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Determining factors of fast corneal sensitivity recovery after pterygium excision

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ABSTRACT

Purpose: To establish determining factors for fast corneal sensitivity (CS) recovery after pterygium excision.

Methods: Thirty-two eyes of 14 males and 18 females with primary nasal pterygium were recruited. Differences in CS (in the four quadrants and the center using Cochet-Bonnet esthesiometer), pterygium corneal area (PCA), tear osmolarity, tear break up time, Schirmer test, and ocular symptoms were analyzed before and 1 month after lesion excision. The relationship between CS recovery (difference between the two time points; CS_1-CS_0) and the other features was assessed.

Results: All the studied locations exhibited normal (6 cm) or near normal mean CS at the 2 time points, except tendency for moderate hypoesthesia in nasal CS_0 (median 4.5; range: 1.5 - 6.0 cm). Point by point comparison revealed significant postoperative improve in nasal location (p=0.008; Wilcoxon rang test) with normal values in 17 eyes (53%) and a median CS_1= 5.0 cm (2.5 - 5.5 cm) in 15 eyes with no complete recovery. No significant correlation was found between CS_0 and the studied variables and CS_1 was only significantly correlated with PCA (rho: - 0.441; $p<0.05$). CS recovery also showed significant correlation with PCA (rho= -0.516; $p<0.01$).

Conclusions: Corneal sensitivity recovery after pterygium excision showed important variability and the only studied factor that seems to be determinant could be PCA. It would be advisable to operate while lesion is relatively small, with lower surgical injury, and faster and complete recovery, thus protecting ocular surface homeostasis.

INTRODUCTION

The cornea is one of the most densely innervated tissues in the body that exert important trophic influences on the corneal epithelium and contribute to the maintenance of a healthy ocular surface. Corneal nerves are routinely injured following modern refractive surgical procedures or in certain corneal diseases. This damage can lead to transient or chronic neurotrophic deficits, loss of protective neural response from further injuries (extreme environmental temperatures, wind, foreign bodies, and chemicals), decrease of tear flow, and significantly impairs the ability of the corneal epithelium to heal itself after corneal epithelial wounds[1,2].

Pterygium, from the Greek pterygos, meaning ‘‘wing’’ is a common ocular surface lesion, characterized by degradation of Bowman’s layer, elastotic degeneration of collagen, fibrovascular proliferation, with angiogenesis, and an overlying covering of epithelium. Hypothesis of pterygium pathogenesis have implicated chronic UV light exposure as a major causative factor[3,4,5] that could damage stem cell and nerve fiber bundles[6] thus affecting the normal self-renewing capability of the corneal surface. Lesion excision is the current treatment and multiple surgical approaches have been described in order to reduce recurrences. One of the most useful and successful is the excision with a free limbal-conjunctival autograft[7].

To our knowledge, two studies[8,9], with a limited number of cases, have analyzed corneal sensitivity (CS) in pterygium patients and both reported evidence of corneal hypoesthesia. In agreement with these findings, changes in the sub-basal nerve plexus were observed in affected corneas, using *in vivo* laser scanning confocal microscopy[10,11]

Additionally, clinical complete recovery is, usually, achieved 1 month after pterygium excision. Nevertheless, previous data[9] suggest that CS is not at all recovered and nothing is known about factors that could affect the process. To know these factors could help clinicians to establish the right time for surgery with a successful and speed CS recovery, thus protecting the ocular surface.

The aim of this study was to establish the determining factors of fast CS recovery after pterygium excision. Differences in CS, lesion dimension, tears clinical signs, and ocular symptoms were analyzed before and 1 month after surgery and the relationship between the CS recovery and the other studied features was assessed. Knowing these determining factors would help clinicians to establish ideal conditions for this frequent surgical event.

METHODS

Subjects

Thirty-two eyes of 32 patients (14 males and 18 females aged between 28 and 72; mean age ± standard deviation: 45 ± 10 years) with primary nasal pterygium were included in this study. Patients with a history of contact lens wear, or ocular disease, except for pterygium, were excluded. The study was approved by the Ethics Committee at Consorci Sanitari de Terrassa and informed consent was obtained from each patient. The methods adhered to the tenets of the Declaration of Helsinki.

