Corneal neovascularisation following deep anterior lamellar keratoplasty for corneal ectasia: incidence, timing and risk factors

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ABSTRACT

Background The purpose of this study was to evaluate the incidence, timing and risk factors of corneal neovascularisation (NV) after deep anterior lamellar keratoplasty (DALK) for corneal ectasia.

Methods This study included 616 eyes who underwent DALK between 2012 and 2020 in two tertiary referral centres. In one centre topical corticosteroids were discontinued after complete suture removal 1 year after surgery, whereas in the other they were discontinued 3–4 months after surgery. The presence and severity of corneal NV was ascertained based on slit lamp photographs. Potential risk factors for corneal NV were evaluated using the Cox proportional hazards model.

Results The cumulative incidence of corneal NV was 8.7% at 1 year after surgery and 13.2% at 5 years. Mean time interval from surgery to development of corneal NV was 12.8±16.2 months, with 68.9% of cases occurring before complete suture removal. Early discontinuation of topical steroids, older age and ocular allergy were associated with an increased risk of developing corneal NV (respectively, HR=2.625, HR=1.019, HR=3.726, all p<0.05).

Conclusions The risk of corneal NV is higher in the first year following DALK. Early discontinuation of topical steroids, ocular allergy and older age are significant predictors of corneal NV.

INTRODUCTION

Deep anterior lamellar keratoplasty (DALK) offers several advantages over penetrating keratoplasty (PK) in terms of intraoperative and postoperative complications. In particular, it avoids the risks associated with open-sky surgery and eliminates the possibility of endothelial rejection, thereby improving the chances of long-term graft survival.[1–5]

Nevertheless, the postoperative course of DALK can be marred by complications including immunological stromal rejection and corneal neovascularisation (NV).[6–8] These may compromise corneal clarity to the extent that a repeat DALK or even PK may be deemed necessary. While stromal rejection has been assessed in previous studies,[9 10] the factors leading to corneal NV after DALK, as well as its clinical relevance remain undetermined. Since corneal NV can cause loss of vision and increase the risk of immunological rejection,[11 12] identification of possible predictors is important to develop individualised approaches for the improvement of surgical outcomes.

The present study aimed at assessing the incidence, timing and factors associated with the development of corneal NV after DALK for eyes with corneal ectasia in the absence of preoperative corneal vascularisation.

METHODS

This was a retrospective review of consecutive eyes with corneal ectasia that underwent DALK in two tertiary referral centres (Ospedali Privati Forlì 'Villa Igea', Forlì, Italy=Group 1 and Department of Ophthalmology, University of Magna Græcia, Catanzaro, Italy=Group 2) from January 2012 to January 2020. Exclusion criteria were the presence of preoperative corneal vascularisation due to any cause, as well as lack of good-quality slit-lamp photographs for the evaluation of corneal NV.

All operations were performed by either a senior surgeon or a fellow supervised by a senior surgeon as per our previously described technique.[13]

Surgical technique

A trephination of 9 mm diameter was performed to a depth of 450–550 µm. At the base of the trephination, a blunt probe was inserted and advanced 1 mm centripetally. The probe was exchanged with a cannula, which was further advanced 1 mm along the same track. Pneumatic dissection was then attempted. Following en bloc keratectomy to approximately 80% depth, the roof of the bubble was incised under viscoelastic protection and excised with corneal scissors. When pneumatic dissection failed, ophthalmic viscoelastic device was injected into the stromal tunnel used for pneumatic dissection to obtain a viscobubble.[14] If viscoelastic-assisted dissection also failed, layer-by-layer manual dissection was performed. The donor tissue was punched to 9 mm punch and sutured into place using double running 10–0 nylon sutures. Triamcinolone acetonide and gentamicin sulphate, 0.3%, were injected subconjunctivally at the end of the procedure.

