Relationship between Postoperative Intraocular Pressure and Refractive Outcomes in Patients after Deep Anterior Lamellar Keratoplasty

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Abstract

Purpose: To study the effect of intraocular pressure (IOP) on refractive outcomes after deep anterior lamellar keratoplasty (DALK).

Methods: This retrospective study included eyes which underwent DALK. DALK technique involved either modified Anwar big-bubble if possible or manual anterior lamellar dissection. Our main outcome measures are postoperative IOP and refractive outcomes at postoperative week and months 1, 3, 6, and 12.

Results: Fifty-nine eyes of 59 patients were included. DALK was performed for optical (93.2%) and tectonic (6.8%) purposes. 76.3% of the patients had keratoconus. Anwar's big-bubble technique was successful in 30 cases. Linear mixed-model was used to analyze the effect of the highest postoperative IOP measured prior to measurement of postoperative cylinder. Patients with greater maximum postoperative IOP measured had worse postoperative cylinder ($P = 0.015$) and spherical equivalent ($P = 0.012$). Those with IOP more than 21 mmHg had worse postoperative cylinder ($P = 0.050$) and spherical equivalent ($P = 0.054$). The method of DALK and presence of suture removal were not shown to statistically affect postoperative cylinder.

Conclusion: Our study shows a positive correlation between postoperative IOP and worse spherical equivalent and cylinder post-DALK, emphasizing the need for good IOP control with IOP-lowering medication(s).

Keywords: Big-bubble, Deep anterior lamellar keratoplasty, Intraocular pressure, Refractive outcomes

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Submitted: 01-Jul-2021; **Revised:** 14-Nov-2021; **Accepted:** 14-Nov-2021; **Published:** 16-Apr-2022

Introduction

Deep anterior lamellar keratoplasty (DALK) is a partial-thickness corneal transplant.[1] It removes and replaces most of the diseased stroma with a donor lamellar graft without substituting the host endothelium.[2] This technique is most useful for treating corneal pathologies in the circumstances of a normally functioning endothelium.[1,3] The majority of patients with keratoconus who undergo corneal transplantation are young.[2] Having a clear corneal graft is not sufficient to determine the success of the keratoplasty. The establishment of an acceptable visual acuity with a minimal refractive error that lasts for the majority of a lifetime has become the primary aim.

Huang *et al*. reported an episode of elevated intraocular pressure (IOP) occurring in 36.1% of post-DALK cases, of which 11.4% occurred within the 1st week.[4] Another study done by Dada *et al*. showed a positive correlation between the IOP reduction and the change in the corneal elevation, possibly

Access this article online
Quick Response Code:
Website: www.jcurrophthalmol.org
DOI: 10.4103/joco.joco_211_21

How to cite this article: Wei Wei DY, Shen L, Manotosh R, Wee Tien AT, Hui-Chen CC. Relationship between postoperative intraocular pressure and refractive outcomes in patients after deep anterior lamellar keratoplasty. J Curr Ophthalmol 2022;34:30-6.

indicating that in addition to inherent corneal pathology which leads to corneal ectasia in vernal keratoconjunctivitis (VKC), the IOP may play an additional role in producing corneal steepening and increasing the posterior corneal elevation.[5] As with penetrating keratoplasty, residual myopia and astigmatism after complete suture removal are the most common morbidities after DALK, preventing patients from achieving acceptable visual acuity.[2] Elevated IOP has been assumed to cause scleral stress and creep, resulting in axial eye elongation with scleral stretch.[6] Decreased rigidity of the ocular wall in keratoconus, which is one of the indications for DALK, might predispose the eye to the effect of raised IOP postoperatively and affect refractive outcomes. We hypothesize that the greater the postoperative IOP, the worse the postoperative refractive outcomes would be.

Few studies examine the relationship between postoperative IOP and its effect on postoperative refractive outcomes. A search on PubMed, EMBASE, and CENTRAL without any language restrictions, using keywords "DALK", "intraocular pressure", "astigmatism", and "refraction" found no previous articles reporting how IOP affects refractive outcomes following DALK. Our study aims to describe the relationship between postoperative IOP and refractive outcomes in patients who underwent DALK.

