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CLINICAL STUDY

Antiviral treatment following penetrating keratoplasty for herpetic keratitis

JFB Goodfellow[1], S Nabili[1], MNA Jones[2], DQ Nguyen[1], WJ Armitage[3], SD Cook[1] and DM Tole[1] on behalf of the NHSBT Ocular Tissue Advisory Group and Contributing Ophthalmologists (OTAG audit study 6)

Abstract

Purpose **To assess the effect of antiviral treatment on corneal graft survival following penetrating keratoplasty for herpetic keratitis.**
Methods **Retrospective cohort study of 454 patients receiving primary penetrating keratoplasties (PKs) for viral infection reported to NHS Blood and Transplant (NHSBT) between April 1999 and June 2005. Follow-up data were available on 403 PKs. Kaplan–Meier survival estimates were used to determine graft survival for the three treatment groups: no medication, topical antiviral, and oral antiviral medication. A Cox regression model was used to investigate the combined effects of all additional factors on graft failure. The model was fitted using all pre-operative factors first and then post-operative factors including type of antiviral medication were included.**
Results **Patients who received oral antiviral medication post-operatively had consistently better graft survival than those receiving no medication or only topical medication. Patients receiving oral antivirals were less than a third as likely to have a failed graft at 5 years compared with those on no antiviral medication (relative risk (RR) 0.3, CI: 0.2–0.7, $P = 0.002$). Other factors that were found to influence the risk of graft failure were the presence of deep corneal vascularisation ($P = 0.009$), PK performed for therapeutic reasons ($P = 0.03$), large diameter grafts ($P = 0.04$), and experiencing a rejection episode ($P = 0.003$).**
Conclusion **Oral antiviral treatment reduces the risk of graft failure in patients undergoing primary PK for herpetic keratitis and should be routinely used in this group of patients post-operatively unless contra-indicated.**
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[1]Bristol Eye Hospital, Bristol, UK

[2]NHS Blood and Transplant, Bristol, UK

[3]Department of Clinical Science, University of Bristol, Bristol Eye Hospital, Bristol, UK

Correspondence:
JFB Goodfellow, Bristol Eye Hospital, Lower Maudlin St, Bristol BS1 2LX, UK
Tel: +44 (0)1242 222222;
Fax: +44 (0)8454 222585.
E-mail: jonathangoodfellow@hotmail.com

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Introduction

Herpetic keratitis is a major cause of corneal scarring and consequent visual loss in developed countries.[1] Penetrating keratoplasty (PK) may be undertaken to visually rehabilitate patients, yet graft survival in patients with herpetic keratitis remains lower than that of other common corneal conditions such as keratoconus, Fuchs' endothelial dystrophy, and non-herpetic corneal scarring.[2] This reduced survival may be attributable to the indefinite potential for recurrence of herpetic keratitis, which represents a leading cause of graft failure in patients who undergo PK for this indication.[3]

Clinical practice has therefore moved towards the use of antiviral prophylaxis against reactivation of herpes simplex virus (HSV)—a concept that was initially used for reducing recurrences of genital herpes simplex.[4] In ocular herpetic infection, antiviral treatment was initially focused on topical medication, but in view of complications from epithelial toxicity and persistent epithelial defects, its use did not extend to routine prophylactic treatment following PK. The Herpetic Eye Disease Study Group found that using prophylactic oral acyclovir helped to prevent relapses in patients with recurrent herpetic eye disease, but the study group excluded patients who had previously undergone keratoplasty surgery.[5] Smaller scale studies have since found reduced graft failure in patients receiving prophylactic post-operative oral acyclovir,[3,6,7] although no benefit in rates of graft failure have also been reported.[8]

In the United Kingdom, data on corneal transplants are routinely collected by NHS

Blood and Transplant (NHSBT) through the United Kingdom Ocular Tissue Transplant Audit. This study aims to analyse these data for patients undergoing primary PK for herpetic infection to determine whether the use of oral antiviral medication affects graft survival, after allowing for other confounding factors.

