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ORIGINAL PAPER

Novel grid and sectoral analyses in monitoring corneal scars

Ka Wai Kam · Anita Li · Rachel Pui Wai Kwok · Michael W. Belin · Alvin L. Young

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Abstract

Purpose We aim to design two sampling methods, the grid and sectoral methods, to provide more precise detection of focal corneal scar changes with time following pterygium excision with the Pentacam imaging system.

Methods This is a retrospective study of our previous prospective observational case series. Thirty patients underwent primary pterygium excision with adjuvant topical mitomycin-C application were followed up and imaged with Pentacam system at postoperative weeks 1, 4, 12 and month 18. Grid and sectoral methods were used to sample density changes (in grayscale units, GSU) over the scarred areas as well as the clear pole of the same cornea.

Results Using the grid method, the average corneal densities were 39.4, 37.1, 36.7 and 34.7 GSU at postoperative 1, 4, 12 weeks and 18 months, respectively. On the other hand, using the sectoral method, the average corneal densities were 35.3, 33.3, 32.5 and 31.9 GSU at postoperative 1, 4, 12 weeks and 18 months, respectively. Paired t tests achieved statistical significance when comparing all follow-up time points to first postoperative visit. A statistically significant effect of time on the average density was shown on ANOVA ($p < 0.001$) using both analyses over the scarred areas, but not over the clear pole of the same cornea ($p > 0.05$).

Conclusion Our novel approach to monitor corneal density changes using the grid or sectoral sampling methods seemingly enhances the power in monitoring density changes in corneal scars when compared to conventional total-diameter average densitometry.

Keywords Cornea · Scar · Pterygium · Densitometry · Scheimpflug image

Introduction

Pterygium is a common degenerative condition of the conjunctiva [1, 2]. Large lesions often require surgical excision; however, residual scars in the cornea are often present after removal of the pterygium [3–5]. These scars are mostly commonly located in the anterior corneal stroma and the peripheral cornea and may contribute to astigmatism and hence suboptimal vision [6, 7].

K. W. Kam · R. P. W. Kwok · A. L. Young (✉)
Department of Ophthalmology and Visual Sciences, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, New Territories, Hong Kong
e-mail: youngla@ha.org.hk

A. Li · A. L. Young
Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Shatin, Hong Kong

M. W. Belin
Department of Ophthalmology and Visual Science, University of Arizona, Tucson, USA

From our previous studies, we measured corneal density changes following pterygium excision with Pentacam Scheimpflug system (OCULUS GmbH, Wetzlar, Germany). Using the total-diameter analysis, the average anterior corneal densities significantly reduced by 9.9% at postoperative week twelve, and by 12.7% at postoperative month eighteen [8, 9]. The reduction at postoperative week four, however, did not achieve statistical significance [9].

An alternative method to analyze our data in addition to numerical values is by evaluating the color-coded average densitometry maps. By comparing the density values at the scarred areas over time, we often notice a greater reduction percentage in these areas as compared to the total-diameter numerical data (see Fig. 1). This may be explained mathematically by a dilutional effect when the whole cornea is sampled for analysis; hence, the genuine magnitude of focal change would be masked if it is divided by the sum of both unchanged and changed areas in the total-diameter sampling setting.

In view of this, a subgroup analysis using the 10–12-mm annulus was attempted to neutralize the dilutional effect. However, the results from these subgroup analyses did not achieve statistical significance. This might be explained by possible contamination from blinking artifact and missing data which may be located in areas outside the scarred region despite satisfactory image quality specifications. Furthermore, adopting either the total-diameter average density, or the 10–12-mm annulus approach, relies on the assumption that the unoperated cornea retains the same density through time. The long-term repeatability and reproducibility over such a long period of time have not been proven; hence, the more area we sample, the higher the variability would exist within the data as opposed to sampling a smaller area.

In view of the limitations outlined above, we proposed a novel method to sample data points directly over the scarred areas, excluding areas of clear corneas, artifacts or missing data, in hope to evaluate more precisely focal changes in the cornea and reduce the amount of noise and dilution from the un-related parts of the cornea.

Methods and materials

This is a retrospective analysis of our earlier prospective observational case series for which ethics approval was obtained from the Joint Chinese University of Hong Kong—New Territories East Cluster Clinical Research Ethics Committee.

Thirty-one subjects who underwent primary pterygium excision with adjuvant topical mitomycin-C 0.02% for 5 min were imaged with the Pentacam at postoperative week 1, 4, 12 and month 18. Informed consent was obtained from all individual participants included in the study. Details of the operation, postoperative management and image capture protocol were described in our earlier report [9].

Based on the large color maps on the Pentacam system, we designed two novel sampling methods using the average corneal density display and named them the grid method and sectoral method.