Methods

The study reviewed patients who had DALK procedures performed in a tertiary institution between January 2011 and January 2019. This study was approved by the National Health Group Institutional Research Board, which is in charge of research done in the National University Health System. Waiver of informed consent was obtained.

Patients were identified retrospectively from operating theatre records. We excluded eyes that had raised IOP prior to surgery, and/or had prior diagnosis of glaucomatous eye(s) as cause of raised IOP might not be due to the surgery *per se*, and/or had concurrent procedures done intraoperatively on top of DALK and/or had any other procedures done postoperatively that might have affected astigmatism during the data collection period. A retrospective review of patients' medical records was carried out in patients who were at least 6 months' post-DALK, as that is usually the time period where refractive parameters would be evaluated and for the cornea graft to stabilize.

Baseline characteristics including visual acuity, refraction, indication for surgery, and IOP were recorded. IOP measurements were taken by the surgeon using Tono-Pen AVIA (Reichert Technologies) was used. Visual acuity was taken with a Snellen chart and converted to logMAR for statistical analysis. The reciprocal of the Snellen visual acuity was converted to log10 form to obtain the logMAR value.

Surgeries were performed by 2 corneal surgeons, using the modified Anwar technique or a manual layer-by-layer deep dissection technique if the big-bubble technique was unsuccessful or deemed unsuitable for the case.[7] All surgeons were fully accredited to perform corneal transplants in Singapore.

The modified Anwar big-bubble technique[8] involved partial trephination using a Hanna trephine followed by manual dissection of the stroma to a depth of approximately 50%–70%. This left 150–200 mm of residual stroma. A 27-gauge needle or DALK air injection cannula (Rycroft Air Injection Cannula; ASICO, Illinois, USA) attached to an air-filled 5-mL syringe was inserted bevel-down into the paracentral cornea. Air was injected to create a cleavage plane between the Descemet's membrane (DM) and the posterior stroma. After a big bubble had been successfully created, a slit was created in the posterior stroma to break the big bubble and gain access to the DM, and the remnant posterior stromal tissue was removed in 4 quadrants. If the creation of a big bubble was unsuccessful, the procedure would then be converted to a manual technique.

The manual technique used a crescent blade to dissect the anterior lamellar. The dissection was done layer-by-layer down to the predescematic plane.

In both the techniques, the donor cornea was punched using a Hanna trephine, and the DM, endothelium, and epithelium were stripped off. The donor cornea was sized to match the recipient bed, typically about 8 mm to ensure adequate removal of the diseased cornea. It was then sutured onto the recipient bed with 10-0 nylon monofilament sutures in a double continuous fashion. Placido's disk was used on table, and suture tension was adjusted accordingly to achieve astigmatic neutrality as best as possible. A bandage contact lens was placed to aid re-epithelialization. The patient was then started on 3 hourly prednisolone acetate and levofloxacin eye drops that were gradually tapered over a few months and eventually stopped. Patients were reviewed at postoperative week 1, months 1, 3, 6, and year 1. Postoperative visual acuity, IOP, and examination findings were recorded at the various time points when available after removal of bandaged contact lens. Postoperative cylindrical and spherical results were recorded at postoperative months 3, 6, and year 1 at the various time points when available.

Statistical analysis was performed using SPSS software for Windows (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY, USA). A $P \leq 0.05$ was considered to be statistically significant. Patients' demographics and baseline characteristics were analyzed descriptively. Linear mixed-model analyses were used to assess the influence of postoperative IOP, operation type, suture removal, and pathology type, on the postoperative cylinder and spherical equivalent measured at 3, 6, and 12 months after the operation.

Results

There was a total of 87 eyes that underwent DALK during the study period. After excluding cases as per the exclusion criteria, 59 eyes from 59 patients were included in our study.