Patients and methods

NHSBT routinely collect data on patients undergoing PKs through the Unite Kingdom Ocular Tissue Transplant Audit. These data are collected from across the United Kingdom, although excludes corneas supplied by East Grinstead and Moorfields eye banks. Data submission by surgeons is through a standard set of forms. A form is completed at the time of surgery, recording details such as age, sex, indication for transplantation, type of procedure, donor and recipient trephine size, pre-operative risk factors, and best corrected visual acuity (BCVA). Surgeons are required to submit follow-up data at 1, 2, and 5 years postoperatively, recording whether the graft has failed and, if so, the reason for failure, postoperative complications (recurrence of original disease, infection, loose/broken sutures, wound leak), subsequent cataract, or other ocular surgery, rejection episodes, topical and oral medications (antiviral, steroid, glaucoma, or other immunosuppressant therapy), and details of BCVA, best day-to-day visual acuity and refractive outcomes.

We retrospectively analysed patients who received a primary PK for viral infection between April 1999 and June 2005. Statistical analysis was performed using SAS V9.1 software (SAS Institute Inc., Cary, NC, USA). Three treatment groups were defined: no antiviral medication, only topical antiviral, and oral antiviral (with or without topical antiviral). Kaplan–Meier survival estimates were used to determine graft survival and a Cox proportional hazards regression model was used to investigate the combined effects of all additional factors on graft failure. The model was fitted using all pre-operative factors first and then post-operative factors were included (post-operative antiviral medication, steroid medication, recurrence of original disease, and time to first rejection episode). The factors considered are listed in Table 1.

The type of antiviral medication may change from one visit to the next, so the effect of this factor was modelled as a time-dependent variable. The same approach was used to assess the impact of rejection by including time to first rejection episode in the model. The level of significance was set at 5%. Relative risks from the Cox model are quoted with 95% confidence intervals (95% CI).

Results

Patients

During the study period, 454 primary PKs for viral infection were reported to NHSBT. Follow-up data were

Table 1 Variables considered in the Cox proportional hazards model

Grouping	*Variable*	*Significant in final model*
Donor factors	Donor sex	
	Endothelial assessment	
Recipient factors	Recipient age	
	Recipient sex	
	Donor-recipient age difference	
Surgeon/operation factors	Graft size	$P = 0.04$
	Donor-recipient trephine difference	
Reason for graft	Visual only	
	Therapeutic	$P = 0.03$
Pre-op risk factors	Inflammation/infection	
	Glaucoma	
	Ocular surface disease	
	Pre-operative visual acuity	
	Pre-operative complications/surgery	
Vascularisation	Deep only	$P = 0.009$
	Superficial only	
	Deep or superficial	
Postoperative factors	Antiviral medication	$P = 0.002$
	Steroid medication	
	Recurrence of original disease	
	Rejection episodes	$P = 0.003$

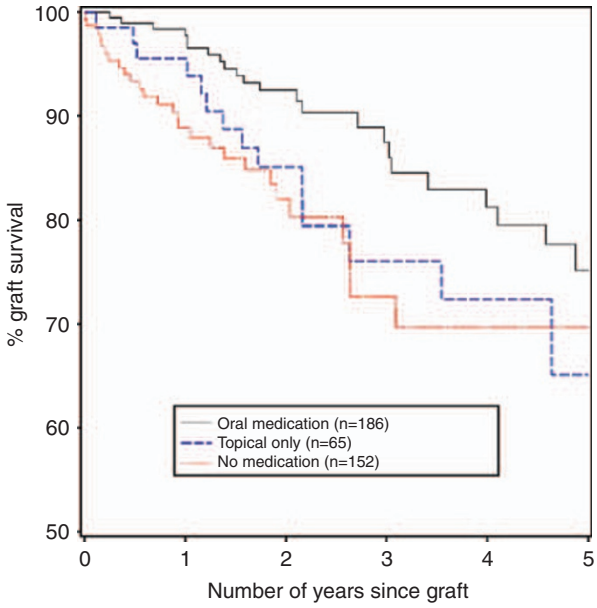

Figure 1 Influence of antiviral medication on 5-year Kaplan–Meier survival.

available for 403 PKs; there were 235 males and 168 females with median ages, respectively, of 63 years (IQ 49–74) and 65 years (IQ 50–78).

Univariate graft survival

Univariate Kaplan–Meier survival curves for the three treatment groups are shown in Figure 1.