The grid method consists of nine data points in a 3 × 3 configuration (see Fig. 2), and the sectoral method is defined by a 90° arc which contains more

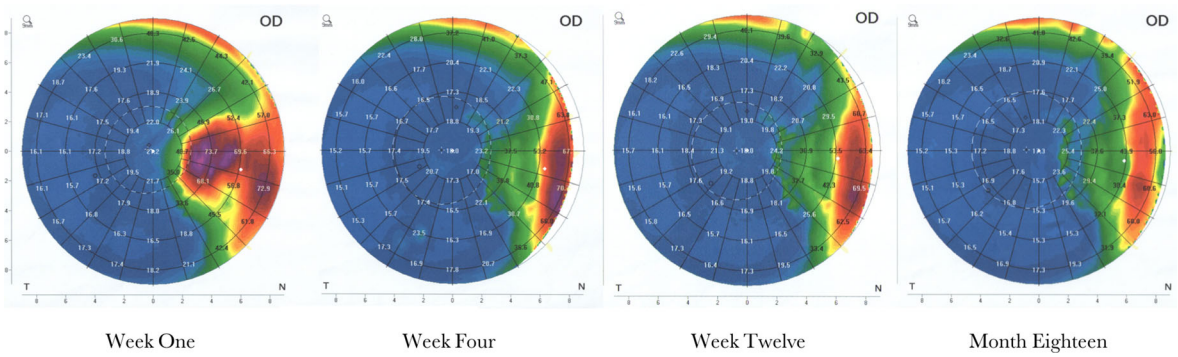

Fig. 1 Changes in average densitometry maps of the same patient at postoperative week 1, week 4, week 12 and month 18, showing the resolution of corneal density over the pterygium scar

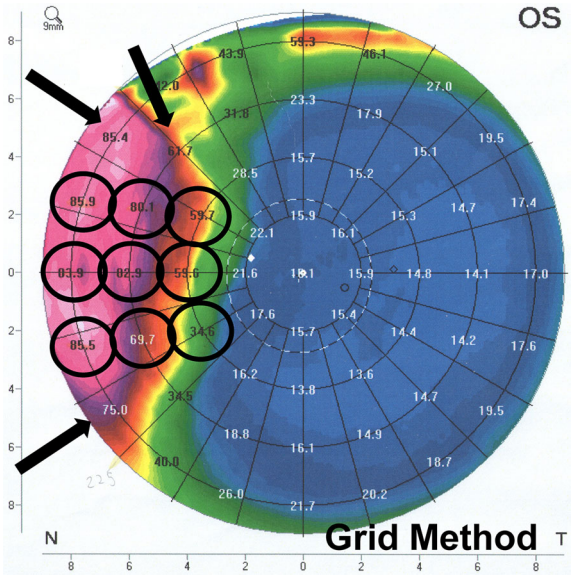

Fig. 2 Limitation of the grid method as it misses the entire scarred area (black arrows)

than nine data points (see Fig. 3). Density data were recorded in grayscale units (GSU) using the large average corneal density map, on which the software would automatically generate grid lines and data points in standard default locations in all the analyzed maps. The advantage of this is to enhance repeatability

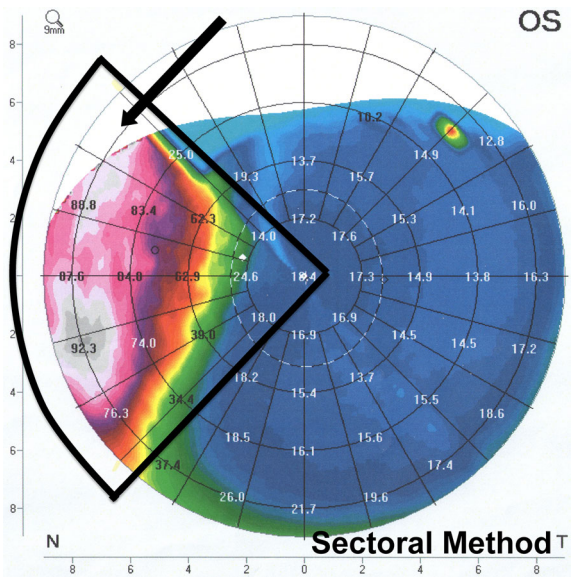

Fig. 3 Limitation of the sectoral method as it includes missing data as shown (black arrow)

over serial scans which were taken using the automatic release setting, and compensate the inherent lack of tracking feature in the Pentacam device.

Average values were taken from the nine points, and all the data points enclosed by each sector as a summary value for each patient at postoperative week 1, week 4, week 12 and month 18. Two assessors would place the grid and sector on the large maps independently over the area that they thought most represent the scarred region. If the two assessors' selections were in agreement, then those data points would be utilized for analysis. In case of discrepancy between two assessors, the arithmetic mean of the two assessors' average would be taken.

