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Automated digital analysis of intraoperative keratoscopy and its correlation with postoperative astigmatism after big-bubble deep anterior lamellar keratoplasty

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Abstract

Purpose To investigate the correlation between postoperative corneal astigmatism (PCA) and values of intraoperative keratoscopy analyzed with a newly developed automated technique in patients undergoing big-bubble (BB) deep anterior lamellar keratoplasty (DALK).

Methods Photographs of keratoscope rings taken at the end of BB-DALK were analyzed using ImageJ for the calculation of "roundness" (*R*): values = 1 indicate a perfect circle. Pearson's correlation was used to evaluate the relationship between *R* and PCA that measured 1 week (V1), 3 months (V2), and 18 months (V3), postoperatively. The area under the curve (AUC) of receiver operating characteristic (ROC) curve was used to evaluate the accuracy of *R* for identifying patients with PCA < 3 diopters (D). The point on the ROC curve nearest to the coordinate (0,100) was used as a cutoff to determine sensitivity and specificity.

Results Data from 121 patients were included. The mean value of *R**was 0.93 ± 0.04 (range 0.76–0.99). *R* showed a significant correlation with PA at V3 ($R = -0.42$, $P < 0.01$). The ROC curve had an AUC of 0.69 (95% CI 0.59–0.79). A cutoff value of $R = 0.93$ had a sensitivity of 70.3% and specificity of 61.0% for identifying patients with PA < 3D at V3.

Conclusions This new digital analysis of keratoscope rings allows to identify with reasonably good diagnostic accuracy patients with low values of post-DALK astigmatism correctable with spectacles.

Keywords DALK · Deep anterior lamellar keratoplasty · Keratoscopy · Digital analysis · Astigmatism

Introduction

Deep anterior lamellar keratoplasty (DALK) consists of the replacement of diseased anterior corneal layers without removing the healthy Descemet's membrane and endothelium. The main advantages of DALK over penetrating keratoplasty (PK) include the reduced rate of either the immunological graft rejection and endothelial cell loss or the preservation of eye integrity [1–5]. Despite continuous refinements in the surgical techniques, high astigmatism remains an important drawback of the procedure that may require further surgery in up to 10% of cases [6, 7].

Factors that may contribute to post-DALK astigmatism include, among others, the size and centration of recipient trephination [8], the thickness distribution in the donor button [9], and the suturing technique used [10].

Recently, different attempts have been conducted to try to improve postoperative refractive outcomes in the setting of DALK. Among these, the use of large (9 mm in diameter) grafts has shown to reduce refractive error without any detrimental effects on the safety, thanks to the retention of recipient healthy endothelium that avoids irreversible immunologic rejection [11]. Additionally, the advent of femtosecond laser-assisted donor and recipient trephination has opened a new fascinating scenario, but to date the data are not significantly different from

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Key Messages

- Nowadays,the use of intraoperative keratoscopy haslimited practical value since provides qualitative information and the surgeon has to adjust the sutures according to his/her experienceu ntil achieving the shape of a presumed perfect circle.
- We developed and validated a new automatic system able to digitally analyze the pictures of keretoscopy rings obtained at the end of deep anterior lamellar keratoplasty with good inter-observer reliability.
- A good correlation between roundness of keratoscopy rings and late suture-out post-operative astigmatism was found.
- By applying the value of roundness of 0.93,we were able to identify patients with astigmatism lower than 3 diopters with a reasonably good diagnostic accuracy.a

the ones obtained with manual trephination; furthermore, there is no universal consensus on the type of laser-assisted wound design that could improve postoperative refractive outcomes [12, 13].

Both handheld and microscope-integrated keratoscopes are used since decades at the end of the surgery by many corneal surgeons to set an appropriate amount of astigmatism with the suture tension, thereby reducing postoperative astigmatic errors [14, 15]. A randomized clinical trial comparing visual and refractive outcomes after PK with and without intraoperative suture adjustment showed that the first group exhibited after surgery a decreased astigmatism and a more regular corneal topography [16]. Another subsequent trial confirmed that intraoperative suture adjustment was able to reduce both final astigmatism and the need for postoperative suture manipulation [17].

