Int Ophthalmol (2019) 39:2889–2896
https://doi.org/10.1007/s10792-019-01137-1

ORIGINAL PAPER

Therapeutic penetrating keratoplasty for acanthamoeba keratitis: a review of cases, complications and predictive factors

Mehdi Roozbahani · Kristin M. Hammersmith · Christopher J. Rapuano · Parveen K. Nagra · Qiang Zhang

Received: 17 May 2018 / Accepted: 13 June 2019 / Published online: 18 June 2019

Abstract

Purpose To review 12 acanthamoeba keratitis (AK) patients who required a therapeutic penetrating keratoplasty (TPK) and determine whether there are factors at the presenting visit that can predict the need for TPK.

Materials and methods This was a retrospective case series. All diagnosed AK patients between January, 2009 and February, 2016 at Wills Eye Hospital, Philadelphia, PA, USA, were enrolled. Information regarding demographics, disease manifestation, management and complications was collected. Potential predictors for TPK were obtained by comparing TPK cases with those who were treated medically.

Results Sixty-three eyes from 63 patients were diagnosed with AK. Twelve eyes (19%) required TPK during the course of treatment, and 51 eyes (81%) were treated medically. Reasons for performing TPK included medically non-responsive ulcer in seven eyes (58%), perforated ulcer in three eyes (25%) and significant corneal thinning in two eyes (17%). The most common post-TPK complications included graft failure (75%), cataract (50%) and uncontrolled glaucoma required glaucoma surgery (17%). Reactivation of AK was seen in one (8%) patient. Anti-amoebic treatment beginning after 25 days from the start of AK symptoms [odds ratio (OR) = 7.63; confidence interval (CI) = 1.01–55.33; $p = 0.041$] and poorer presenting vision (OR = 5.42; CI = 1.91–15.36; $p = 0.002$) were independent predictors of the need for TPK in multivariate analysis.

Conclusion TPK is a procedure with significant postoperative complications but is required by some patients with AK. Eyes with higher risk for needing TPK can be identified earlier and thus provided more intensive treatment and closer follow-up care.

Keywords Acanthamoeba keratitis · Therapeutic penetrating keratoplasty · Predictive factors · Corneal ulcer

M. Roozbahani (✉) · K. M. Hammersmith · C. J. Rapuano · P. K. Nagra
Cornea Service, Wills Eye Hospital, Sidney Kimmel Medical College, Thomas Jefferson University, 840 Walnut Street, Suite 920, Philadelphia, PA 19107, USA
e-mail: meroozbeh@yahoo.com

Q. Zhang
Vision Research Center, Wills Eye Hospital, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA, USA

Introduction

Acanthamoeba is an amoebic parasite which is found in fresh water, soil and nasopharyngeal mucosa of healthy people [1, 2]. It lives in two forms: active pathogenic form called trophozoite and inactive dormant form known as cyst. Given its resistance to biocides, antibiotics and chlorination, cysts are very

difficult to eradicate [2]. Acanthamoeba is responsible for severe indolent keratitis in humans. Contact lens wear and eye trauma are the main risk factors for acanthamoeba keratitis (AK) in developed and developing countries, respectively [1].

Prompt diagnosis of AK is challenging. Perineuritis is a typical clinical presentation of AK at relatively early stages of disease. However, it is variably seen in 2.2% to 52% of eyes [3–5]. Ring infiltration is another typical sign seen in 32–40% of eyes; however, it is observed in late stages of disease [3–5]. AK has some signs in common with herpetic keratitis, and consequently, it is treated initially as a herpetic infection in more than 50% of patients [6]. This delay in proper diagnosis and treatment can lead to an intractable keratitis that is occasionally not manageable with medical treatment alone.

Therapeutic penetrating keratoplasty (TPK) has been used for medically non-responsive or perforated AK ulcers. It is useful in removing the main reservoir of acanthamoeba parasite in the cornea and saving the globe [7]. We conducted this study to review our experience with TPK for AK patients in a referral hospital and evaluating predictive factors associated with the need for TPK.