Tobramycin 0.3% and dexamethasone 0.1% eye drops were administered every 2 hours for the first 2 weeks after surgery then gradually tapered off. Protocol for discontinuation of therapy varied according to the centre: in Group 1, corticosteroids

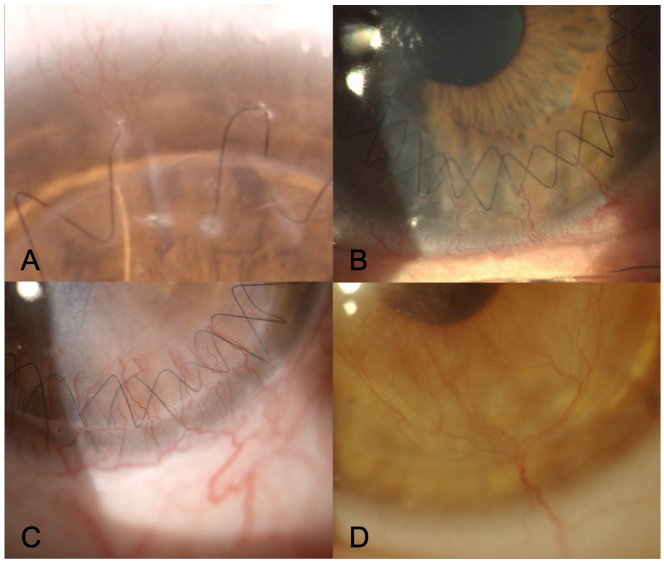

Figure 1 Grading of corneal neovascularisation. (A) Vessels between the limbus and the distal end of the double-running suture (grade 1). (B) Vessels between the distal end of the suture and the graft-host junction (grade 2). (C) Vessels extending across the donor cornea (grade 3). (D) Deep vessels invading the graft-host interface (grade 4).

were discontinued after complete suture removal 1 year after surgery; in Group 2, they were discontinued 3–4 months after surgery. In case of corneal NV, patients were treated with dexamethasone 0.1% eye drops every 2 hours for 2 weeks and then slowly tapered off. Besides topical corticosteroids, no other anti-inflammatory drugs were used in any of the patients of this series.

The first running suture was removed 2–3 months after surgery, whereas the second one was removed at 1 year from surgery. Follow-up visits were scheduled at month 1, 3, 6, 12 and yearly thereafter. The presence of corneal NV and the number of involved quadrants were evaluated based on slit lamp photographs. Corneal NV was graded according to the following criteria: grade 1: vessels between the limbus and the distal end of the double-running suture (figure 1A); grade 2: vessels between the distal end of the suture and the graft-host junction (figure 1B); grade 3: vessels extending across the donor cornea (figure 1C); grade 4: deep vessels invading the graft-host interface (figure 1D). Furthermore, other complications associated with corneal NV such as loose or broken sutures, immunological rejection or infectious keratitis were recorded.

Statistical analysis was performed using R (V.4.0.0) and RStudio (V.1.2.5042) software. The incidence of corneal NV was reported based on cumulative incidence curves. Cox proportional hazards regression analysis was used to determine association between baseline characteristics and the development of corneal NV. Variables evaluated were age at surgery, recipient gender, method of lamellar dissection (pneumatic vs viscoelastic-assisted or manual dissection), postoperative steroid regimen (early vs late discontinuation) and presence of ocular allergy. Two sensitivity analyses were performed: the first including only patients with keratoconus; the second excluding cases with broken or loose sutures, immune rejection and infectious keratitis. Mann-Whitney U test was used to compare time to corneal NV, grade and number of involved corneal quadrants in cases managed with early vs late steroid discontinuation. Kaplan-Meier analysis with log rank test was used to compare re-grafting rates between both groups. A p value of less than 0.05 was considered statistically significant.

Table 1 Demographical and clinical characteristics of included patients

Characteristic	Patients (n=616)
Age (years)	38.2±15.3
Gender (male/female)	389/227
Indication	
Keratoconus	592 (96.1%)
Post-refractive ectasia	19 (3.1%)
Pellucid marginal degeneration	5 (0.8%)
Technique	
Air bubble	450 (73.1%)
Manual dissection	138 (22.4%)
Visco bubble	28 (4.5%)

RESULTS

A total of 616 eyes of 562 patients that underwent DALK for corneal ectasia were included. The mean follow-up was 30.9±22.2 months (range 1–96 months). Demographic and baseline clinical characteristics are reported in table 1. In 278 eyes (45.2%), topical steroids regimen was discontinued 3–4 months after surgery. Conversely, in 338 eyes (54.9%), the postoperative regimen included prolonged administration of topical steroids, which were tapered off over a 12-month period of time and discontinued after complete suture removal that is, later than 12 months after surgery.

