 (50%)	0.901[1]
Age (years)	40.24 + 10.59	31.83 + 14.47	0.072[2]
pre-BSCVA (logMAR)	2.04 ± 0.16	1.83 ± 0.80	0.555[2]

Table 1: Demographic data;PK = therapeutic penetrating keratoplasty; BSCVA = best spectacle corrected visual acuity; 1 Chi-square**;** [2]Independent t-test.

(Table 2) shows the characteristics and the outcomes for Group 1 and Group 2. Follow-up period was similar for both groups, being 117.0 + 79.61 months in Group 1, and 105.50 + 60.90 months in Group 2 (p = 0.376). The mean clinical treatment time between the first symptoms and surgical procedure was 1.80 + 0.915 months in group 1, and 7.83 + 2.48 months in group 2 (*p < 0.001*).

	Group 1	Group 2	P value
Time from symptoms to PK, months	1.80 ± 0.915	7.83 ± 2.48	< 0.001
Follow-up time, months	117 ± 79.61	105.50 ± 60.90	0.376
Post-treatment BSCVA (logMAR)	0.61 ± 1.07	0.98 ± 0.85	0.416[2]
Post-BSCVA Snellen ≥ 20/40	9 (52.9%)	2 (33.3%)	0.408[1]
Surgical margins, clear	4/10 (40%)	2/4 (50%)	0.277[1]
Recurrence	2 (11.8%)	3 (50%)	0.051[1]
Rejection	6 (35.3%)	4 (66.7%)	0.183[1]
Glaucoma	3 (17.6%)	4 (66.7%)	0.025[1]

Table 2: Results of the 23 eyes undergoing therapeutic penetrating keratoplasty for Acanthamoeba keratitis; PK = therapeutic penetrating keratoplasty; BSCVA = best spectacle corrected visual acuity; [1] Chi-square; [2] Independent t-test.

Patients in Group 1 achieved a final mean BSCVA of logMar 0.61 + 1.07 versus 0.98 + 0.85 in Group 2, which corresponds to BSCVA Snellen 20/80 (logMar 0.60) and 20/200 (logMar 1), respectively (p = 0.416). Within Group 1, nine eyes (52.9%) achieved a final BSCVA equal to or better than Snellen's 20/40, while this percentage was 33.33% (2/6) in Group 2 (*p = 0.408*). Analyzing the improvements in the BSCVA, 94.1% (16/1) of the eyes had a final vision better than the baseline in Group 1 and 66.7% (4/6) in Group 2 (*p = 0.86*).

Recurrence of the AK infection occurred in 11.8% (2/17) of the early PK group (Figures 1 and 2), and in 50% (3/6) of the eyes that underwent a late therapeutic PK (more than five months from the symptoms) (Figure 3 and 4) (*p = 0.051*). Cornea rejection was the most reported complication following PK, and it affected 35.3% (6/17) of the eyes receiving early surgical treatment in Group 1 versus 66.7% (4/6) of the eyes in Group 2 (*p = 0.183*).

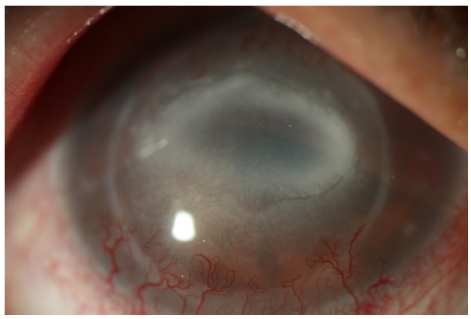

Figure 1: Acanthamoeba keratitis in a scleral contact lens wearer post-PK for keratoconus,with failure to clinical treatment for two months.

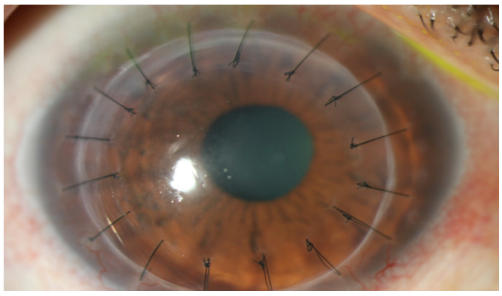

Figure 2: The same eye of Fig 1 shows the postoperative outcome one year after keratoplasty - no signs of recurrence.

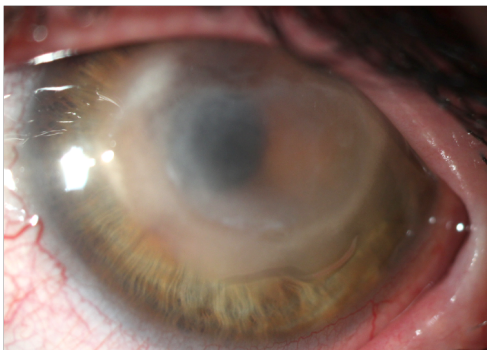

Figure 3: Acanthamoeba keratitis was clinically treated for 15 months before surgery.