Materials and methods

This study adhered to the tenets of the Declaration of Helsinki. After receiving approval from the Wills Eye Hospital (WEH), Philadelphia, PA, USA, Institutional Review Board, a retrospective evaluation of charts was performed. All patients diagnosed with AK at WEH between January, 2009 and February, 2016 were identified thorough a review of the electronic medical records. Information including demographics, clinical manifestations, medications, surgeries and visual outcomes was collected. Reasons for TPK, potential predictors, details of complications and clinical outcomes were obtained. We included patients with at least 3 months of follow-up time after surgery or after stopping anti-amoebic medications. The main objective was to review our experience in the management of patients who underwent TPK for AK. Moreover, we wanted to determine what information from presenting visit could predict need for a TPK in patients with the diagnosis of AK.

Diagnosis of AK was made by direct visualization of the cysts under the microscope of corneal scrapings, corneal biopsy or the involved contact lens. Confocal microscopy and acanthamoeba culture were not routinely performed. We also made a clinical diagnosis for those patients with a typical presentation of AK and response to anti-amoebic therapy but negative corneal scrapings. The severity of keratitis was staged as **mild** or **advanced** based on the slit-lamp examination at the presenting visit. Mild keratitis represented eyes with epithelial involvement, perineuritis or anterior stromal involvement. The advanced stage included those with ring infiltration, deep stromal infiltration, hypopyon or thinning more than 50% of corneal thickness.

Standard topical anti-amoebic medication including propamidine isethionate 0.1%, polyhexamethylene biguanide 0.02% (PHMB) or chlorhexidine 0.02% was used as solo or combined regimens (either PHMB or chlorhexidine in combination with propamidine) for treatment. For those who did not show expected response to the combined standard agents, an additional adjuvant medication such as voriconazole, itraconazole or neomycin was added. Non-responsive ulcer defined as spreading of the ulcer to the paracentral area, deepening of the infiltration and developing significant corneal thinning (e.g., descemetocele) while receiving a full regimen of medications. Indications for therapeutic keratoplasty (TPK) included a non-responsive ulcer or corneal perforation during medical treatment course. Patients who presented with a perforated ulcer or descemetocele on their first visit were excluded from the study.

Statistical methods

Continuous variables were summarized using mean, standard deviations, median and were compared using two sample independent t test or Wilcoxon rank-sum test. Categorical variables were summarized using percentages for each group and compared using Fisher's exact test. Odds ratios and 95% confidence intervals were obtained from logistic regression models. Multivariable analyses were carried out to assess the effects of potential risk factors based on univariate analyses. Final model was selected based on forward and backward selection methods as well as clinical importance. All analyses were performed using SAS

version 9.4 (SAS Institute, Inc, Cary, NC). All tests were two-sided with an alpha level of 0.05.

Results

Sixty-three eyes from 63 patients met inclusion criteria of this study. Of the 63 patients, 51 patients (81%) did not require TPK. Those 51 patients included 25 men (49%) and 26 women (51%). The mean age ± standard deviation (SD) was 32 ± 16 years (median 27, range 13–80). Average presenting best corrected visual acuity (BCVA) was 20/132 (0.82 ± 0.79 LogMAR, median 0.90, range 0.00–3.00) which improved to 20/53 (0.43 ± 0.62 LogMAR, median 0.30, range 0.00–3.00) at the last follow-up visit. Average time between symptom onset and starting treatment for AK was 36 ± 42 days (median 21, range 3–220). Twenty-seven patients (53%) were treated with corticosteroid, and 25 patients (49%) received anti-viral medications before the initiation of AK treatment. Thirty-six eyes (71%) were diagnosed with mild keratitis, and 15 (29%) had advanced keratitis at presentation to our Service.

