Factors Predictive of Double Anterior Chamber Formation Following Deep Anterior Lamellar Keratoplasty

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- PURPOSE: To identify risk factors predictive of postoperative double anterior chamber formation after deep anterior lamellar keratoplasty (DALK).
- DESIGN: Retrospective institutional cohort study.
- METHODS: The study group included all consecutive eyes undergoing primary DALK between May 2015 and October 2018 at Villa Igea private hospital (Forlì, Italy). The indications for surgery were categorized as (1) keratoconus without scarring; (2) keratoconus with scarring; (3) non-keratoconus without scarring; and (4) non-keratoconus with scarring. Multivariate binary logistic regression analysis was performed, introducing, as independent variables, those that reached a significance level of less than .05 in univariate analysis. The main outcome measure was whether or not postoperative double anterior chamber (AC) occurred.
- RESULTS: A total of 591 eyes of 591 patients were included. The main indication for DALK was keratoconus (67.2%, n = 397), and pneumatic dissection was achieved in 72.9% (n = 431) of patients. Postoperative double AC was observed in 8.1% (n = 48) of cases. Age, intraoperative central DM perforation, type 2 bubble formation, and presence of scar in keratoconic and nonkeratoconic corneas were all associated with an increased risk of postoperative double AC formation in the univariate analysis. Manual dissection was not associated with double AC formation. The factors that remained significant in multivariate analysis were keratoconus with scarring (odds ratio [OR] = 3.56, P = .02), non-keratoconus with scarring (OR = 5.09, P = .002), intraoperative central perforation (OR = 6.09, P = .03), and type 2 bubble formation (OR = 14.17, P < .001).

- CONCLUSIONS: Scarred corneas of both normal and abnormal shape are independent risk factors for double AC formation following DALK, along with intraoperative perforation and the occurrence of a type 2 bubble. (Am J Ophthalmol 2019;205:11–16. © 2019 Elsevier Inc. All rights reserved.)

DEEP ANTERIOR LAMELLAR KERATOPLASTY (DALK) is a technique whereby diseased corneal stroma can be selectively removed while retaining host endothelium.[1] Outcomes of DALK vs penetrating keratoplasty (PK) have been well described previously, and, broadly, DALK minimizes the risk of complications associated with open-sky surgery, eliminates endothelial rejection,[2] and offers earlier visual rehabilitation[3] compared with PK. The commonest surgical technique used for DALK is that of the "Big Bubble,"[1] whereby the anterior stroma is cleaved from the underlying Descemet membrane (DM) by way of pneumatic dissection, and results in a cleavage plane either above or below the pre-Descemet layer (PDL). A pre-Descemetic pneumatic dissection is anatomically favorable because of the inherent strength lent by the PDL to the underlying DM[4] and the subsequent reduced risk of intraoperative perforation, compared with leaving bare DM alone.

Inadvertent perforation of DM, even if surgery is still successfully completed without the need for conversion to PK, has been described to lead to an increased risk of early postoperative detachment of the recipient bed[5] and consequent double anterior chamber (AC) formation (Figure). Although there are reports of spontaneous resolution, this complication usually requires rebubbling of the AC with air or gas to be managed successfully.[6]

However, in the past few years our group has noted that double AC formation may occur without a perforation detected intraoperatively, while, on the other hand, an intraoperative perforation does not necessarily lead to formation of a double anterior chamber. To our knowledge, risk factors other than intraoperative perforation have not been identified, but should be investigated in an attempt at reducing the risk of postoperative double AC following DALK, which may have an impact on final visual outcomes.[7,8]

The purpose of this study therefore was to identify factors predictive of postoperative double anterior chamber

formation after DALK using a large institutional database. We hypothesized that nonkeratoconic, scarred corneas were associated with an increased risk of postoperative double AC formation when compared with keratoconic, nonscarred corneas.

METHODS

• STUDY DESIGN: This was an institutional retrospective cohort study performed at Villa Igea private hospital (Forli, Italy). The medical records of all successfully completed DALKs for all indications performed between May 1, 2015 and October 31, 2018 were evaluated. All data had been initially collected prospectively and entered into the institutional database. The study followed the tenets of the 2013 Declaration of Helsinki and was approved by the local ethics committee of Villa Igea Hospital (Forlì, Italy).

All operations were performed at Villa Igea Hospital by either a senior surgeon or a fellow supervised by a senior surgeon.