Procedure

The surgeries were always performed by the same surgeon using the same technique: excision of the pterygia following by a free limbal-conjunctival autograft, taken from a superior position. After surgery, all patients received an

identical regimen of topical chloramphenicol and dexamethasone eye drops (Colircusi de Icol®, Alcon http://www.alcon.es) which were tapered off over 1 month. Nylon sutures were removed at week 1. All the clinical measurements (described below) were made before and 1 month after surgery.

CS was studied using the Cochet-Bonnet esthesiometer with a 0.12 mm diameter filament. The device activates mechano and polimodal nociceptors that represent about 90% of all the corneal nociceptors[1]. The force exerted by the filament when it touches the cornea is inversely proportional to its length. Five corneal points (one in each quadrant and the center of the cornea) were evaluated (Figure 1) with perpendicular contacts using ascending method of limits, starting with a length of 6 cm and decreasing in steps of 0.5 cm. Two positive responses in three attempts at each filament length were regarded as a positive result, that is, the threshold to stimulation. Results are presented as centimeters of length of the nylon filament, being 6.0 cm maximum sensitivity of the cornea, and 0 cm corneal anesthesia at that point tested.

The patients completed a slightly modified version of the Salisbury Eye Evaluation Questionnaire[12]. This six item questionnaire included questions regarding ocular symptoms of dryness, gritty or sandy sensation, burning sensation, redness, crusting eyelashes, and eyes stuck shut in the morning. Itchiness was also added, as this symptom is commonly reported by dry eye patients and used in other dry eye questionnaires[13]. Patients were asked to grade each ocular symptom from 0 to 4 in terms of frequency of occurrence, based on response options: never (0), rarely (1), sometimes (2), often (3) or all the time (4). We chose this questionnaire because it is simple and easy to be self-reported regardless of age or cultural level of the patient.

Participants were also administered a battery of clinical tests of tear film evaluation including, in this order: mean tear osmolarity (three times assessed with the TearLab® Osmolarity Test; TearLab Co., Sant Diego, CA), tear break-up time (TBUT) (5 µl of non-preserved, 2% sodium fluorescein was instilled and the mean of three consecutive measurements was considered) and Schirmer test (without anesthesia). All testing procedures took place at the same time of day, and under temperature and humidity controlled conditions. To minimize bias, all clinical measurements were made by the same experienced examiner.

In addition, pterygium corneal area (PCA) was quantified. For this purpose, the affected eye of each patient was photographed with a digital camera and the area within the corneal outline demarcation of the lesion was measured, in a semiautomatic way, by the Analyse/Measure command of ImageJ analysis software (W Rasband, National Institutes of Health, Bethesda, MD; http://rsb.info.nih.gov/ij/) using the polygon selection tool. A ruler was used as the scale bar in the image for converting the squared pixels calculated by the program into square millimeters.

Statistical analysis

Exploratory analysis of the point by point corneal sensitivity pattern before and after surgery was carried out. In order to analyze changes, Wilcoxon rang test and paired t-test were applied for intraindividual comparisons and student t test, Mann-Whitney U test or Chi^2 test for interindividual comparisons. Correlations were studied using Spearman's ρ test and stepwise multivariate analysis was applied to explain differences in CS through tear clinical signs, ocular symptoms, PCA, age and sex of the patients.

SPSS V19 was used for statistical analysis and a significant level of $p < 0.05$ was considered. Normal variable distribution was assessed with the Kolmogorov–Smirnov test.

RESULTS

All the patients completed the study. Mean PCA was 8.1 ± 4.3 mm^2 (range 0.1 to 15.9 mm^2). Figure 2 illustrates PCA distribution. The surgery was always uneventful and no remarkable clinical complications were found during the follow-up period. No lesion recurrence was detected according to Prabhasawat criterion[14] 1 month after surgery.

Corneal sensitivity

All the studied locations exhibited normal or slight loss of corneal sensation, except for nasal CS before surgery. Summary statistics of the point by point CS pattern before (CS_0) and 1 month after surgery (CS_1) are displayed in table 1. The lowest value was always found in nasal CS_0, thus evidencing a tendency for moderate hypoesthesia in the corneal area affected by the lesion.