Cases were performed for optical (93.2%) and tectonic (6.8%) purposes. Patients had cornea scar from interstitial keratitis, previous cornea laceration, and previous pterygiectomy. Anwar's big-bubble technique was successful for 30 cases while 29 cases required manual dissection. Table 1 illustrates the baseline characteristics of the cases included. There were no cases of chronic graft rejection or failure. Postoperatively, one patient developed glaucoma and underwent trabeculectomy while two patients had a double anterior chamber that required surgical intervention with anterior chamber re-bubbling. Postoperative outcomes are shown in Table 2. Measurements were taken at different time points. At postoperative months 12, mean spherical equivalent was −3.15 (range, −11.50 diopter [D] to 4.13 D), and mean cylinder was −3.26 D (range, −9.00 D to 0.00 D). Figure 1a-d demonstrate the refractive outcomes postoperatively.

In Table 3, the linear mixed-model, with maximum IOP as a continuous variable, showed that the maximum postoperative IOP measured before or at the follow-up visit is associated with the cylinder measured at 3, 6 and 12 months after surgery (P = 0.015). For clinical recommendation, we dichotomized the maximum IOP to >21 mmHg and less or equal to 21 mmHg, depicted in Table 4. We kept the other variables compared constant, i.e., type of surgery, suture removal, and pathology type. Patients with a maximum postoperative IOP measured before or at the follow-up visit more than 21 mmHg would have a worse postoperative cylinder by 0.92 D (95% confidence interval [CI] −1.832–0.002, P = 0.050). The postoperative cylinder was not shown significantly different between two methods of DALK (big-bubble versus manual dissection). Pathology type and whether suture removal was done were not significantly associated with the postoperative cylinder either. Patients without sutures removed have 1.15 D worsening in mean cylinder compared with those with suture removed (P = 0.107, 95% CI − 0.255–2.556). The details of the linear mixed-model result are summarized in Table 3. Figure 2 depicts the cluster error bar chart of postoperative cylinder over time.

Table 3 also summarizes the linear mixed-model result for the postoperative spherical equivalent. It showed a significant association between the maximum postoperative IOP measured before or at the follow-up visit and the postoperative spherical equivalent (P = 0.012). Table 4 shows the linear mixed-model after dichotomizing the maximum IOP. Patients with maximum postoperative IOP measured before or at the follow-up visit more than 21 mmHg would have worse postoperative spherical equivalent by 1.72 D (95% CI − 3.462–0.030, P = 0.054) compared with those with maximum postoperative IOP ≤21 mmHg. The method of DALK (big-bubble vs. manual dissection) was not shown to statistically affect postoperative spherical equivalent. Pathology type and presence of suture removal did not affect outcomes postoperatively as well. Figure 3 depicts the cluster error bar chart of postoperative spherical equivalent over time.

Table 1: Baseline characteristics of deep anterior lamellar keratoplasty cases

Variables	n (%)
Gender	
Male	34 (57.6)
Female	25 (42.4)
Age (years), mean±SD	30.25±15.30
Race	
Chinese	18 (30.5)
Malay	10 (16.9)
Indian	24 (40.7)
Others	7 (11.9)
Pathology	
Keratoconus	45 (76.3)
Cornea scar	13 (20.0)
Others	1 (1.7)
Lens status	
Phakic, no cataract	51 (86.4)
Cataract	4 (6.8)
Pseudophakic	4 (6.8)
Surgical technique	
Manual dissection	29 (49.2)
Big-bubble	30 (50.8)
Preoperative best corrected visual acuity (logMAR), mean±SD	0.86±0.10
Preoperative intraocular pressure (mmHg), mean±SD	13.4±0.6
Mean follow-up period (month), mean±SD	11.7±1.32

SD: Standard deviation

Discussion

Our study showed that maximum postoperative IOP was significantly correlated with higher spherical equivalent post-DALK (P = 0.012). Maximum IOP of >21 mmHg had marginal significance (P = 0.054). Optical integrity depends on various rheological factors: how the ocular tissues (cornea, sclera, and lens) deform in response to forces applied. The ratio of force or stress, to deformation or strain, is termed the elastic (Young's) modulus.[9,10]

A study done by Hjortdal on 18 human corneas showed that in the limbal region, Young's modulus of elasticity is highest circumferentially and lowest meridionally.[11] This is suggestive that with increase in IOP, there is less expansion of the cornea diameter at the limbus, with increased flexibility to expand in thickness. Cornea curvature is supported, and shape changes that may occur with fluctuations of IOP are regulated and restricted. However, with the limbal integrity being affected during a DALK transplant, the ability of the cornea to restrict any changes might be limited, resulting in spherical and astigmatic changes.