However, currently the use of keratoscopy has a limited practical value since the information provided is qualitative and the surgeon has to adjust the sutures according to his/her experience until the keratoscope rings achieve the shape of a presumed perfect circle.

In the present study, we employed and validated a novel technique based on digital image analysis to measure objectively the shape of the rings reflected by patient's cornea during intraoperative keratoscopy. We used this technique to analyze pictures of intraoperative keratoscopy taken at the end of DALK surgery and correlated these values with short- (suture-in) and long-term (suture-out) postoperative astigmatism. Furthermore, we calculated the diagnostic performance of this digital image analysis system to predict low values of post-DALK astigmatism that are fully correctable with spectacles.

Methods

Study design

This retrospective study was conducted at the Department of Ophthalmology of the University of Magna Graecia (Catanzaro, Italy). The study followed the tenets of the Declaration of Helsinki and was approved by the local Institutional Review Board. Data from medical charts of consecutive patients who underwent big-bubble DALK between January 2017 and September 2018 were retrieved. Data from patients who did not attend regular and complete follow-up visits or experienced any type of postoperative complications (e.g., eyes with inflammation/infection, corneal neovascularization, immunological rejection, infection and wound dehiscence) that are associated with astigmatism changes were excluded from the analysis.

Surgical procedure

Surgery was performed in all eyes by a single experienced surgeon (V.S.), as per our previously described technique [18]. Briefly, the geometric center of the cornea was marked, and a 9-mm circular incision was created with a disposable Hessburg-Barron suction trephine (Katena Products Inc., Denville, NJ). The incision had a depth of approximately 80% of the total corneal thickness. Pneumatic dissection was attempted by first advancing a dedicated probe and then a cannula up to 2–3 mm centripetally from the bottom of the deep trephination. Then, an anterior keratectomy was performed to debulk approximately 80% of the recipient anterior stroma. When pneumatic dissection succeeded, adhesive viscoelastic substance (IAL-F, Fidia, Padova, Italy) was laid centrally onto the bubble roof, and a 15° blade was used to enter the bubble. The inferior arm of a blunt Vannas scissor was inserted into the collapsed bubble through the slit obtained with the 15° blade, which was enlarged to allow completion of the removal of the bubble roof by means of corneal scissors. When pneumatic dissection failed, the procedure was continued, attempting injecting ophthalmic viscoelastic device (OVD) (VIVACY sodium hyaluronate 1.55%, I-SPACE Laboratoires, La Ravoire, France) through a cannula inserted into the same stromal path used for pneumatic

dissection, according to the surgical steps previously described [19]. If also OVD-assisted dissection failed, a layer-by-layer manual dissection was performed aiming at reaching a level in the deep stroma free from all micro-bubbles. The donor cornea was punched from the endothelial side with a Barron donor punch (Katena Products, Inc.) of the same diameter of the trephine used on the recipient cornea. Then, after staining with 0.06% Trypan blue dye (VisionBlue; D.O.R.C., Zuiland, the Netherlands), the Descemet's membrane and endothelium were gently stripped off using a dry Weck-Cel sponge. Four interrupted 10-0 nylon sutures was secured temporarily the graft into the recipient bed, and the surgery was completed with 2 running, 10-0 nylon sutures of 16 bites each. In all patients, 1 of the 2 running sutures was removed 3 months postoperatively, while the second suture was removed 12 months postoperatively.

Keratometric astigmatism evaluation

The Casia swept-source optical coherence tomography (Casia; Tomey, Tokyo, Japan) was used to determine the corneal keratometric before surgery (V0), and 1 week (V1), 6 months (V2), and 18 months (V3) after surgery (suture-out). Refractive astigmatism was measured by means of autokeratorefractometer (ARK-1; Nidek, Tokyo, Japan). The same experienced examiner (G.G.) performed all measurements according to the manufacturer's guidelines. For each visit, three consecutive values of K steep, K flap, and keratometric astigmatism (for the 3-mm central zone) and refractive astigmatism were recorded, and the mean value was used for the statistical analysis. In order to stratify patients also according to the regularity of the astigmatism, we recorded and analyzed the parameter "asymmetry" that was automatically calculated by the instrument.