Point by point comparison between CS_0 and CS_1 in the whole sample revealed significant postoperative improve in nasal location 1 month after surgery ($p=0.008$; Wilcoxon rang test). The rest of the points tested showed no significant changes.

Nasal corneal sensitivity

Figure 3 illustrates nasal CS_0 and CS_1 distribution. Ten eyes (31%) showed normal values before surgery and 22 (69%) displayed CS_0 below normal. There were no significant differences in age, sex or PCA between the two groups

($p>0.05$; student t test for age and PCA comparisons and Chi^2 test for sex comparisons).

One month after pterygium excision, 17 eyes (53%) displayed CS_1 normal values. Among these, 6 (19%) kept unaltered CS and 11 (34%) were cases with initial loss that completed recovery process 1 month after pterygium surgery. Median nasal CS_1 in the 15 eyes (47%) with partial CS recovery was 5.0 cm (range 2.5 - 5.5 cm). No significant differences in age, sex or CS_0 were found between cases with complete and partial CS recovery ($p>0.05$; student t test for age, Chi^2 test for sex and Man-Whitney U test for CS_0 comparison). Nevertheless, PCA was significantly larger ($p=0.001$; student t test) in eyes with partial CS recovery (mean difference = 5.5 mm^2; 95% confidence interval: 2.6 – 8.4 mm^2).

Tear film signs and ocular symptoms

Summary statistic of the tear clinical signs before and 1 month after pterygium excision is presented in table 2. Only TBUT showed a clear tendency for abnormal values, both, before and after surgery. No significant changes in any sign were disclosed when comparing the two time points (table 2). Coincidentally, no significant differences in tear film signs were found when comparing eyes with normal and altered nasal CS_0 or between complete and partial CS recovery 1 month after pterygium excision ($p>0.05$; student t test and Mann-Whitney U test , where appropriate).

Regarding ocular symptoms, 26 patients (81%) related one or more symptoms with a frequency of often or all the time, before pterygium excision (figure 4). One month after surgery, it was reduced to 15 patients (47%). Paired comparisons in the two time points revealed a significant decrease of ocular symptoms 1 month

after surgery (p= 0.0001; Wilcoxon rang test). In addition, no significant differences in symptoms were found between eyes with normal and altered nasal CS_0 or between complete and partial CS recovery (p>0.05; Mann-Whitney U test).

Assessment of the determining factors of corneal sensitivity recovery

No significant correlations were found between nasal CS_0 and the rest of the studied variables measured before surgery (PCA, tear osmolarity, TBUT, Schirmer, symptoms, age and sex). Nasal CS_1 was only significantly correlated with PCA (rho= -0.441; p<0.05) and no significant correlation was disclosed between nasal CS_0 and CS_1. Spearman's correlations between the nasal CS recovery (the difference in CS between the two studied times in each eye) and the other variables did not show any significant result, except for PCA (rho= -0.516; p<0.01). In this sense, the larger the size of the PCA, the lower the CS recovery in nasal location. The stepwise multivariate analysis displayed PCA as the only explanatory variable significantly related to nasal CS recovery (adjusted R^2= 0.202 p=0.006). Thus, the resulting equation (with standardized coefficients) was nasal CS recovery = 2.071 – 0.477 * PCA.

DISCUSSION

According to the findings of this study, nasal CS_0 showed a tendency for moderate hypoesthesia while it was normal or slight altered in the rest of the corneal points tested, out of the lesion.

These results agree with those reported in previous studies. Stapleton and coworkers[8] found reduced mechanical sensitivity in the central cornea of 10 patients with pterygium, using a modified Belmonte aesthesiometer. Sakarya et al[9], also found slight corneal hypoesthesia, by Cochet-Bonnet aesthesiometer, in

all the quadrants and the central cornea of 17 affected eyes, with the lower values at nasal location. Observations using *in vivo* laser scanning confocal microscopy showed morphological changes that also support corneal hypoesthesia in pterygia[10,11].