Asejczyk-Widlicka and Pierscionek studied the relationship of IOP fluctuations and the aberration formation, in addition to the elastic properties of the human eye.[12] They showed significant associations between the changes in IOP and variations in corneal radius and spherical equivalent found between midday and afternoon measurements. Variations in IOP observed in

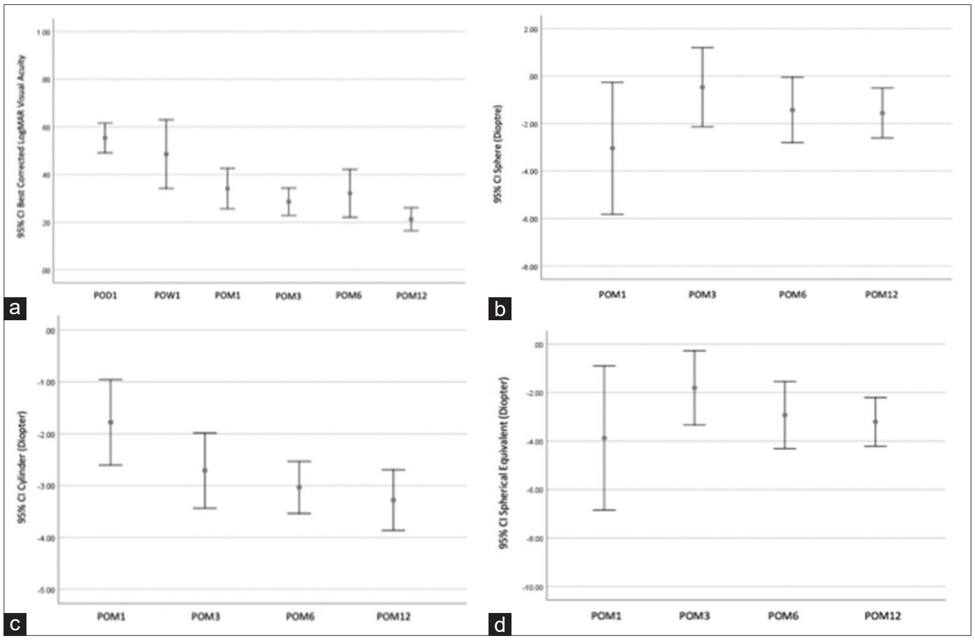

Figure 1: Changes of visual acuity (a), spherical refraction (b), cylinder (c) and spherical equivalent (d) over time. POM1: Postoperative month 1, POM3: Postoperative months 3, POM6: Postoperative months 6, POM12: Postoperative months 12, CI: Confidence interval

Table 2: Postoperative outcomes

Outcome	Postoperative week 1	Postoperative month 1	Postoperative month 3	Postoperative month 6	Postoperative month 12
IOP (mmHg)					
Mean±SD	16.8±2.9	20.1±7.0	19.2±7.3	18.1±6.4	15.5±4.4
n	47	49	48	47	42
Maximum IOP (mmHg) measured before or at the current visit					
Mean±SD			22.6±7.7	23.7±7.8	23.8±7.7
n			57	59	59
Spherical equivalent (D)					
Mean±SD	-	-	−2.19±4.201	−2.93±3.974	−3.15±3.173
n			27	34	42
Cylinder (D)					
Mean±SD	-	-	−3.03±2.521	−3.04±1.460	−3.26±1.901
n			29	35	45
Postoperative best corrected visual acuity (logMAR)					
Mean±SD	0.664±0.630	0.509±0.570	0.380±0.367	0.350±0.406	0.243±0.273
n	55	57	54	56	55

IOP: Intraocular pressure, SD: Standard deviation

humans could lead to slight alterations in corneal curvature, causing a change in its dioptric power and axial length of the eye to an extent that could affect visual quality.

Our study demonstrated worsening astigmatism trends with greater IOP ($P = 0.015$) and when IOP >21 mmHg post-DALK ($P = 0.050$). The presence of suture was not shown to statistically affect the astigmatic outcome of our study. Feizi and Javadi evaluated factors that predicted refractive outcomes after DALK in patients with keratoconus.[2] Postoperative refractive outcomes were not correlated with elevated IOP. However, specific measurements and *P* values were not stated in the paper. It was noted that these results were taken after suture removal as such wound healing and scarring might have decreased the effects of IOP.