Log-rank tests revealed differences in graft survival between the three groups ($P = 0.04$). Patients who received oral medication postoperatively had consistently better graft survival than those receiving no medication or only topical medication. At 5 years, the graft survival rates for the three groups were 75% (95% CI: 64–84) for oral antivirals, 65% (95% CI: 44–80) for topical antivirals only, and 70% (95% CI: 56–80) where no antivirals had been used postoperatively.

Multivariate analysis of graft failure

There was a more marked reduction in risk of graft failure in the group receiving oral antivirals after adjusting for the effects of all additional factors on graft failure, using the Cox model. These patients were less than a third as likely to have a failed graft at 5 years compared with those on no antiviral medication (RR 0.3, CI: 0.2–0.7, $P = 0.002$). The impact of topical medication was less certain but cannot be dismissed (RR 0.2, CI: 0.02–1.2, $P = 0.07$). The other factors found to significantly influence graft failure are shown in Table 2.

These factors increasing the risk of graft failure included the presence of deep corneal vascularisation

Table 2 Relative risk of graft failure at 5 years

Factor	n	*Relative risk*	*95% CI*	P [a]
Antiviral medication (P = *0.002*)[b]				
No medication	152	1.0	—	
Topical only	65	0.2	0.02–1.2	0.07
Oral medication	186	0.3	0.2–0.7	0.002
Grafted for therapeutic reasons (P = *0.03*)				
No	319	1.0	—	
Yes	84	1.9	1.1–3.3	0.03
Deep vascularisation only (P = *0.009*)				
No	392	1.0	—	
Yes	11	3.4	1.4–8.7	0.009
Graft size (P = *0.04*)				
⩽8 mm	301	1.0	—	
>8 mm	102	1.7	1.0–3.0	0.04
First rejection episodes (P = *0.003*)[b]				
0	327	1.0	—	
1+	76	2.3	1.3–3.8	0.003

[a]Wald test.
[b]Time-dependent covariates.

(110 (27%) with 1 quadrant, 57 (14%) with 2 quadrants, 3 (4%) with 3 quadrants, and 4 (4%) with 4 quadrants), PK performed for therapeutic reasons (that is, not just to improve vision) and large diameter grafts (>8 mm). Postoperatively, the 76 patients who experienced a rejection episode were more than twice as likely to have a failed graft at 5 years (RR 2.3, 95% CI: 1.3–3.8, $P = 0.003$).

Discussion

Herpetic keratitis is a common indication for corneal transplantation, but carries an increased risk of graft failure,[2] prompting investigation into the use of postoperative antiviral medication to improve graft survival. Antiviral treatment following PK initially focused on topical antivirals, although complications from epithelial toxicity, delayed wound healing and persistent epithelial defects limited routine prophylactic use.[9] Ficker *et al*[10] in 1988 found that topical antiviral prophylaxis during intensive steroid treatment for graft-rejection episodes both reduced the incidence of HSV recurrence complicating rejection, and improved the outcome following rejection. Beyer et *al*[11] in 1989 went on to investigate the use of systemic acyclovir in a rabbit model of HSV keratitis and demonstrated a reduction in viral shedding, geographical ulceration and stromal keratitis in the treatment group after keratoplasty. Barney and Foster[3] subsequently performed a small prospective randomised trial of oral acyclovir after PK for herpes simplex keratitis and found a reduction in both HSV recurrence and graft failure.

Van Rooij *et al*[8] found prophylactic oral acyclovir reduced the risk of HSV recurrence following PK, but did not find a benefit in overall graft failure compared with placebo, although other studies have found reduced rates of graft failure in patients receiving oral acyclovir.[3,6,7] Our study found a graft survival rate of 75% at 5 years in patients receiving oral antiviral treatment. These patients showed a more than threefold reduction in risk of graft failure at 5 years compared with those not receiving any antiviral medication when the bias from additional variables were accounted for. Our analysis therefore, adds to the weight of evidence favouring the use of oral antiviral treatment and supports its routine use following PK for HSV in all patients unless contra-indicated.

Acyclovir is the most commonly used oral antiviral and this is generally accepted to be a safe, well-tolerated drug. Acyclovir is an acyclic purine nucleoside analogue that inhibits DNA replication, thereby reducing the risk of reactivation of latent HSV in the trigeminal ganglion. Topical antivirals will only function locally on the cornea and before common usage of postoperative systemic antivirals, Moyes *et al*[9] demonstrated decreased rates of HSV recurrence and rejection episodes with topical antiviral prophylaxis, but the benefit did not extend to an improvement in overall graft survival. Our analysis also did not provide unequivocal support for the routine use of topical antiviral medication. Kaplan–Meier univariate analysis showed no benefit, and although multivariate analysis was suggestive of a reduced risk of graft failure with topical treatment, this did not reach the 5% level of significance.