Cumulative incidence of corneal NV was 8.7% at 1 year, 12.2% at 2 years and 13.2% at 5 years (figure 2). Mean time interval from surgery to development of corneal NV was 12.8±16.2 months (range 1–93 months). In 51 eyes (68.9%), corneal NV developed before complete suture removal (5.8±3.8 months after surgery). Neovessels regressed after complete suture removal in 13.7% of those cases. Immunological rejection occurred more frequently in patients with corneal NV compared with those without NV (21.4% vs 5.5%, p<0.001). In total, 10 patients required re-grafting due to corneal NV. No significant differences between corrected distance visual acuity (CDVA)

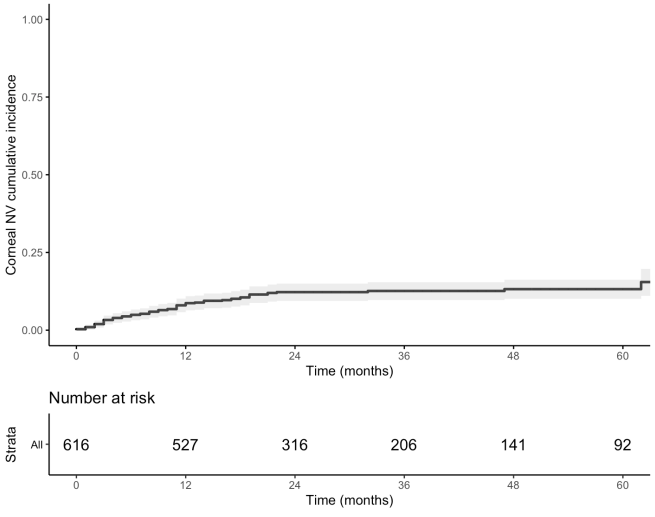

Figure 2 Kaplan-Meier curve of corneal neovascularisation (NV) after deep anterior lamellar keratoplasty.

Table 2 Cox proportional hazard regression analysis of the development of corneal neovascularisation

Predictor	HR	95% CI	P value
Steroids discontinuation (early vs late)	2.625	1.581 to 4.361	<0.001
Ocular allergy	3.726	1.785 to 7.778	<0.001
Age	1.019	1.004 to 1.035	0.013
Gender	1.141	0.695 to 1.874	0.602
Dissection (manual vs big bubble)	1.580	0.918 to 2.718	0.099
Type of bubble (viscoelastic vs air)	1.433	0.598 to 3.480	0.427

before corneal NV and final CDVA were found (0.22±0.16 vs 0.21±0.16 LogMAR; p=0.563).

The risk factors examined for an association with corneal NV are shown in table 2. The Cox proportional hazard regression showed that early discontinuation of topical steroids was associated with an increased risk of developing corneal NV (HR=2.625, p<0.001). Moreover, the risk of corneal NV was higher in older patients and those with ocular allergy (respectively, HR=1.019, p=0.013; HR=3.726, p<0.001). Recipient gender and method of lamellar dissection were not associated with the development of corneal NV (both p>0.05). Early steroids discontinuation was also associated with an increased risk of re-grafting (p=0.040). In a sensitivity analysis performed including only cases with keratoconus, early discontinuation of topical steroids, older age and ocular allergy remained significant predictors for corneal NV (respectively, HR=2.715, p<0.001; HR=1.017; p=0.038; HR=3.912, p<0.001).

Thirty-eight of 74 eyes (51.4%) with corneal NV were associated with complications including loose or broken sutures in 23/38 eyes (figure 3A), immunological rejection in 10/38 eyes (figure 3B) and infectious keratitis in 5/38 eyes (figure 3C). Conversely, in 36 of 74 eyes with corneal NV (48.6%), no associated complications were identified. Interface bleeding was observed in two patients (figure 3D). A sensitivity analysis was performed by excluding cases that developed loose or broken sutures, immunological rejection and infectious keratitis. Early discontinuation of topical steroids and older age still remained significant predictors for corneal NV in this model (respectively, HR=2.377, p=0.020; HR=1.029, p=0.009).