• SURGICAL TECHNIQUE: DALK was performed as per our previously described technique.[6] Briefly, a deep trephination of 9 mm diameter was performed to a depth of 450-550 μm, and a blunt probe was advanced 1 mm centripetally from the base of the trephination. The probe was replaced by a cannula, which was advanced 1 mm further along the same track created by the probe, before pneumatic dissection was performed. Following debulking of the anterior stroma, a 6 mm optical zone of PDL or DM was bared, depending on the plane of dissection achieved. A 9 mm anterior lamellar graft was prepared by means of a 400 μm microkeratome head and sutured into place.

• INTRAOPERATIVE PNEUMATIC DISSECTION: Using the classification described by Dua,[4] a "type 1" bubble was defined as a well-circumscribed dome-shaped elevation extending up to 8.5 mm in diameter, and "type 2" as a larger-diameter bubble, starting peripherally and enlarging centrally. Cases in which pneumatic dissection failed were either recorded as having undergone successful layer-by-layer manual dissection or excluded from the study if macroperforation mandated conversion to PK.

• INTRAOPERATIVE PERFORATION: If intraoperative microperforation occurred, the location of the perforation was recorded as being "central" (within the central 4 mm) or midperipheral (within 4-6 mm of the center). Since we only bare 6 mm of PDL/DM, all perforations are within these parameters. Any patient with intraoperative microperforation identified underwent prophylactic AC tamponade with air postoperatively.

• POSTOPERATIVE DOUBLE ANTERIOR CHAMBER DIAGNOSIS AND MANAGEMENT: Double AC was diagnosed as the appearance of fluid between the posterior stroma and the residual host bed to any extent (Figure), confirmed with anterior segment optical coherence tomography (ASOCT). All cases of postoperative double AC underwent "rebubbling" of the AC with filtered air within 48 hours. Complete AC air fill was maintained for 2 hours before release of air at the slit lamp to achieve a fluid level at the height of the inferior pupillary border, eliminating the risk of pupil block.

• INDICATION GROUPING: We categorized the indications for surgery as follows: (1) keratoconus without scarring; (2) keratoconus with scarring; (3) non-keratoconus without scarring; and (4) non-keratoconus with scarring.

• SURGEON GROUPING: In keeping with published definitions of experience relevant to the learning curve in DALK,[9] we allocated the surgeons in the study to 3 groups representing relative surgical experience based on the number of keratoplasties previously performed. The 3 groups were labeled "experienced," "relatively experienced," and "inexperienced" surgeons (>100, 10-100, and <10 previous keratoplasties performed, respectively).

• STATISTICAL ANALYSIS: All data collected in the study were entered into an electronic database via Microsoft Excel 2007 (Microsoft Corp, Redmond, Washington, USA) and analyzed with Minitab Software, version 17 (Minitab Inc, State College, Pennsylvania, USA). Whenever appropriate, for the analysis of quantitative measures the Student t test for normally distributed variables and the Kruskal-Wallis test for nonparametric variables were used. χ^2 or Fisher exact test were used, as indicated, for the analysis of categorical variables. Multivariate binary logistic regression analysis was then performed, introducing, as independent variables, those that reached a significance level of less than .05 in univariate analysis. The normit link function was chosen as it produced the best goodness-of-fit results. Variables that reached a significant level of less than .05 in multivariate analysis were considered significant.