A same-sized grid and sector was placed in the opposite or clear pole of the cornea on the large average corneal densitometry map to act as control. This was the region where no scar was observed in the cornea on slit-lamp biomicroscopy clinically, and hence it was safe to assume that no significant change in density should take place in this part of the cornea. This is a very important measure to assess the reproducibility or variation in density of a clear cornea detected by the same method with time.

Statistical analysis

Univariate analysis is presented with mean, proportion, percentage, standard deviation and 95% confidence interval. Data have been assessed for normality using histogram to assess distribution. Both t tests and repeated measures analysis of variance (ANOVA) were used to compare change in densities from week 1 to week 4, week 12 and month 18. The Greenhouse–Geisser correction was applied when test of sphericity is violated with $p < 0.05$. Sample size calculation was described in our earlier study, with a power of 80 and 10% dropout rate. A p value of less than 0.05 was considered statistically significant.

Results

Thirty-one patients were enrolled in the study; however, one patient was excluded from analysis due to the presence of a large recurrence extending 5 mm beyond limbus. Sampling over the recurrent pterygium would adversely affect the reliability of the data,

Table 1 Comparison of mean corneal densities in grayscale units (GSU) at postoperative weeks 1, 4, 12 and month 18 following pterygium excision using both grid and sector methods on scarred part of the cornea as well as the clear control part of the same cornea

	1 week	4 weeks	12 weeks	18 months
Scar				
Grid				
Mean corneal density	39.4	37.1	36.7	34.7
Percentage reduction (%)		5.8	6.9	11.9
p value		0.007	0.006	<0.001
Sector				
Mean corneal density	35.3	33.3	32.5	31.9
Percentage reduction (%)		5.7	7.8	9.7
p value		0.005	0.001	<0.001
Control				
Grid				
Mean corneal density	17.9	16.8	16.5	16.1
Percentage reduction (%)		6.1	8.2	10.5
p value		0.194	0.087	0.031
Sector				
Mean corneal density	19.2	18.2	17.8	17.0
Percentage reduction (%)		5.1	7.3	11.0
p value		0.226	0.085	0.012

p values were obtained by paired t tests to show the statistical significance of comparisons with the respective postoperative week 1 data. This table shows strong statistically significant reduction in the mean corneal densities of the corneal scars following pterygium excision up to 18 months postoperatively

p value obtained from paired t tests comparing to 1 week data

p value of < 0.01 was considered statistically significant

and hence this patient was excluded. A summary of our findings was presented in Table 1.

Grid method

Average corneal densities were 39.4 grayscale units (GSU), 37.1, 36.7 and 34.7 GSU at postoperative 1, 4, 12 weeks and 18 months, respectively. Average corneal densities reduced by a mean of 2.3 (5.8%) [95% confidence interval (95% CI) − 3.94 to − 0.68, $p = 0.007$] at postoperative week 4 when compared to week 1; it further reduced by a mean of 2.73 GSU (6.9%) (95% CI − 4.60 to − 0.87, $p = 0.006$) at week 12, and 4.68 GSU (11.9%) (95% CI − 6.46 to − 2.91, $p < 0.001$) at 18 months postoperatively. A statistically significant effect of time on the average density was shown on ANOVA ($p < 0.001$).

Sectoral method

Average corneal densities of the 30 included eyes were 35.3, 33.3, 32.5 and 31.9 GSU at postoperative 1, 4, 12 weeks and 18 months, respectively. On comparing week 1 with week 4, we detected a mean reduction of 2.02 GSU (5.7%) [95% confidence interval (95% CI) − 3.37 to − 0.67, $p = 0.005$). At week 12, there was a further decrease in mean 2.75 GSU (7.8%), (95% CI − 4.24 to − 1.26, $p = 0.001$). At 18 months postoperatively there was a mean reduction of 3.43 GSU (9.71%) (95% CI − 5.12 to − 1.73, $p < 0.001$). A statistically significant effect of time on the average density was also achieved on ANOVA ($p < 0.001$).

As a control, we sampled average corneal densities from the opposite pole in the clear corneas of the same 30 patients using both the grid and sectoral methods. For the Grid method, using paired t test comparing

week 1 to week 4, there was a mean reduction of 1.11 GSU (95% CI − 2.82 to − 0.60, $p = 0.194$). At week 12, there was a decrease in mean 1.48 GSU (95% CI − 3.18 to − 0.23, $p = 0.087$). At 18 months postoperatively there was a mean reduction of 1.88 GSU (95% CI − 3.57 to − 0.19 $p = 0.031$). No statistically significant effect of time on the average density was shown by ANOVA with $p = 0.062$.