Analysis of intraoperative keratoscopy

The intraoperative keratoscopy was performed at the end of surgery with a ring illuminator mounted on the operating microscope (OPMI LUMERA 700, Carl Zeiss, Germany). The tension of running sutures was adjusted until the ring reflected by patient's cornea was subjectively considered regular by the surgeon (Fig. 1, Part A). The photographs acquired with the operating microscope were analyzed using the public domain software ImageJ 1.51s (National Institutes of Health, Bethesda, MD). Briefly, the original photograph was cropped to a square image displaying the reflection on the cornea of the keratoscope (Fig. 1, Part B). After conversion to an 8-bit image, the auto threshold tool was applied to binarize the image, and the internal part of the ring was flood filled (Fig. 1, Part C). Finally, the "Analyze Particles" function of the software was applied to calculate the roundness of the binarized keratoscopy image. Roundness is defined as $4*\text{area}/(\pi*\text{major axis}^2)$. A value of roundness of 1 indicates a perfect circle; as the value approaches 0, it indicates an increasingly elongated shape. To evaluate the inter-observer reliability of the procedure, the analysis of each single digital images was analyzed separately by two examiners (M.P. & F.B.), and intraclass correlation coefficients (ICCs) were calculated.

Statistical analysis

The SPSS statistical software (SPSS, Inc., Chicago, IL) was used for data analysis. Values were expressed as mean ± standard deviation (SD). The inter-observer reliability of the intraoperative keratoscopy analysis technique was estimated using ICCs. A repeated measures ANOVA was used to compare the keratometric parameters among the different time points. Pearson's correlation analysis was used to evaluate the

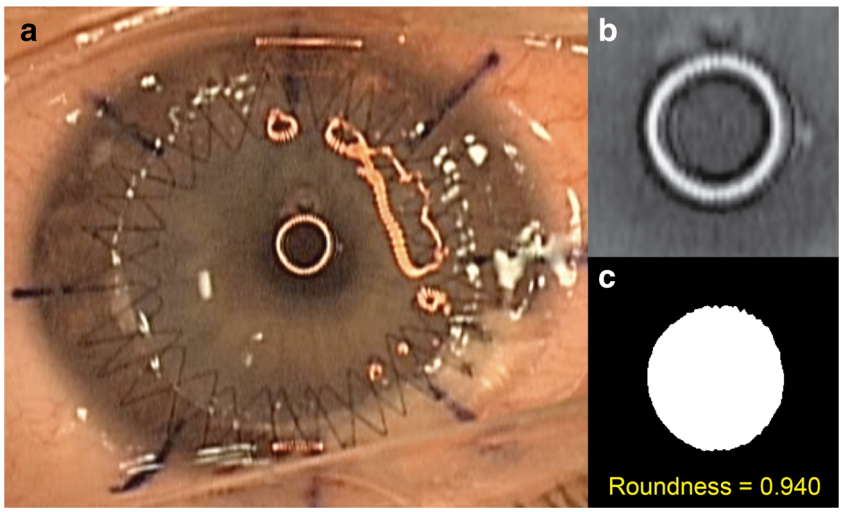

Fig. 1 Representative image of intraoperative keratoscopy at the end of surgery (Part A). The original photograph was cropped to a square image displaying the reflection on the cornea of the keratoscope (Part B). After conversion to an 8-bit image, the auto threshold tool was applied to binarize the image, and the internal part of the ring was flood filled (Part C)

relationship between the roundness of the intraoperative keratoscopy image and postoperative astigmatism and asymmetry, as well as to correlate keratometric and refractive astigmatism. The area under the curve (AUC) of receiver operating characteristic (ROC) curve was used to evaluate the accuracy of roundness for identifying patients with less than 3 diopters (D) of postoperative astigmatism. The point on the ROC curve nearest to the coordinate (0,100) was used as a cutoff to determine sensitivity and specificity. A P value < 0.05 was considered statistically significant.

Results

Overall, 143 patients underwent BB-DALK during the study period regardless of indication and postoperative outcome. Of these, 121 patients (71 M, 50 F; mean age 42.8 ± 17.8 years) were finally included in the study, while 22 patients were excluded due to the following complications that hampered an accurate evaluation of postoperative corneal topography maps: corneal neovascularization (n = 11; 7.7% of the total), infectious keratitis (n = 7; 4.9%), immunological rejection (n = 2; 1.4%), wound dehiscence (n = 1; 0.7%), and persistent epithelial defect (n = 1; 0.7%).