RESULTS

DURING THE STUDY PERIOD THERE WERE 705 DALKS ATTEMPTED in total, 114 of which (16.2%) were converted to a mushroom-shaped PK.[10,11] The indications for conversion to PK included failure to clear the optical zone of full-thickness opacity and/or macroperforation. The remaining 591 eyes having undergone successfully completed DALK were included for analysis. The mean age was 41.1 ± 16.3 years (range: 3-87 years), and 62.1%
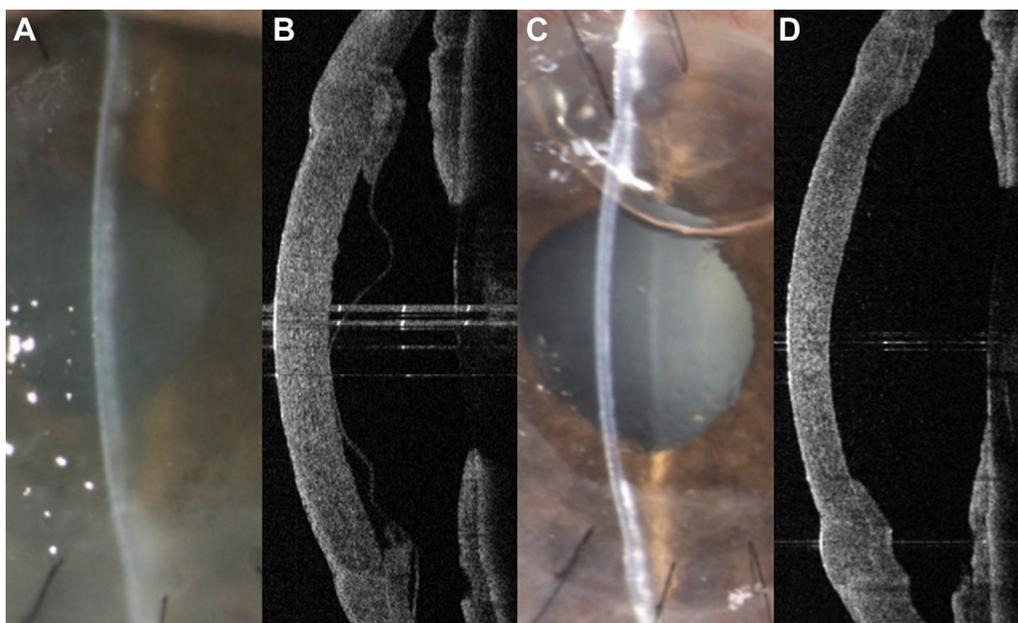
FIGURE. Before and after rebubbling of a postoperative double anterior chamber with air. (A–D) Stromal edema 1 day postoperatively (A), suggestive of double anterior chamber formation, confirmed with anterior segment optical coherence tomography (ASOCT; B). (C) Successful rebubbling with reattachment of Descemet membrane, confirmed with ASOCT (D).

TABLE 1. Diagnosis in Patients Undergoing Deep Anterior Lamellar Keratoplasty

Diagnosis	Number of Patients (N = 591)
Keratoconus	397
Scar secondary to herpes simplex keratitis	88
Scar secondary to bacterial keratitis	31
Corneal stromal dystrophy	30
Ocular surface disease (rosacea, exposure keratitis)	23
Refractory corneal haze following excimer laser	5
Previous superficial surgery (Salk, Intacs)	7
Previous trauma	10

were of male sex. The indications for DALK are summarized in Table 1, but the main indication was keratoconus (67.2%, n = 397). Pneumatic dissection was achieved in 72.9% (n = 431) of patients. No cases underwent simultaneous cataract surgery. There was no significant difference (P = .28) between postoperative intraocular pressure in the double AC group (15.8 ± 3.6 mm Hg) and the control group (16.4 ± 3.9 mm Hg). There was a difference in type 2 bubbles among the 4 indications for surgery (P < .001). Non-keratoconus with scarring had an 8.5% incidence of type 2 bubble; non-keratoconus without scarring, 3.5%; and keratoconus with scarring, 2.6%; and no type 2 bubbles were noted in the keratoconus without scarring group.

The presence of a double AC was identified in 8.1% (n = 48) of cases. One single rebubbling attempt was successful in resolving the double AC in 87.5% (42/48) of the cases. However, 8.3% (4/48) of cases required rebubbling twice, and 4.2% (4/48) required rebubbling 3 times for successful management of postoperative double AC. No cases had persistent detachment requiring conversion to PK.

• UNIVARIATE ANALYSIS: Table 2 depicts a comparison between patients with postoperative double AC and those without. Briefly, the rebubbling group was older (49.4 ± 16.4 vs 40.4 ± 16.1 years, P = .001), had a greater proportion of intraoperative central perforation (8.3% vs 1.1%, P = .001), had a greater proportion of type 2 bubble (25.0% vs 1.3%, P < .001), and had a greater proportion of pseudophakic patients (12.5% vs 4.8%, P = .02). When compared to keratoconus without corneal scarring as the reference group, keratoconus with scarring (odds ratio [OR] = 4.42, P = .007) and non-keratoconus with scarring (OR = 9.61, P < .001) were associated with postoperative double AC, while non-keratoconus without scarring was not (P = .15). When comparing the rate of double AC formation between surgeons of differing experience, no difference was found (P = .40). Central intraoperative perforation was associated with double AC formation

TABLE 2. Comparison Between Patients With and Without Double Anterior Chamber Formation After Deep Anterior Lamellar Keratoplasty