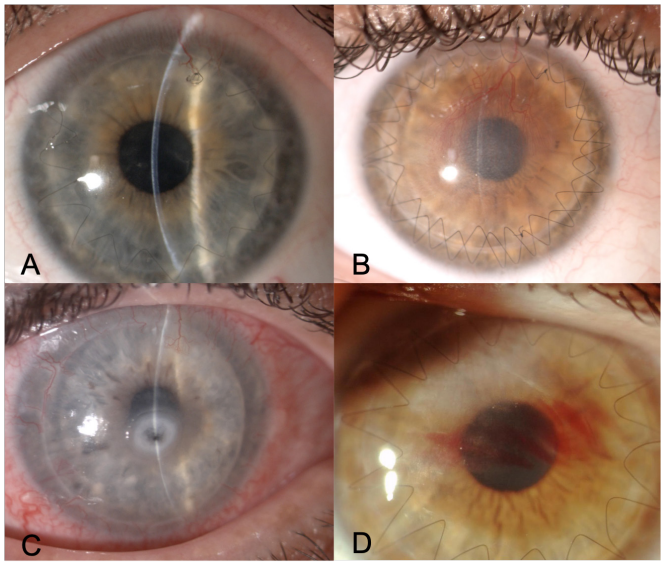

Figure 3 Representative cases of corneal neovascularisation (NV) after deep anterior lamellar keratoplasty. (A) Corneal NV associated with a broken suture. (B) Corneal NV associated with stromal rejection. (C) Corneal NV associated with infectious keratitis. (D) Interface bleeding in a patient with corneal NV.

Table 3 Characteristics of patients who developed corneal neovascularisation

Characteristic	All patients (n=74)	Early steroids discontinuation	Late steroids discontinuation	P value
Age (years)	41.3±16.3	40.2±16.9	43.2±15.2	0.370
Gender (male/female)	46/28	27/18	19/10	0.816
Time to neovascularisation (months)	12.8±16.2	9.9±11.9	17.3±20.7	0.014
Grade of neovascularisation				0.985
Grade 1	10 (13.5%)	9 (20.0%)	1 (3.4%)	
Grade 2	6 (8.1%)	3 (6.7%)	3 (10.3%)	
Grade 3	18 (24.3%)	7 (15.6%)	11 (37.9%)	
Grade 4	40 (54.0%)	26 (57.8%)	14 (48.3%)	
Number of quadrants				0.001
1	32 (43.2%)	12 (26.7%)	20 (69.0%)	
2	20 (27.0%)	16 (35.6%)	4 (13.8%)	
3	8 (10.8%)	6 (13.3%)	2 (6.9%)	
4	14 (18.9%)	11 (24.4%)	3 (10.3%)	

The mean time elapsing between surgery and the observation of corneal NV was 9.9±11.9 months in patients who underwent early steroids discontinuation and 17.3±20.7 months in those with late discontinuation (p=0.014) (table 3). The number of quadrants of corneal NV was significantly higher in patients who underwent early topical steroids discontinuation compared with those with late discontinuation (2.4±1.1 vs 1.6±1.0, p=0.001). Conversely, the corneal NV grade showed no significant difference in patients with early and late topical steroids discontinuation (3.1±1.2 vs 3.3±0.8, p=0.985). Similarly, no significant relationship was found between ocular allergy and the timing, grade or number of involved quadrants (p>0.05). The most frequent site of corneal NV was the superonasal quadrant (64.9% of eyes with NV), followed by the superotemporal (54.1%), inferonasal (47.3%) and inferotemporal (39.2%) ones.

DISCUSSION

Although neovessels involving the graft periphery may not affect vision, the resulting interruption of immune privilege increases the risk of subsequent stromal rejection. Furthermore, when neovessels extend towards the central cornea, lipid deposition and scarring may affect vision and eventually require repeat surgery. Finally, deep neovessels can invade the recipient stromal bed and persist even after lamellar graft exchange, thereby necessitating conversion to full-thickness keratoplasty.[11 12]

In this series, the cumulative incidence of corneal NV after DALK for corneal ectasia was 13%. Although corneal NV did not significantly affect the final CDVA, it was associated with increased risk of immune rejection and eventually required re-grafting in 13% of cases. The average keratoplasty-to-NV time was approximately 1 year, with most episodes (70.0%) occurring with sutures still in place, and few ones (6.8%) after the second year. As previously shown for stromal rejection,[9 15 16] the risk of corneal NV appears to decrease over time. Although much less frequent (<1%), the potential for late development of corneal NV underscores the need for continued follow-up.