A study on VKC patients exhibited flattening of corneal curvature and significant reduction in mean posterior corneal elevation (from 64.9 ± 22.36 µm to 35.7 ± 28.91 µm at 3 months) after reduction of IOP ($P = 0.001$). There was also a positive correlation between the change in corneal elevation and IOP reduction, suggesting that IOP may play a role in producing corneal steepening and increasing posterior corneal elevation, on top of the inherent corneal pathology which leads to corneal ectasia in VKC.[5] McMonnies and Boneham reviewed corneal responses to IOP elevations in keratoconus eyes and

Table 3: Summary of linear mixed-model after adjustment for visit time correlation, with continuous maximum intraocular pressure (cylinder and spherical equivalent)

Variable	*P*	Mean difference of postoperative cylinder (D)	95% CI	
			Lower boundary	Upper boundary
Cylinder				
Follow-up visit				
Month 3	0.510	0.29	−0.577	1.150
Month 6	0.422	0.26	−0.379	0.889
Month 12		-	-	-
Type of surgery				
Manual dissection	0.646	0.23	−0.787	1.254
Big-bubble		-	-	-
Suture removed before follow-up visit				
Yes	0.107	1.15	−0.255	2.556
No		-	-	-
Pathology type				
Cornea scar and others	0.274	0.66	−0.538	1.850
Keratoconus		-	-	-
Maximum IOP before/during follow-up visit	0.015	−0.08	−0.139	−0.016
Spherical equivalent				
Follow-up visit				
Month 3	0.284	0.63	−0.542	1.811
Month 6	0.791	0.11	−0.691	0.901
Month 12		-	-	-
Type of surgery				
Manual dissection	0.519	0.73	−1.523	2.976
Big-bubble		-	-	-
Suture removed before follow-up visit				
Yes	0.629	−0.48	−2.480	1.511
No		-	-	-
Pathology type				
Cornea scar and others	0.807	0.31	−2.266	2.895
Keratoconus		-	-	-
Maximum IOP before/during follow-up visit	0.012	−0.16	−0.280	−0.037

IOP: Intraocular pressure, CI: Confidence interval, D: Diopter

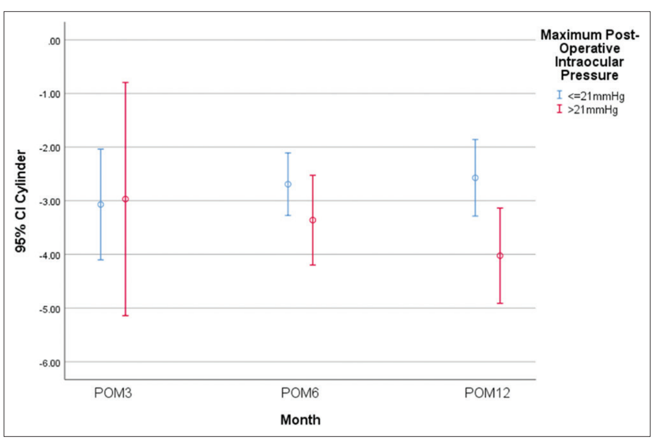

Figure 2: Cluster bar chart of postoperative cylinder over time. POM3: Postoperative months 3, POM6: Postoperative months 6, POM12: Postoperative months 12, CI: Confidence interval