Different hypotheses have been postulated to explain CS reduction in pterygium eyes. Sensitivity loss in fellow eye of unilateral pterygia might suggest neural damage prior to clinically detectable lesion changes. This would imply that peripheral UV light focused at the limbus damages not only limbal stem cells but nerve fibers bundles[8,15]. Indirect evidence of this interesting argument was reported by Chui and coworkers[16]. The authors found elevated presence of substance P preferred receptor in pterygia and demonstrated that this neuropeptide could contribute to the lesion shape though its profibrogenic and angiogenic action.

Another possible cause of the corneal hypoesthesia in eyes affected by pterygium may be chronic inflammation in the cornea and conjunctiva of these patients[3, 10, 11, 17]. Intravascular inflammation also is present in a high percentage of cases[3]. The chronicity of this situation, common to other ocular surface diseases[18-22], has been described as one of the causes of corneal nerve injury[2]. In any case, multifactorial origin of corneal hypoesthesia in eyes with pterygium should not be dismissed. Further assessments are needed to elucidate this question.

No significant differences were found in this study between normal (31%) and abnormal nasal CS_0 in age, sex, PCA, tear film signs or ocular symptoms. Other no studied factors as the anatomical variability of the healthy corneal plexuses[23] or the intensity of the tissue changes[24] may be plausible explanations of CS_0

variability. These differences may originate variable CS_0 but new studies with a high number of cases are required to establish factors for CS_0 decrease.

One month after pterygium excision, nasal CS_1 significantly improved while no changes were found in the other locations. Nasal CS_1 were normal in 53% of the cases and, among the studied variables, only PCA was significantly different when comparing eyes with complete and partial CS recovery process. In this sense, PCA tended to be larger in cases with abnormal CS_1.

Nasal CS improvement was variable and tended to be relatively fast in about a half of the sample. However, Sakarya et al[9] reported that 1 month after surgery nasal CS was significantly reduced compared to initial values. It is worth mentioning that, surgical procedures in both studies were similar except for the use of fibrin glue and a pressured eye patch during 1 week in Sakarya's work. In addition, pterygium dimensions may not be comparable, which would explain these differences (unfortunately, the authors did not report these data).

The findings of the present work suggest that the only studied factor that seems to lead to a rapid CS improving could be a reduced lesion area at the time of pterygium excision. In fact, CS_0 did not display significant correlation with CS_1, evidencing the influence of an external factor, likely, the surgical traumatism, inherent in any resection, that seems to affect CS_1. As magnitude of the surgical injury depends on pterygium dimensions, a variable number of corneal nerves could be discontinued in any case and, therefore, the time for complete CS recovery could be longer or shorter. Several studies have reported a significant relationship between the depth of the dissection in a surgical procedure and the time for complete CS recovery[25-28]. In addition, the ideal time to operate the eyes

with pterygium seems to be related with small lesions not only because the CS recovery could be faster but also because final astigmatism seems to be lower[29].

Normality in almost all the studied tear signs while nasal CS improved support the idea that only pterygium lesion is the main cause of nasal corneal hypoesthesia. Tendency for abnormal TBUT remained during all the study but irregularity in corneal surface due to the lesion or the surgery scars could trigger this constant tear film instability. Actually, previous studies[30,31] have reported both normal and abnormal tendency in TBUT and also in tear film osmolarity[32,33] but always with mean normal values of Schirmer test. Hence the disagreement may be produced by compensatory mechanisms such as reflex production of aqueous components resulting in transient improvements in tear film signs.

In summary, eyes with pterygium showed a tendency for moderate hypoesthesia in the affected area while the other tested locations remained normal. One month after the surgery CS was normal in about one half of the cases and differences in CS recovery were only related to corneal affected area that seems to condition final CS. Measures of CS in both times did not show relationship, evidencing an external factor, such as the surgical injury, as a determining of SC recovery process. Therefore, it would be advisable to operate while the lesion is still relatively small, since the SC recovery seems to be faster.

