Quantitative central corneal anatomy and anaesthetic eye drops effects: Comparison between 0.4% oxybuprocaine and a combination of 0.1% tetracaine and 0.4% oxybuprocaine

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Summary

We aimed to analyse the changes in central corneal thickness values following the instillation of 0.4% oxybuprocaine eye drops and following a combination of 0.1% tetracaine and 0.4% oxybuprocaine eye drops.

Orbscan pachymetry (Orbscan II Corneal Topography System; Orbscan, Inc., Salt Lake City, UT, USA) was carried out before and three minutes after the instillation of 0.4% oxybuprocaine eye drops, and before and three minutes after the instillation of a combination of 0.1% tetracaine and 0.4% oxybuprocaine eye drops in 35 healthy subjects (n=35; aged 20-30 years). After the instillation of 0.4% oxybuprocaine eye drops there was a mean increase in central corneal thickness of 25±11 microns. After the combination of 0.1% tetracaine and 0.4% oxybuprocaine eye drops it rose to 48±20 microns. The combination of 0.1% tetracaine and 0.4% oxybuprocaine anaesthetic eye drops causes higher increases in central corneal thickness values than 0.4% oxybuprocaine eye drops.

Key words: Central corneal thickness – Topical anaesthesia – Pachymetry – Oxybuprocaine – Tetracaine

Introduction

In recent years, quantitative anatomic study of the corneal thickness has gained importance owing to the relationship between the anatomic values of central corneal thickness (CCT) and intraocular pressure values in glaucomatous, ocular hypertensive, and normal eyes (Wolfs et al., 1997; Bron et al., 1999; Shah et al., 1999; Lleó et al., 2003). Corneal thickness values also are important in preoperative refractive laser in situ keratomileusis surgery (Price et al., 1999) because the thickness of the cornea limits the degree of correction of refractive errors; it is known that there is a relatively fixed amount of refractive correction that occurs for each micron of cornea ablated.

Ultrasound pachymetry is the technique most commonly used for measuring corneal thickness in vivo (Doughty and Zaman, 2000) and different quantitative anatomic corneal thickness studies have been carry out using this technique (Longanesi et al., 1996; Sanchis-Gimeno et al., 2001; Sanchis-Gimeno et al., 2003). However, ultrasound pachymetry requieres the use of anaesthetic eye drops, and different studies have detected changes in CCT values following the instillation of such drops (Herse and Siu, 1992; Asensio et al., 2003; Asensio et al., 2004). Currently, 0.4% oxybuprocaine HCL anaesthetic eye drops and a combination of 0.1% tetracaine HCL and 0.4% oxybuprocaine HCL anaesthetic

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eye drops are used to anesthetise the cornea. Changes in CCT values must be expected after anaesthetising the cornea with these two anaesthetics. However, do both these anaesthetic eye drops cause similar effects on CCT values? Which anaesthetic migth cause a greater change in these values? To date no study has analysed the effect of different anaesthetic eye drops on the thickness values of the same cornea when carrying out quantitative anatomic studies on the central cornea.

In view of the above, we were prompted to study the CCT changes induced by the instillation of 0.4% oxybuprocaine HCL anaesthetic eye drops and a combination of 0.1% tetracaine HCL and 0.4% oxybuprocaine HCL anaesthetic eye drops by analysing the CCT values of the same cornea before and after topical anesthesia using these two different anaesthetics.

Material and Methods

We carried out a prospective study involving 35 eyes of 35 subjects. The work was performed in accordance with the World Medical Association's Declaration of Helsinki and written informed consent was obtained from all patients. Approval from the Ethics Committee of the Faculty of Medicine of Valencia was obtained.

Preliminary evaluation of the volunteers

Two physicians carried out an ophthalmologic examination on all the volunteers that included best-corrected visual acuity, cycloplegic refraction (KR 7000-P Topcon Corp, Tokyo, Japan), slit-lamp examination (Haag Streit Biomicroscope 900, Bern, Switzerland), applanation tonometry (Goldmann Applanation Tonometer, Haag Streit, Bern, Switzerland), non-contact specular microscopy Topcon SP-2000P non-contact specular microscope, (Topcon Corp., Tokyo, Japan) and dilated fundus examination. Special care was taken to study the subjects' anaesthetics background and possible allergic reactions and systemic diseases. All the subjects were healthy.