Information from patients who underwent TPK is summarized in Table 1. Among the 63 patients, 12 eyes from 12 patients (19%) required TPK included four men (33%) and eight women (66%). The mean age was 49 ± 18 years (median 51, range, 16–73). Average BCVA at presentation to WEH was 20/2350 (2.07 ± 1.00 LogMAR, median 2.50, range, 0.54–3.00). The mean delay between initiation of symptoms and starting anti-amoebic treatment was 49 ± 37 days (median 40, range, 10–130). Together with standard topical medications, either topical/systemic voriconazole or systemic itraconazole was given to nine (75%) of the 12 patients. Eight patients (67%) had been treated with anti-virals before being diagnosed with AK. Eight patients (67%) had also been treated with topical corticosteroids before presentation to us. A total of five patients (42%) had been treated with a combination of anti-viral and topical corticosteroid. Mean BCVA right before proceeding with first TPK was available for 11 cases and was 20/7100 (2.55 ± 1.12 LogMAR, median 3.00, range 1.00–3.00). Reasons for performing TPK included medically non-responsive ulcer in seven eyes (58%), perforated ulcer in three eyes (25%) and impending to perforation (descemetocele) in two eyes (17%). All corneal buttons were positive for acanthamoeba cyst and/or trophozoite on histopathology evaluations. The first graft failed in nine of the 12 eyes (75%). Of these nine eyes, four eyes underwent a second TPK and five are awaiting their second PK at the time of data collection. The second PK was successful in one of the four patients and failed in three of them. Of the 12 eyes, six (50%) developed visually significant cataract after TPK and two (17%) needed tube shunt implantation to control their post-TPK glaucoma. Case number 9 showed vitritis; vitreous sampling during pars plana vitrectomy ruled out posterior segment involvement with acanthamoeba. Average BCVA at the last visit was 20/1350 (1.83 ± 1.16 LogMAR, median 2.00, range, 0.18–3.00). Mean time between symptom initiation and TPK was 155 ± 68 days (median 150, range 43–305). Mean follow-up time after last TPK was 17 ± 13 (median 15, range 3–50) months.

Those patients who required TPK were significantly older (49 vs. 32 years, $p = 0.013$), were more likely to present after 25 days from initiation of AK symptoms (75% vs. 42%, $p = 0.05$), presented with worse BCVA (20/6325 vs. 20/132, $p < 0.01$) and were more likely to be diagnosed with advanced keratitis on presentation (73% vs. 29%, $p = 0.013$) compared to those who were treated non-surgically. Differences among other variables were not statistically significant. Using data from the presenting visit, predictors of TPK were obtained and tabulated in Table 2. To adjust for the confounders, a multivariable regression analysis was also performed. More than 25 days between initiation of symptoms and starting anti-amoebic treatment and worse vision at the presenting visit were independent predictive factors for the need for PTK.

Discussion

In the current study, we report on 12 patients who underwent TPK for AK and compared them with 51 patients who did not require TPK during the same time period at a tertiary eye hospital. We wanted to learn whether data from the presenting visit could help ophthalmologists predict the need of requiring a TPK.

In the presence of topical cysticidal anti-amoebic eye drops, TPK is reserved for those with fulminant corneal infiltrations and medically non-responsive,

Table 1 Information from 12 patients who underwent TPK from 2009 to 2016 at WEH

Patients number	Age at presentation (years)	Gender	Presenting BCVA at WEH	Days from symptom onset and treatment initiation	Keratitis stage	Adjuvant anti-AK medication	Using steroid before AK diagnosis	Using anti-viral before AK diagnosis	BCVA at the visit before first TPK
1	51	F	20/70	10	Mild	Y	N	Y	HM
2	16	F	20/200	28	Adv.	Y	N	N	20/200
3	58	F	20/400	31	Adv.	Y	Y	N	HM
4	51	M	HM	42	Adv.	Y	Y	N	Unknown
5	73	F	CF	31	Adv.	N	N	Y	CF
6	45	F	HM	84	Adv.	N	Y	Y	HM
7	22	M	20/100	130	Mild	Y	Y	Y	CF
8	45	F	HM	10	Mild	Y	Y	Y	HM
9	71	M	HM	21	Adv.	Y	N	Y	HM
10	29	F	HM	69	Adv.	Y	Y	N	HM
11	68	F	LP	95	Adv.	N	Y	Y	LP
12	54	M	20/400	48	Adv.	Y	Y	Y	HM