One of the perceived advantages of DALK over PK is the reduced need for long-term steroids. The Ophthalmic Technology Assessment report by the American Academy of Ophthalmology suggests that topical steroids can be discontinued as early as 3–4 months after surgery.[17] However, there is still no consensus regarding the optimal postoperative regimen after DALK. While several authors discontinue steroids within 3–6 months,[18–21] others suggest continued steroid use for up to 2 years.[22] In this study, the postoperative steroid course was a strong predictor of corneal NV. Compared with eyes for which steroidal treatment was stopped only after complete suture removal, the eyes with early discontinuation of steroid treatment were twice as likely to develop corneal NV. Moreover, a shorter steroid regimen was associated with more aggressive corneal NV, with earlier onset and a significantly higher number of involved quadrants. Thereby, based on our results a prolonged steroid regimen following DALK is effective in preventing corneal NV. Though this therapeutic approach may lead to an increased risk of intraocular pressure elevation and cataract progression, these complications can be easily managed in most cases without affecting the long-term success of the transplant. Conversely, early discontinuation of steroid therapy appears to decrease graft survival, as indicated by the higher rate of re-grafting observed in this study.

Our results are in contrast with those of a previous study which did not find any association between the duration of postoperative steroid therapy and corneal NV.[23] There are several possible explanations for this discrepancy. First, different postoperative regimens were used. Second, PK may provide a stronger stimulus for corneal angiogenesis compared with DALK. Elimination of the endothelial antigenic load in DALK may decrease the immunological stimuli leading to corneal NV. This may also explain why the incidence of corneal NV observed in this study (13.2%) was remarkably lower compared with those reported after PK, which range from 41% to 67%.[23–25]

With regards to other risk factors, ocular allergy and older recipient age were significant predictors of corneal NV. Keratoconus is frequently associated with ocular allergic diseases such as vernal keratoconjunctivitis. Patients with both conditions tend to be operated earlier due contact lens intolerance and more rapid progression of ectasia.[26 27] Our results are in agreement with a previous comparative study which reported significantly higher rate of corneal NV in eyes that underwent DALK for vernal keratoconjunctivitis.[28] Although the long-term visual outcomes and graft survival in the two groups were comparable, the authors recommended closer monitoring in those with vernal keratoconjunctivitis.[28]

The association between age and corneal NV was unexpected and stands in contrast to the notion of a more active immune response in younger patients.[12] In fact, previous studies found younger age to be associated with higher risk of immune rejection after both PK and DALK,[9 29] The association might be mediated by other mechanisms such as poorer ocular surface status in older patients. However, since the magnitude of the association was low, this result should be interpreted with caution.

We recognise that the complications following DALK including the presence of broken sutures, immune rejection and infectious keratitis may either be cause or consequence of corneal NV. In such patients, corneal NV may not be related to the preoperative risk factors assessed in the regression analysis. Thus, we performed a sensitivity analysis excluding those cases to account for this potential source of bias. It is worthy to note that early discontinuation of topical steroids and older age still remained significant predictors for corneal NV.

Corneal NV most commonly occurred in the superior quadrants, as previously shown also for PK.[30] Conversely, the number of patients with high-degree corneal NV was higher than those reported after PK,[23 30] with neovessels crossing the graft-host junction and invading the donor cornea in more than half of cases. Previous studies on PK have documented frequent regression of corneal NV after suture removal,[26] while this was less likely to occur in our study. However, the causes of these differences between DALK and PK are yet unknown.

As with any retrospective study, the main limitations of our study were the loss to follow-up and the possible effect of unmeasured confounders such as the presence of floppy eyelid syndrome or the use of contact lens. Specifically, other variables besides the postoperative therapeutic regimen could have contributed to the differences observed in the two centres. However, inclusion of DALK cases for a single indication using of a standard technique and statistical analysis with multivariate adjustment support the association between steroids regimen and NV. Moreover, the temporal relationship between steroid regimen discontinuation and corneal NV further supports their association.

In conclusion, the risk of corneal NV is higher in the first year following DALK. Early discontinuation of topical steroids, ocular allergy and older age are independent risk factors for corneal NV. Prolonged steroid therapy should be considered to prevent corneal NV after DALK.

Contributors Concept and design of the study: MP, VS and MB. Data acquisition: VS, GG, AL, SV, CB and RS. Data analysis/interpretation: MP, VS, ACY and MB. Drafting the manuscript: MP, VS, GG, ACY and MB. Critical revision of manuscript: VS, MB and RS. Statistical analysis: MP and ACY. Final approval: MP, VS, GG, AL, SV, CB, ACY, CB, MB and RS.

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Competing interests None declared.

Patient consent for publication Not required.

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Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. All data relevant to the study are included in the article or uploaded as supplementary information

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