Exclusion criteria included subjects who had had prior corneal and/or ocular surgery, subjects with corneal disease, contact lens wearers, subjects with clinical corneal changes and Goldmann applanation tonometry ≥ 21 mm Hg. Patients with systemic disease, best-corrected visual acuity < 20/40, and subjects taking any kind of medication were also excluded.

Characteristics of the subjects analysed

The mean age of the 35 subjects analysed was 26.4±0.4 years old (range, 20-30 years). The sphere ranged from -1.75 to -3.25 diopters (mean±SD, -2.27±0.41 diopters) while the cylinder ranged from 0 to -0.75 diopters (mean±SD, -0.39±0.25 diopters). Best-corrected visual acuity was ≥ 20/22 in 29 eyes (82.85%). Mean tonometry was 15.9±1.8 mmHg (range, 12-19 mmHg).

Corneal thickness measurements

CCT measurements were carried out by two other physicians with the Orbscan II Corneal Topography System (Orbscan, Inc., Salt Lake City, UT, USA). The Orbscan is an elevation topography that measures anterior and posterior corneal elevation (relative to a best-fit sphere), surface curvature, and corneal thickness using a scanning-slit mechanism. Two scanning slit-lamps project beams at 45º to the right or left of the instrument axis. 40 images, 20 with slit beams projected from the left and 20 from the right, are acquired in two intervals, each 0.7 seconds in duration. Surface data points are measured in the x, y, and z axes, creating colour coded topographic maps. Corneal thickness is obtained, showing the differences in elevation between the anterior and posterior surfaces of the cornea.

The mean of five consecutive measurements was used as the CCT value; it takes approximately 90 seconds to carry out these five measurements. One physician carried out five consecutive measurements of CCT. Immediately afterwards, two 0.4% oxybuprocaine HCL eye drops were instilled. Three minutes after anesthetising the cornea the CCT was measured again by another physician who was not aware of the previous results obtained by physician 1. The same protocol was followed one week later using two drops of a combination of 0.1% tetracaine HCL and 0.4% oxybuprocaine HCL.

The first 10 measurements were named anaesthetic A measurements (oxybuprocaine measurements), and the second 10 measurements were named anaesthetic B measurements (combination of tetracaine and oxybuprocaine).

When all the CCT measurements had been made, the results were collected and transferred to an Excel file by another physician who was not aware of the composition of anaesthetic A and B.

Anaesthetic eye drops used

We used 0.4% oxybuprocaine (Prescaina® 0.4%) anaesthetic eye drops and a combination of 0.4% oxybuprocaine and 0.1% tetracaine (Colircusí anestésico doble®). 0.4% oxybuprocaine anaesthetic eye drops contain thimerosal, edetate disodium salt, boric acid, sodium chloride, and purified water as preservatives; while the combination of 0.4% oxybuprocaine and 0.1% tetracaine contains chlorobutanol, monopotassium phosphate, disodium phosphate, and purified water.

Statistical analysis

Only the right eye was contemplated for the statistical analysis. The choice of limiting the

study to the right eye instead of the left eye was random. All results were analysed with the SPSS v11.5 statistical software package (SPSS Inc, Redmon, WA, USA) using a common significance level of $\alpha = 0.05$ for all tests.

RESULTS

Our aim was to compare the CCT measurements of four experimental conditions (*baseline* and *post-anesthesia* with oxybuprocaine, and *baseline* and *post-anesthesia* with the combination of tetracaine and oxybuprocaine), in order to detect differences in the corresponding mean values. Table 1 shows means and standard deviations for these four variables.

Table 1.- Central corneal thickness values before and after anaesthetic eye drops (mean microns±SD)

Oxybuprocaine		Tetracaine with oxybuprocaine	
Baseline	Post-anesthesia	Baseline	Post-anesthesia
552±5	577±11	553±5	601±21

According to Pearson's correlation coefficients, no significant correlation between the following was found: *baseline* and *post-anesthesia* with oxybuprocaine (r=0.204; p=0.240), *baseline* and *post-anesthesia* with the combination of tetracaine and oxybuprocaine (r=0.094; p=0.593), *post-anesthesia* with oxybuprocaine and *post-anesthesia* with the combination of tetracaine and oxybuprocaine (r=0.202; p=0.244). As expected, only the correlation between the two *baseline* variables was significant (r=0.637; p<0.001).