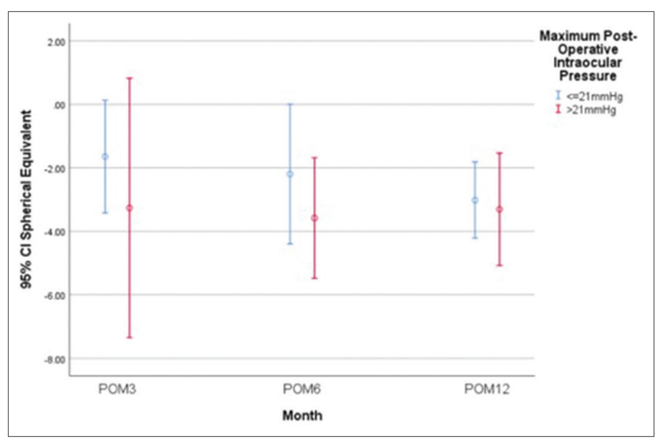

Figure 3: Cluster bar chart of postoperative spherical equivalent over time. POM3: Postoperative months 3, POM6: Postoperative months 6, POM12: Postoperative months 12, CI: Confidence interval

found that the control group showed minimal responses to IOP elevation. However, in response to IOP elevation, some keratoconus corneas showed abnormal distensibility with significant changes in steepest point curvature and both flat and steep simulated keratometry reading.[13] Following DALK, the host DM and endothelium are left intact. The presence of

Table 4: Summary of linear mixed-model after adjustment for visit time correlation, with dichotomized maximum intraocular pressure (cylinder and spherical equivalent)

Variable	*P*	Mean difference of postoperative cylinder (D)	95% CI	
			Lower boundary	Upper boundary
Cylinder				
Follow-up visit				
Month 3	0.497	0.23	−0.571	1.164
Month 6	0.378	0.28	−0.353	0.913
Month 12		-	-	-
Type of surgery				
Manual dissection	0.675	0.22	−0.827	1.265
Big-bubble		-	-	-
Suture removed before follow-up visit				
Yes	0.096	1.20	−0.216	2.615
No		-	-	-
Pathology type				
Cornea scar and others	0.357	0.56	−0.657	1.784
Keratoconus		-	-	-
Maximum IOP before/during follow-up visit (mmHg)				
>21	0.050	−0.92	−1.832	0.002
≤21		-	-	-
Spherical equivalent				
Follow-up visit				
Month 3	0.262	0.67	−0.514	1.849
Month 6	0.691	0.16	−0.638	0.953
Month 12	-	-	-	-
Type of surgery				
Manual dissection	0.537	0.72	−1.608	3.044
Big-bubble		-	-	-
Suture removed before follow-up visit				
Yes	0.655	−0.45	−2.451	1.553
No		-	-	-
Pathology type				
Cornea scar and others	0.924	0.13	−2.534	2.789
Keratoconus		-	-	-
Maximum IOP before/during follow-up visit (mmHg)				
>21	0.054	−1.72	−3.462	0.030
≤21		-	-	-

IOP: Intraocular pressure, CI: Confidence interval, D: Diopter

residual peripheral host corneal rim, which is still affected by the ectatic process, has been postulated to be the reason why postsurgical corneal biomechanics are unlike those of healthy corneas.[14] The human cornea has been found to change curvature in response to IOP increments of 5 mmHg, 8 mmHg, and 16 mmHg.[15-17] With limbal integrity being affected during DALK, cylindrical changes might be more pronounced with higher IOP.

We further hypothesized that the increase in astigmatism may be contributed by a slight differential point of weakness from donor cornea centration, which is exaggerated by the rise of postoperative IOP.

There are several limitations to our study including the retrospective nature and the relatively small sample size which limits the value of the regression analysis model; hence, a mixed-model analysis was used. An astigmatically neutral cornea was assumed to be achieved at the end of surgery with the use of a placido's disk, reducing the suture influence on refractive outcomes postoperatively. Ideally, axial length and topographical analyses should be carried out. To ensure that cause of high IOP was not due to angle closure, gonioscope, or anterior segment, optical coherence tomography findings should be evaluated. However, in view of the retrospective nature, these variables were not available. A large randomized control trial that objectively measures the corneal curvature and axial length at different time points after DALK and correlating this with postoperative IOP is necessary to further support our findings. Further research is also necessary to determine the duration of IOP rise that can result in permanent corneal topography changes.

In conclusion, our study shows a positive correlation between postoperative IOP and worse spherical equivalent and cylinder post-DALK. This emphasizes the need for good IOP control post-DALK through the use of IOP-lowering medications, which has important implications on the patient's eventual refractive and visual outcome. Target IOP postoperatively of <21 seems to be reasonable, with marginal significance correlation with astigmatism and spherical equivalent.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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