Patients number	Age at presentation (years)	Gender	Reason for TPK	BCVA at the last visit	Days from initiation of symptoms to TPK	F/U duration after last TPK (months)	Complications	Surgeries other than TPK	Clinical outcome at the last visit
1	51	F	NR	20/50	150	50	First TPK melted; second TPK failed; cataract	Tube shunt; CE & PCIOL; AMT; DSEK for the second TPK	No haze
2	16	F	NR	20/200	165	3	ED	AMT	Clear graft with ED
3	58	F	Perf.	20/100	118	30	First TPK failed; cataract; underwent second TPK	CE; AMT; OPK	Aphakia; clear graft
4	51	M	Imp. perf.	HM	43	3	First and second TPK failed	–	Edematous graft; awaiting for third TPK
5	73	F	NR	CF	151	21	First TPK failed; cataract	Tube shunt; AMT; CE & PCIOL	Edematous graft; awaiting for second TPK
6	45	F	Perf.	20/200	154	24	First and second TPK failed; underwent third TPK	OPK	Clear graft
7	22	M	Imp. perf	20/30	243	21	Cataract; temporal bleb formation after CE	CE; AMT; CG	Clear graft

Table 1 continued

Patients number	Age at presentation (years)	Gender	Reason for TPK	BCVA at the last visit	Days from initiation of symptoms to TPK	F/U duration after last TPK (months)	Complications	Surgeries other than TPK	Clinical outcome at the last visit
8	45	F	NR	NLP	203	16	Cataract; RD	CE; PPV; AMT	Phthisis bulbi
9	71	M	NR	20/200	116	15	Vitritis; Chr. hem; epithelial down-growth	PPV; CCT; OPK	Moderate edema and thickening of graft; considered a failed graft
10	29	F	NR	HM	115	9	Reactivation of AK after TPK (responded to medical therapy); central corneal scar	AMT	Awaiting for second TPK
11	68	F	Perf.	LP	99	3	Painful eye; Failed TPK; significant APD	PCIOL removal	Diffuse graft edema; awaiting for evisceration
12	54	M	NR	HM	305	8	First TPK failed; cataract	CE & PCIOL	Diffuse graft edema; awaiting for second TPK

Adv. advanced, *AK* acanthamoeba keratitis, *AMT* amniotic membrane, *APD* afferent pupillary defect, *BCVA* best corrected visual acuity, *CCT* cyclocryotherapy, *CE* cataract extraction, *CF* counting fingers, *CG* cyanoacrylate glue, *Chr. Hem* choroidal hemorrhage, *DSEK* Descemet's stripping endothelial keratoplasty, *ED* epithelial defect, *F* female, *F/U* follow-up, *HM* hand motion, *Imp. perf* impending to perforation, *LP* light perception, *M* male, *N* no, *NLP* no light perception, *NR* non-responsive to medical treatment, *OPK* optical keratoplasty, *PCIOL* posterior chamber intra ocular lens, *Perf.* perforated ulcer, *PPV* pars plana vitrectomy, *RD* retinal detachment, *TPK* therapeutic keratoplasty, *WEH* Wills eye hospital, *Y* yes

Table 2 Significant predictive factors for TPK

Predictors for TPK	Univariate model			Multivariate model		
	OR	CI	*p* value	OR	CI	*p* value
Age at presentation (years)	1.04	1.01–1.08	0.012	Not significant		
Presenting BCVA (LogMAR)	3.52	1.64–7.58	0.001	5.42	1.91–15.36	0.002
Keratitis stage (advanced vs. mild)	6.41	1.49–27.77	0.012	Not significant		
Days from symptom initiation to treatment > 25 days[a]	4.20	1.01–17.54	0.049	7.63	1.01–55.33	0.041

OR odds ratio, *CI* confidence interval, *BCVA* best corrected visual acuity, *LogMAR* logarithm of the minimum angle of resolution

[a]This number (25 days) was the median days from symptom initiation to starting treatment in all diagnosed AK cases (63 cases)

perforated or impending to perforation ulcers. The rate of TPK for the management of AK has been reported from 5 to 68% in literature [8] and was 19% in our study. Given differences in many aspects such as study population, inclusion criteria, risk factors, timing of TPK, postoperative management and follow-up duration, the results and complications of AK patients who underwent TPK have been variable in available studies. It has been shown that graft survival is better when penetrating keratoplasty (PK) is performed on a non-inflamed eye after a medically cured AK [7–10]. Other factors that influence TPK results include time of starting corticosteroids after TPK, glaucoma, disease reactivation, inflammation due to active infection and cataract development [11].