Among patients included in the study, 92 patients were affected by keratoconus while the remaining 29 by other stromal diseases (corneal scarring n = 26; corneal dystrophy n = 3). The keratometry values collected before and after surgery at each time point are reported in Table 1.

Compared with preoperative values, the keratometric astigmatism significantly decreased at V1, V2, and V3 (respectively, P < 0.01, P < 0.01, and P = 0.011). Conversely, the changes in the keratometric astigmatism between different postoperative time points (V1 vs V2 and V2 vs V3) did not differ significantly (P = 0.72 and P = 0.05, respectively). The preoperative keratometric astigmatism showed no significant correlation with postoperative values (always, P > 0.05). At V3, keratometric astigmatism was strongly correlated with refractive astigmatism (R = 0.92, P < 0.01).

The mean roundness of the intraoperative keratoscopy images evaluated with the digital image analysis system was 0.93 ± 0.04 (range 0.76–0.99). The analysis showed a good inter-observer reliability when repeated by a second investigator, with an ICC of 0.966 (95% confidence interval [CI] = 0.95–0.97). Roundness of the keratoscopy image showed a significant correlation with keratometric astigmatism at V3 (R = − 0.42, P < 0.01). Conversely, no significant correlation between the roundness and astigmatism was found at V1 and V2 (P = 0.56 and P = 0.41, respectively) as well as between roundness and asymmetry (P = 0.51).

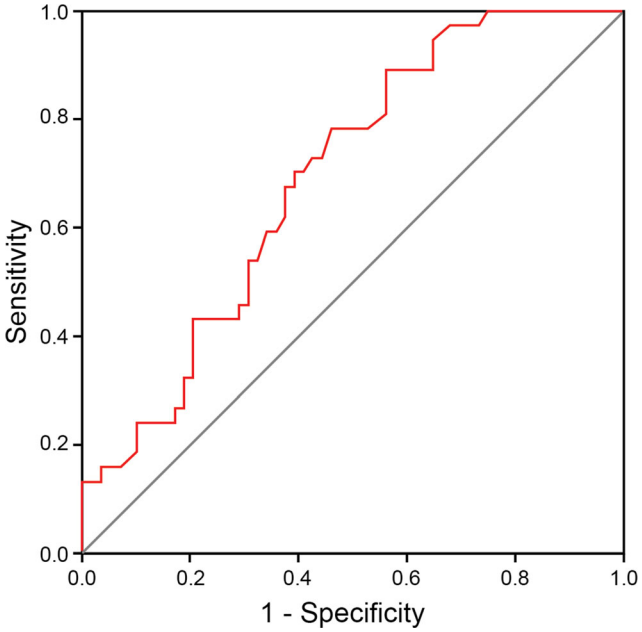

Fig. 2 Receiver operating characteristic curve of roundness for identifying patients with < 3 D of keratometric astigmatism (area under the curve of 0.69)

At V3, 39 patients (32.2%) had a keratometric astigmatism < 3 D. The ROC curve of roundness for identifying patients with < 3 D of keratometric astigmatism is presented in Fig. 2 (AUC of 0.69 [95% CI 0.59–0.79]). A cutoff value of 0.93 for roundness had a sensitivity of 70.3% and a specificity of 61.0% for identifying patients with keratometric astigmatism < 3 D.

Discussion

The idea of surgical keratoscopy for qualitative intraoperative assessment of corneal sphericity by reflecting the images of multiple concentric circles was introduced decades ago for the purpose of controlling surgically induced astigmatism [20]. Since then, the technique has evolved, and keratoscopes fixed

Table 1 Keratometry values in patients undergoing DALK before surgery (V0) and 1 week (V1), 6 months (V2), and 18 months (V3) postoperatively

Parameter	V0	V1	V2	V3
Keratometric astigmatism (D†)	5.4 ± 4.0	3.6 ± 3.5	3.8 ± 2.6	4.2 ± 2.8
K steep (D)	57.2 ± 9.1	44.8 ± 6.1	45.1 ± 3.7	46.5 ± 2.9
K flat (D)	51.8 ± 8.8	41.1 ± 4.9	41.3 ± 3.5	42.2 ± 3.0