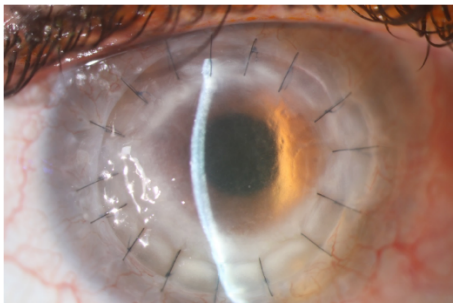

Figure 4: The same eye of Fig 3 reveals recurrence and corneal failure following penetrating keratoplasty.

Secondary glaucoma affected 17.6% (3/17) of patients who have undergone early PK versus 66.7% (4/6) of the eyes where surgery was delayed ($p = 0.025$). When analyzing the variable that might have influenced the recurrence rate in addition to the time of surgery, the presence of a clear surgical rim did not achieve a significant correlation ($p = 0.072$), as shown in (Table 3). The group division according to the time between symptoms and surgery had a moderate correlation ($p = 0.054$).

	Correlation	P value
Group	-0.407	0.054
Time of treatment	-0.305	0.156
Surgical margins, clear	-0.125	0.072

Table 3: Nonparametric correlations associated with recurrence rates; Spearman's rho correlation.

Discussion

Diagnosis and treatment of AK are very challenging. Although there are common symptoms such as significant pain disproportionate to biomicroscopic findings, photophobia and tearing, the clinical findings might lead to an initial misdiagnosis, and the time is usually playing against the success of the treatment for Acanthamoeba Keratitis. Although, there is always a chance of a correct treatment once the Amoeba is isolated.

Laurik et al. [4] compared postoperative outcomes and complications following PK in patients with AK. They observed that patients who underwent surgery in the early stages presented with better final BSCVA than the ones who had undergone a late PK after 5.3 months of disease.

Furthermore, the early surgical approach may have a favorable impact on epithelial healing and graft survival. In our study, the final BSCVA was not statistically different. Still, the percentage of eyes achieving BSCVA equal to or better than Snellen's 20/40 was higher in Group 1 (52.9%) versus 33.3% in Group 2, trending to the same impact reported. Not to mention that in the group of eyes that had an improvement in postoperative BSCVA, group 1 had 94.1% of eyes with better final vision than the pre-op evaluation, while the same happened in only 66.7% of eyes in group 2.

Recurrence of AK occurred in only 11.8% of the eyes submitted to the early surgical treatment, and in 50% of the eyes that underwent a late therapeutic PK, which is clinically very meaningful when treating these patients. Kitzmann et al. [7] reported that, among 31 eyes with AK treated with keratoplasty, the recurrence rate was as high as 41% in a mean time of 6 months from the onset of symptoms and surgery. On the other hand, Zhang T et al. [8]. reported a postoperative recurrence of AK infection in 16.7% with a median time of 56 days from symptoms' onset and therapeutic surgery. These two studies suggest that early surgical approaches might have a protective effect on those patients. Likewise, Bonini et al. [9].

Also reported that DALK in AK patients, performed within 30-60 days of the onset of symptoms, is beneficial in eradicating infection associated to antiamoebic treatment and showed a statistically significant improvement in final postoperative best-corrected visual acuity.

In addition to the time from symptoms to surgery, Zhang et al. [8] analyzed the recurrence rates of AK following therapeutic keratoplasty and reported that corticosteroids used before antiamoebic therapy (AAT) and hypopyon are the two important risk factors for recurrence. We did not segregate patients according to the specific previous treatment. However, our patients did not receive corticosteroids as a therapy before the AAT as a routine. Secondary glaucoma was the most critical complication in our patients, affecting 17.6% of Group 1 (early PK) versus 66.7% of Group 2 (late PK). This difference was statistically significant and showed that the PK performed in the early stages of the disease might help prevent long-term complications such as glaucoma.

It might be influenced by the anatomically induced differences in the anterior chamber and angle, with the need for larger grafts in the late stages. In the literature, glaucoma is reported in 32% of the eyes undergoing PK for AK for therapeutic purposes, similar to our results [7]. On the other hand, lamellar keratoplasty for AK patients might have a lower incidence of this complication, as low as 4.3% of eyes, as reported by Zhang et al.[8] and should be considered when possible.

We recognize that our sample size is not very large, and that this is a retrospective study. However, this infection is relatively rare, such as the percentage of patients needing surgical procedures. The outcomes presented in this study should be considered when identifying patients not responding to the clinical treatment. This study suggests that early therapeutic PK has a higher cure rate than late therapeutic PK, as well as fewer complications, such as corneal rejection and glaucoma.

Conclusion

Early therapeutic PK for Acanthamoeba keratitis is likely to have more beneficial results concerning the cure of infection, fewer complications, and best visual acuity recovery than a late one. Identifying the characteristics of patients that would have advantages with this approach is still a challenge, but it is a goal to achieve the cure and better outcomes.

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Declaration of Conflicting

The Authors declare that there is no conflict of interest.

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