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The corresponding author of this manuscript takes responsibility for the integrity of the data and the accuracy of the data analysis

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FIGURE LEGENDS

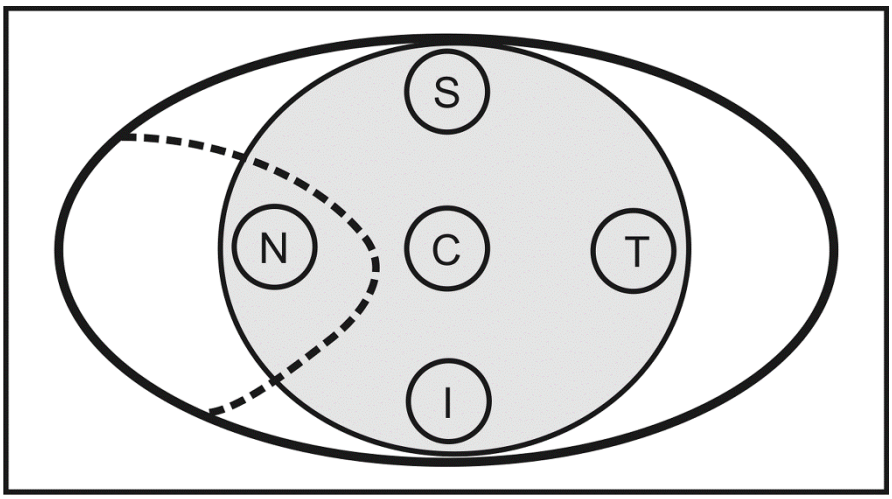

Figure 1. Eye diagram with the different locations tested for corneal sensitivity. The dotted line represents the limits of the lesion before surgery.

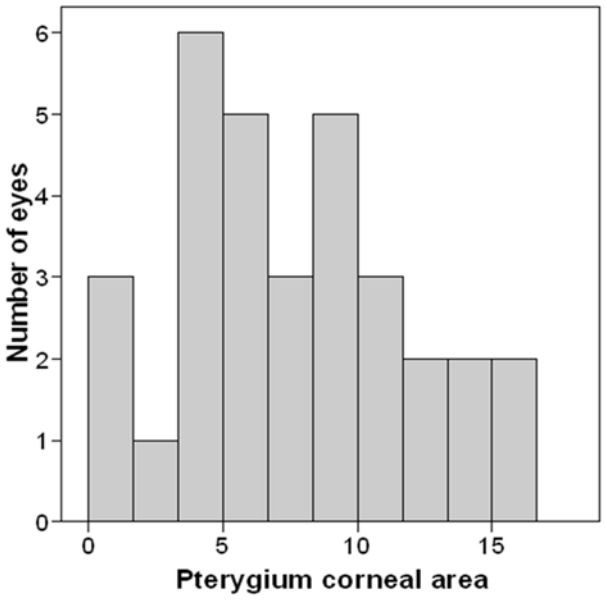

Figure 2. Distribution of the pterygium corneal area.

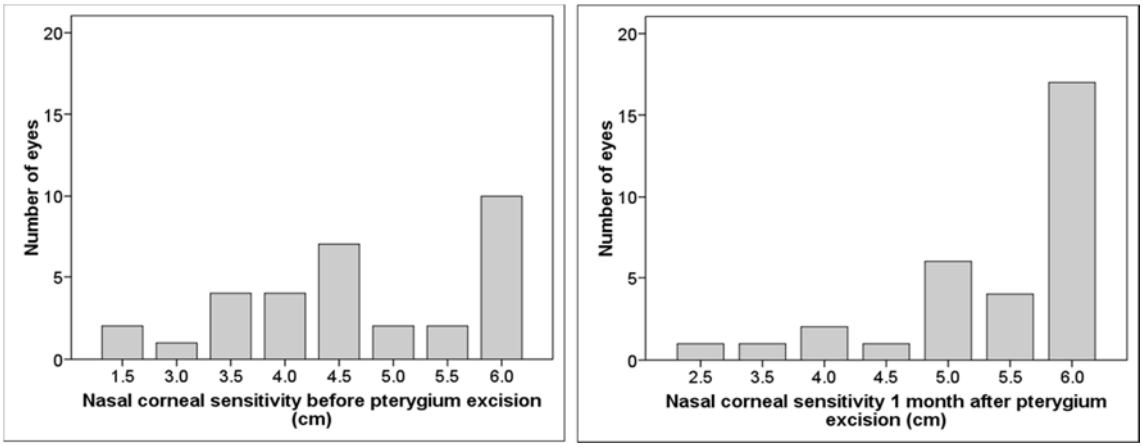

Figure 3. Distribution of the nasal corneal sensitivity at the two studied time points.