We noticed significant complications after TPK in many of our patients. Graft failure was the most common complication in 75% of the patients followed by post-keratoplasty cataract in 50% and uncontrollable glaucoma required surgery in 17%. In a case series, Kitzmann et al. [10] reported their experience on performing TPK for 22 eyes with AK over 27 years. Fifty-five percent of the eyes required second grafts and 15% underwent 3–6 grafts. Eighteen percent underwent cataract surgery, 5% had glaucoma surgery, and 5% were complicated with endophthalmitis. In another report by Kashiwabuchi et al. [12], 61% of 32 patients who had a TPK for the management of AK required a second graft; the second graft failed in 55% of these patients. Eye care providers and patients should be prepared for the high probability of complications after TPK. Patients should be informed that the first objective of TPK is to prevent extra corneal extension of the infection and restore anatomical integrity of globe, particularly in those with perforated or near-perforated ulcers.

Reactivation of AK after TPK was reported from 0 to 46% in literature [12]. With the exception of patient number 10, we did not experience reactivation of AK. Among the 12 cases that underwent TPK, the corneal button margin was only positive for AK in this patient. The low number of infection reactivations in our study is attributed to continuing aggressive medical therapy with cysticidal agents after TPK, delayed starting topical corticosteroid after surgery and attempting to obtain clear margins at the time of TPK. Previous studies revealed that topical corticosteroids can increase the number of trophozoites through accelerated excystment and trophozoite replication [13]. Using topical corticosteroids during the early post-TPK period for AK and fungal ulcers is controversial [14–17]. We started steroids in our cases at least 2 weeks after TPK. Delayed initiation of topical corticosteroid can be one of the reasons for the low rate of reactivation of the infection after TPK; however, it can potentially lead to higher rate of graft failure [18].

Three (25%) of the patients ended up with corneal perforation through the treatment course. Two of them were not compliant with their follow-up visits. Identifying predictors for TPK at presenting visit can lead to the better timing of TPK in those who are at higher risk for corneal perforation. Moreover, high-risk patients may benefit from frequent follow-up visits and intensive medical therapy from the beginning.

Delayed diagnosis and treatment has been a significant risk factor for poor outcomes in AK patients in previous studies [4, 7, 8]. Late diagnosis and treatment begins a destructive cycle providing the opportunity

for acanthamoeba trophozoites to penetrate deeply into the corneal stroma [19, 20]. Inflammation secondary to interaction between the immune system and acanthamoeba organisms can lead to necrosis and corneal thinning [21]. Additionally, concurrent use of corticosteroid, generally due to misdiagnosis as herpes keratitis, causes excystment of cysts and can lead to a more recalcitrant form of AK [13]. These factors can advance the keratitis stage which primarily represents infiltration depth. The results of this study reveal that delayed treatment and poor presenting vision at first office visit can be independently used for prediction of requiring TPK. Patients who were treated after 25 days from initiation of AK symptoms were 7.63 times more likely to proceed with TPK. Patients who presented with BCVA 20/200 had a 5.42-fold increased risk of requiring TPK compared to those with BCVA 20/20. Although a more advanced stage of keratitis (OR = 6.41) and older age (OR = 1.04) were significant predictive factors for TPK in univariate analysis, we failed to obtain a predictive association between these variables and TPK in our multivariate model, most likely because of insufficient number of cases.

Our study has some limitations. Due to the rarity of AK, we had 12 patients in the TPK group which made a comparison of these patients with the 51 patients in the non-TPK group difficult. Moreover, proper timing of TPK for non-responsive infections is very variable and patient specific. We also used the most recent BCVA, while the time from last surgery to final visit was variable among cases.

In conclusion, topical anti-amoebic medications are considered the standard treatment for AK. When required, TPK can help replace a severely compromised cornea. Performing TPK in eyes with active infection and inflammation is associated with significant postoperative complications and poor outcomes. Patients with higher risk of requiring TPK can be identified at presentation to receive more aggressive management and more frequent follow-up care.

Compliance with ethical standards

Conflict of interest There is no conflict of interest to declare.

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