Parameter	Double AC (N = 48)	No Double AC (N = 543)	Odds Ratio (95% CI)	P Value[a]
Age (years)	49.4 ± 16.4	40.4 ± 16.1	1.03 (1.01-1.05)	.001
Sex (male)	60.4% (48)	62.3% (338)	0.93 (0.51-1.69)	.80
Indication				<.001
Keratoconus without corneal scarring	10.4% (5)	43.3% (235)	Reference	-
Keratoconus with corneal scarring	27.1% (13)	26.5% (144)	4.42 (1.48, 12.15)	.007
Non-keratoconus without corneal scarring	4.2% (2)	5.0% (27)	3.48 (0.64, 18.82)	.15
Non-keratoconus with corneal scarring	58.3% (28)	25.2% (137)	9.61 (3.62, 25.46)	<.001
Manual dissection	22.9% (11)	27.4% (149)	0.79 (0.39-1.58)	.50
Type 2 bubble	25.0% (12)	1.3% (7)	25.52 (9.47-68.78)	<.001
Pseudophakic	12.5% (6)	4.8% (26)	2.84 (1.11-7.28)	.02
Surgeon				
%Experienced (n > 1000 surgeries)	95.8% (46)	90.1% (489)	reference	-
%Relatively experienced (n = 10-100 surgeries)	2.1% (1)	6.8% (37)	3.48 (0.47-25.95)	.22
%Inexperienced (n < 10 surgeries)	2.1% (1)	3.1% (17)	2.18 (0.13-36.91)	.65
Perforation				
No perforation	79.2% (38)	91.3% (496)	reference	-
Midperipheral perforation (4-6 mm)	12.5% (6)	7.6% (41)	1.91 (0.76-4.78)	.17
Central perforation (4 mm)	8.3% (4)	1.1% (6)	8.70 (2.35-32.15)	.001

AC = anterior chamber.
[a]Student t test for continuous data and χ^2 for categorical data.

TABLE 3. Multivariate Analysis of Factors Associated With Postoperative Double Anterior Chamber Formation After Deep Anterior Lamellar Keratoplasty

Parameter	R^2 (Total = 20.29%)	Odds Ratio (95% CI)	P Value[a]
Age	3.85%	1.02 (1.00-1.04)	.06
Indication	6.75%		.006
Keratoconus without corneal scarring	-	Reference	-
Keratoconus with corneal scarring	-	3.56 (1.22, 10.43)	.02
Non-keratoconus without corneal scarring	-	1.86 (0.31, 11.29)	.50
Non-keratoconus with corneal scarring	-	5.09 (1.80, 14.35)	.002
Perforation	1.72%	2.78 (1.17-6.62)	.04
No perforation	-	Reference	-
Midperipheral perforation (4-6 mm)	-	2.19 (0.79-6.04)	.13
Central perforation (4 mm)	-	6.09 (1.17-31.65)	.03
Type 2 bubble	7.90%	14.17 (4.90-40.98)	<.001
Pseudophakic	0.07%	1.44 (0.44-4.69)	.55

[a]Binary logistic regression including all variables that were $P < .05$ in univariate analysis.

(OR = 8.70, P = .001), while midperipheral perforation was not (OR = 1.91, P = .17).

• MULTIVARIATE ANALYSIS: The results of the multivariate analysis of factors associated with postoperative double AC formation are depicted in Table 3. Briefly, factors that remained significant in multivariate analysis were keratoconus with scarring (OR = 3.56, P = .02), non-keratoconus with scarring (OR = 5.09, P = .002), intraoperative central perforation (OR = 6.09, P = .03), and type 2 bubble formation (OR = 14.17, P < .001). Fifty-one eyes were found to have more than 1 risk factor for double AC formation, comprising 8.6% of the entire cohort.

DISCUSSION

THE AIM OF THIS STUDY WAS TO IDENTIFY RISK FACTORS associated with double AC formation following DALK. The incidence of double AC formation has not been reported before, but in this series of almost 600 consecutive cases amounted to 8%. The most commonly reported association with double AC formation is intraoperative perforation, the incidence of which in a similar sized series was recently reported as 19%,[12] and 16% when macroperforations were excluded. However, in this study the intraoperative perforation rate excluding macroperforation was just under 10%. This may represent a different case mix, although we believe the difference to be consistent with our technique of only baring the central 6 mm optical zone of PDL or DM, and underpins the rationale for our previously described small bubble DALK technique.[6] Since the surface area of a circle is proportional to the square of the radius, by only baring a 6-mm-diameter optical zone of PDL as opposed to the more conventional 8 mm, the surface area that can be potentially perforated is approximately halved. Furthermore, since we found that unlike central intraoperative perforation, peripheral intraoperative perforation does not increase the risk of double AC formation, it is possible that the posterior composition of the wound in this modified technique promotes closer apposition of DM or PDL to the overlying transplanted stroma. It would, however, have been interesting to correlate the site of perforation with the exact site of any preexisting scar, but we unfortunately did not have these data available for comparison.