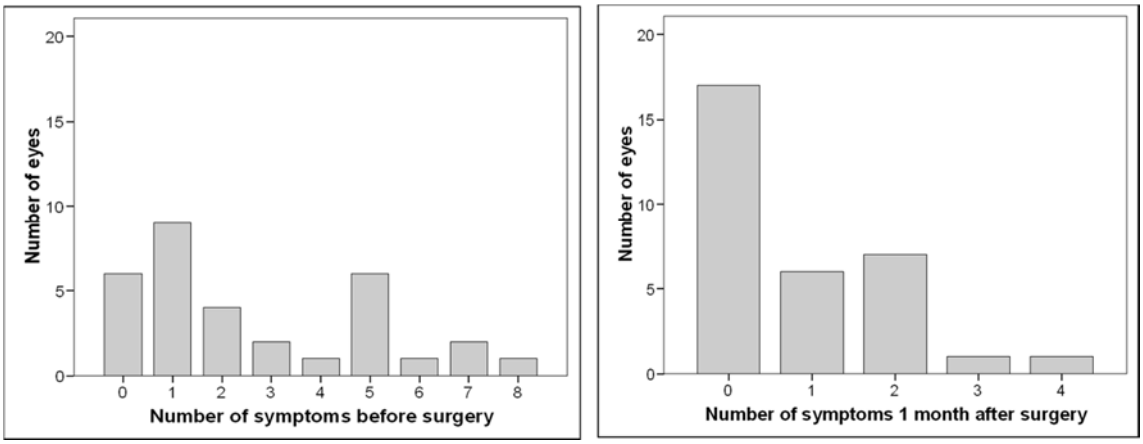

Figure4. Distribution of the number of symptoms reported “often” or “all the time” in the sample.

Table 1. Summary statistic of the corneal sensitivity in each point measured before and one month after pterygium surgery. SD: standard deviation; Min: minimum; Max: maximum; p: p value of before *vs* after comparisons, using Wilcoxon rang test.

Corneal sensitivity (cm)	Time	Mean	Median	SD	Min	Max	p
Nasal	before	4.5	4.5	1.3	1.5	6.0	0.008
	after	5.4	6.0	0.9	3.5	6.0	
Temporal	before	6.0	6.0	0.2	5.0	6.0	0.369
	after	6.0	6.0	0.1	5.5	6.0	
Upper	before	5.8	6.0	0.7	2.0	6.0	0.620
	after	5.7	6.0	0.8	3.0	6.0	
Lower	before	5.8	6.0	0.7	2.5	6.0	0.564
	after	5.8	6.0	0.5	3.5	6.0	
Central	before	6.0	6.0	0.2	5.5	6.0	0.317
	after	6.0	6.0	0.0	6.0	6.0	

Table 2. Summary statistic of the tear clinical signs before and 1 month after pterygium excision. SD: standard deviation; Min: minimum; Max: maximum; p: p value of before *vs* after comparisons, using paired t-test for osmolarity and Wilcoxon rang test for the rest of the studied variables.

Tear film	Time	Mean	Median	SD	Min	Max	p
Osmolarity (cut-off 312 miliOsmol/L)	before	302	303	18.8	292	345	0.989
	after	302	299	18.4	283	350	
TBUT (Cut-off 5 seconds)	before	3.2	3.3	1.3	1.0	6.0	0.734
	after	3.2	2.7	1.9	1.0	7.3	
Schirmer test (Cut-off 5 milimeters)	before	16.3	16.0	10.0	3.0	45.0	0.339
	after	14.3	12.5	10.9	2.0	47.0	