Whereas, using the sectoral method of sampling the clear cornea, comparing week 1 to week 4 there was a mean reduction of 0.98 GSU (95% CI − 2.61 to 0.64 $p = 0.226$), 1.40 GSU (95% CI − 3.01 to 0.21, $p = 0.085$) at week 12, and 2.11 GSU (95% CI − 3.71 to − 0.50 $p = 0.012$) at postoperative 18 months. Unlike using the grid method, a marginally significant effect of time on the average density was observed in ANOVA ($p = 0.032$).

Discussion

While our earlier study showed that significant reduction in average corneal densities of the total diameter took place at 12 weeks after pterygium excision, our current analyses found that focal reduction over the scarred areas, obtained either by grid or sectoral sampling, was significant as soon as 4 weeks after the surgery ($p = 0.007$ and 0.005, respectively). This is further supported by the fact that no significant change in densities took place at the opposite clear cornea using either grid or sectoral method ($p = 0.194$ and 0.226, respectively). Our novel sampling methods provided a more precise alternative to conventional analysis, which is less susceptible to dilution or artifacts. The clinical significance of these methods is to help clinicians monitor localized pathologies such as focal corneal scars and the effect of intervention with time. These sampling strategies help unmask subtle variations in density which may not be accurately represented in the total-diameter density display.

In our study, higher percentage reductions in corneal densities were obtained using either the grid or sectoral sampling at 4 and 12 weeks, when compared to our earlier report using total-diameter analyses. However, to our surprise, the percentage reduction at 18 months detected by either method was similar to the data we obtained with the total-diameter analysis.

Reasons that may explain a lack of discrepancy include the reproducibility of densitometry especially in the setting of peripheral corneal imaging, different nature of sampling, sampling bias and random errors arising from the image capturing system.

The long-term reproducibility of densitometry has not been evaluated. However, there was one report which studied density change in keratoconic eyes following cross-linking treatment and stated that repeatability of densitometry was poor in their study [10]. The authors of that study suggested that factors affecting poor repeatability included poor instrument quality, non-calibration, inadequate methods of data collection and operator inexperience. In our center, the Pentacam device was regularly maintained and calibrated. All images were captured using a standardized technique by the same investigator (K.W.K.) who was experienced in operating the Pentacam machine.

The conventional total-diameter analysis is a horizontal sampling system where it displayed densities in the anterior, central and posterior layers of the cornea. Hence, theoretically the anterior layer data are the most relevant in capturing and measuring scars following pterygium surgery, whereas using the large average densitometry maps, our grid or sectoral methods both function as vertical sampling, and each data point represents the average density values across the entire thickness of cornea from the anterior to posterior layer. From our earlier study, we found that there was a significant rise in posterior layer densities at 12 weeks, and this might dilute the change in anterior layers when grid or sector sampling was used. However, the mean density of posterior layer was found to return to baseline at 18 months [8]; hence, the possibility of dilution using vertical sampling method at 18 months should be minimal.

Sampling bias and random errors might play a role in affecting the selection of data in the scarred area and the control area. Our analyses show that despite much lower density values in the clear parts of the cornea, the percentage reductions over the control side were similar in magnitude to the scarred areas. In some patients, we observed that the whole cornea appeared quite dense at week 1 postoperatively, particularly toward the periphery, on either the pterygium side or the non-operated side (see Fig. 1). These corneas became less dense in subsequent follow-ups, which although may result from random errors arising from the image capturing system, could also reflect a

genuine effect of the surgery to the whole cornea, or result from the postoperative exposure to topical medications. Fellow non-operated corneas of the same patients may therefore act as a better control in this situation to eliminate these potential diffuse effects.

Both grid and sector sampling methods possess their distinct advantages and limitations. Grid sampling is easier and more convenient to use; however, not all pterygium scars conform to the 3×3 pattern. Hence, part of the scars may not be sampled by the square configuration and the density of scarred area would be underestimated (see Fig. 2). Alternatively, sectoral sampling includes a much wider area and therefore it is able to sample all parts of the scars captured by the color map. However, as most sectors extend to the areas of superior corneas, artifacts from blinking or missing data may lead to underestimation or over-estimation of the actual scar density (see Fig. 3).

Conclusion

Our analyses using the grid or sectoral sampling method seemingly enhance the statistical significance in measuring the density changes in scars following pterygium excision. This is evidenced by significantly smaller p values obtained using either sampling methods at postoperative weeks 4, 12 and month 18, than compared to conventional methods used in our earlier papers.

Interestingly, from our control data using the clear cornea opposite to the site of pterygium, similar percentage reductions were detected at postoperative week 4, 12 and month 18. Although not statistically significant, such reduction in density over the clear parts may reflect a diffuse but milder effect of surgery or topical corticosteroid that was given postoperatively over the non-operated side of the cornea.

Compliance with ethical standards

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 and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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