A recent study by Goldblum *et al*[12] also investigated the use of valacyclovir as an alternative to oral acyclovir. This found prophylactic valacyclovir to be at least as effective as acyclovir in preventing recurrence of HSV keratitis following corneal transplantation and equally effective concerning graft survival. The potential benefits include higher plasma levels of the drug and reduced frequency of administration, although in practice the actual dosage and frequency of antiviral medication required remains uncertain. Treatment with acyclovir 400 mg twice daily for at least 1 year postoperatively has been previously recommended[6,8,13] but longer treatment may be indicated. Conversely, Jansen *et al*[14] have reported follow-up data for patients given only 6 months postoperative oral acyclovir following PK for HSV keratitis. At 5 year follow-up, the benefit was still significant with a lower cumulative rate of herpetic recurrence, although the incidence of graft failure was too low to analyse differences between treatment groups. Unfortunately our study does not provide further information on the optimal duration of treatment, as the precise duration of individuals' treatment with antivirals is not recorded: this is a shortcoming of our data and a consequence of the retrospective data collection.

This retrospective nature of our study is its principal limitation. We were confined to data that could be extracted at the 1, 2, and 5 year follow-up points. In the case of medications, if patients were not receiving any of the specified medications, respondents were asked the date of the last reported usage if applicable, but we were unable to collect further data beyond these details specified on the form at each follow-up point. Additionally, although the study group is assumed to represent HSV infection, the inclusion of some patients with HZV cannot be completely ruled out. Herpes zoster virus (HZV) keratitis is an infrequent indication for PK,[2] but clinical differentiation from HSV is not always straightforward[15] and ideally in a prospective study, confirmation of the presence of HSV by culture, PCR, or immunohistochemistry would be sought.

Besides the issue of postoperative antiviral treatment, several other factors were found to have an effect on graft failure. Of the pre-operative factors considered, whether the eye was grafted for therapeutic reasons, the presence of deep neovascularisation, and larger diameter grafts were all associated with a higher risk of graft failure. It would be expected that grafts performed for therapeutic reasons would have a higher risk of graft failure as actively inflamed eyes have been shown to be a risk factor for graft failure in herpetic keratitis.[10,16,17] This lends support to the principle of temporising measures such as gluing or lamellar patch grafting in eyes with, or threatened with perforation. This may allow for PK to be performed at a later date when the eye is quiet.

Many studies have reported on the influence of graft diameter[18–20] and corneal vascularisation[15,21,22] on graft survival; a recent meta-analysis of 24 944 grafts found corneal vascularisation increased the risk of graft failure with a risk ratio of 1.32, with incrementally increasing risk as more quadrants are involved.[23] In addition in our study, patients who had experienced a rejection episode were more than twice as likely to have a failed graft at 5 years (Table 2). Rejection episodes following PK for HSV are as high as 46% during the first 2 years postoperatively[16] and subsequent graft failure following a rejection episode has previously been reported to be similar to our results.[9] Treatment of rejection episodes necessitates the use of intensive topical steroid treatment, thereby increasing the risk of HSV recurrence and graft failure, thus supporting the role of postoperative antiviral treatment.

To our knowledge, this is the largest reported study investigating the effect of antiviral treatment on graft survival in herpetic keratitis. We conclude that our study strongly supports the use of oral antiviral treatment to reduce the risk of graft failure in patients undergoing

primary PK for herpetic keratitis and that this should be routinely used postoperatively unless contra-indicated.

Summary

What was known before

- Corneal graft surgery in patients with herpetic keratitis carries a higher risk of graft failure than other common conditions such as keratoconus, Fuch's endothelial dystrophy, and non-herpetic corneal scarring. Previous studies have shown variable results on the effect of antivirals on graft failure.

What this study adds

- Postoperative oral acyclovir substantially reduces the risk of graft failure at 5 years.

Conflict of interest

The authors declare no conflict of interest.

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