We hypothesized an increased risk of double AC formation in scarred, nonkeratoconic eyes. This hypothesis was supported through the findings of the multivariate analysis, which identified a highly significant ($P = .002$) odds ratio of 5.09 of double AC formation in these eyes relative to nonscarred keratoconic eyes. The rationale for our hypothesis was 2-fold. Firstly, the shape of keratoconic eyes leads to gradual stretching of the DM over time.[13] Accordingly, when the anterior, ectatic stroma of the cone is selectively replaced during DALK, the host DM is subsequently flattened under the pressure exerted by the new donor anterior lamella and may be less likely to detach. The presence of folds in DM observed following DALK is supportive of this mechanical concept of redundant DM.[14] Secondly, our experience is that a "type 2" bubble—that is, in between PDL and DM—is more likely to occur in scarred corneas than in nonscarred corneas. It is likely that when the host stromal bed contains PDL in addition to DM, as is the case in a type 1 bubble, not only is there reduced risk of perforation because of the protection of the PDL overlying the DM, but also the rigidity added by the PDL to the corneal bed means it is less likely to detach. However, the multivariate analysis established type 2 bubble as an independent risk factor to corneal scarring, both in normal and abnormal shaped corneas. Therefore, it is likely that there are other factors inherent to corneal scarring related to double anterior chamber formation other than merely being associated with increased incidence of type 2 bubble formation.

The fact that type 2 bubble formation itself, even in the absence of intraoperative perforation is a risk factor for double AC formation, may be related to the fenestrations found between the origin of the trabecular meshwork and the termination of DM. Unlike a type 1 bubble, which tends not to extend beyond the central 8.5-9 mm, the air in a type 2 bubble extends all the way to the periphery. It is therefore possible that during this maneuver a potential peripheral communication into the space above DM is potentiated, through which aqueous fluid may enter postoperatively.[15] Various management approaches to type 2 bubble have been proposed.[16] Our approach is a combination of Anwar's "DM Baring DALK" and "Microbubble Incision DALK"[17] techniques. Following type 2 bubble creation we perform manual dissection until we reach the plane devoid of microbubbles, which we assume to be the PDL. We then perforate the ceiling of the bubble under viscoelastic protection to avoid its sudden collapse, inject viscoelastic into the bubble cavity to distantiate its floor, and remove only the central 4 mm of PDL. This diameter is sufficient to clear an optical zone large enough to prevent any visual disturbance even in scotopic conditions; and in fact, postoperatively we have not recorded any subjective complaints from any patient.

One further clinical point worth highlighting is the importance of ASOCT imaging in the early postoperative phase. As seen in the Figure, often the main sign at the slit lamp of a double AC is stromal edema, indicative of the loss of endothelial pump function, rather than an easily identifiable interface, and therefore ASOCT is imperative in the management of these patients.

Since the data in this series were collected prospectively, we do not consider the retrospective nature of the study to be a limitation. We do recognize, however, that our technique differs from elsewhere, and it would therefore be interesting for other centers to report on their experiences of postoperative double AC formation. It is possible that keratoconus is disproportionately favored through our technique, owing to our posterior, stepped stromal wound configuration being able to accommodate redundant DM more readily than in a conventional DALK technique. Indeed 1 center reported a similar technique of central optical zone clearance alone being particularly effective in advanced keratoconus.[18] Other risk factors may also emerge from different techniques being reported. For example, there are reports elsewhere of retained host DM on the donor graft being associated with DM detachment postoperatively.[14] However, this is not a factor we could

examine in our series, since our grafts are prepared with a microkeratome rather than manually peeling the DM from the graft.

In conclusion, the results of this study demonstrate that scarred corneas of both normal and abnormal shape are independent risk factors for double AC formation following DALK, along with central intraoperative perforation and the occurrence of a type 2 bubble. Careful preoperative planning is imperative in all cases, including highlighting the possibility of a second procedure to patients. Preemptive AC air tamponade should be considered at the end of cases deemed to be high risk for double AC formation.

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