† *Diopters*

to the microscope have replaced old handheld devices that cannot ensure coaxial positioning. However, the main limitation that hampered the widespread adoption of this technique among cornea surgeons is related to the subjective judgment of circularity of the keratoscopy rings and thus to the lack of objective and reliable metrics. In fact, to date, the surgeon has to adjust the sutures according to his/her experience until the keratoscopy rings achieve the shape of a astigmatism has a multifactorial nature and a variety of prepresumed perfect circle.

In the present study, we developed and validated a new system able to digitally analyze the pictures of keratoscopy rings obtained at the end of DALK surgery. For this task, we employed the particlastigmatism has a multifactorial nature and a variety of prees analysis function of ImageJ in order to binarize keratoscopy images for the calculation of the "roundness." This parameter indicates an increasing circular shape as approaches the value of 1. This analysis has been recently applied to the corneal fluorescein staining pattern with good reliability and diagnostic accuracy [21]. The ultimate goal of employing this technique in the setting of DALK surgery is to help the surgeon to minimize the postoperative astigmatism that often compromises the visual rehabilitation of otherwise successful corneal grafts. Two different examiners performed separately the analysis, and the coefficient of agreement confirmed a good reliability of the technique. Also, a good correlation between roundness and late suture-off post-DALK astigmatism was found. Conversely, no significant correlations were found between roundness and early suture-in astigmatism, as well as with asymmetry that is an index of regularity of astigmatism.

As previously indicated by Dua and collaborators [22], we used the cutoff value of 3 D in order to discriminate between low values of suture-out astigmatism that are astigmatism that are fully-correctable by spectacles from the higher values that need correction with rigid contact lenses. By applying the value of roundness of 0.93, we were able to identify patients with astigmatism lower than 3 D with a reasonably good diagnostic accuracy. The results of our analysis are encouraging considering that intraoperative keratoscopy is currently judged of limited practical value because other variables may be more important determinants of ultimate corneal shape [23]. In fact, post-DALK astigmatism has a multifactorial nature and a variety of pre-, intra-, and postoperativefactors can affect it, including also donor-recipient tissue matching [22–24]. In order to minimize the effects of these additional variables on final astigmatism, we employed large-diameter grafts and excluded from the analysis eyes with inflammation/infection, corneal neovascularization, immunological rejection, and wound dehiscence, all conditions that affect wound healing and are associated with astigmatism changes over time [4].

This study suffers from some limitations. First of all, the retrospective nature of the design did not allow us to consider other variables at the time of intraoperative keratoscopy that could have affected the measurements, such as intraocular pressure (IOP). In fact, we did not quantitatively measure it at the time of keratoscopy, but we only ascertained by finger tension that the globe was not too soft or too hard. We are aware that setting the IOP in a quantitative manner prior to intraoperative keratoscopy would have significantly improved the reliability of the measurements [15].

Besides IOP, irregular or rough epithelium, cornea overflooding, graft swelling, lid speculum tension, and patient posture may further impair keratoscopy accuracy, and we are aware that all these variables would be better controlled in a prospective study [16, 25]. However, at the time of intraoperative keratoscopy, we routinely release the excessive tension from lid speculum, cover the cornea with just a thin meniscus of fluid maintaining the cul-de-sacs free of pooled fluid, and remove the graft epithelium when its poor quality affects the regularity of keratoscopy rings.

In conclusion, the described system of digital analysis of keratoscopy showed a reasonably good reliability and diagnostic accuracy for predicting low values of long-term suture-out astigmatism in the setting of big-bubble DALK. As the procedure is cost-effective and the technique fast and reliable, its routine intraoperative use could contribute to reduce post-DALK astigmatism. In the near future, the integration of this digital analysis system in the microscope-mounted keratoscope would allow to obtain real-time objective values of the *R* of keratoscopy rings, thus helping the surgeon to minimize the amount of postoperative astigmatism by facilitating intraoperative suture adjustment.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee (Comitato Etico Regione Calabria Sezione Area Centro – 280-2019) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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