The four variables involved in the analysis were dependent because they were recorded using the same eye. An appropiate statistical technique for comparing means in such a situation is a randomised block design with cases (eyes) as blocks and the four experimental conditions as categories of the fixed factor. A previous Kolmogorov-Smirnov test indicated normality for all variables (Table 2).

Table 2.- Results of the Kolmogorov-Smirnov test for normality

	Oxybuprocaine		Tetracaine with oxybuprocaine	
	Baseline	Post-anesthesia	Baseline	Post-anesthesia
n	35	35	35	35
p-value	0.316	0.737	0.488	0.619

Table 3 shows the ANOVA table for the randomised block design. The F-value for the experimental conditions rejected the hypothesis of equal means and the F-value for blocks (eyes) was not significant.

Homogenous groups of means were detected with multiple comparisons tests. We used Tukey's and Scheffé's tests in order to have two different approaches that, as is well known, can give different results. This was not the case in our analysis, because the mean differences in CCT were large. As Table 4 shows, three homogenous groups could be established, one with the two *baseline* means, as expected, another with the mean obtained *after anesthesia with oxybuprocaine*, and a third with the mean obtained *after anesthesia with the combination of tetracaine and oxybuprocaine.*

Table 3.- ANOVA table for randomized block design

	F	Significance
Experimental condition	131	<0.001
Eye	1.1	0.243

Table 4.- Subsets of homogenous means

Tukey's technique	Subset		
Experimental conditions	1	2	3
Baseline oxybuprocaine	552		
Baseline combination tetracaine and oxybuprocaine	553		
Post-anesthesia oxybuprocaine		577	
Post-anesthesia combination of tetracaine and oxybuprocaine			601
Significance	0.996	1.000	1.000
Scheffe's technique	**Subset**		
Experimental conditions	1	2	3
Baseline oxybuprocaine	552		
Baseline combination tetracaine and oxybuprocaine	553		
Post-anesthesia oxybuprocaine		577	
Post-anesthesia combination of tetracaine and oxybuprocaine			601
Significance	0.997	1.000	1.000

DISCUSSION

The objective of this study was to determine the effects that oxybuprocaine eye drops and a combination of tetracaine and oxybuprocaine eye drops have on the CCT values in the same eye.

We used scanning-slit topography (Orbscan pachymetry). The interobserver and intraobserver variability of Orbscan pachymetry measurements has been analysed previously; Rainer et al., (2004) obtained correlation coefficients for intraobserver variability of between 0.985 and 0.991. The correlation coefficients for interobserver variability were between 0.987 and 0.989.

Our study was designed to select a sample of healthy subjects without involving the physicians who were to carry out the CCT measurements. The Orbscan pachymetric measurements were carried out by two different physicians in a masked fashion. This methodology made it impossible for the physicians to be aware of the patients' pre- and post-instillation eye drop status, since this could have biased the measurements made in the post-instillation period. Moreover, the physician who collected the CCT results was not aware of the composition of the anaesthetics tested. Thus, we believe the results obtained are valid.

It is known that anaesthetics and their preservatives can result in corneal toxicity (Burnstein, 1980; Penna and Tabbara, 1986; Tripathi et al., 1992; Barry Smith et al., 1996; Yeung et al., 2000). Nevertheless, we did not observe any clinical changes that might represent a toxic effect of the anaesthetics used. Neither were they observed in previous studies analysing the effect of anaesthetic eye drops on CCT values (Herse and Siu, 1992; Asensio et al., 2003; Asensio et al., 2004). However, did find variations of ≥ 15 microns after anesthesia; these have been considered as a clinically relevant outcome (Miglior et al., 2004).

The Orbscan System assesses corneal thickness values by calculating the distance between the air/tear film interface and the posterior corneal surface. The tear film thickness normally ranges from 3 to 40 microns (López García et al., 2003). However, alteration of lacrimation and tear film instability may also occur after anaesthesia (Barry Smith et al., 1996). Thus, one explanation for the results obtained here could be an alteration to the tear film after topical anaesthesia.

Alterations in the degree of corneal hydration after topical anaesthetics have been reported (Weekers, 1974). It is known that corneal hydration can affect corneal thickness values (Ousley and Terry, 1996) and it is also known that anaesthetics can cause a metabolic disturbance of keratocytes in the different layers of the cornea, which may lead to corneal oedema (Penna and Tabbara, 1986). Moreover, it has been observed that anaesthetics can also cause rapid swelling of the cornea, resulting in corneal thickening (Judge et al., 1997). Thus, an explanation for the increase in CCT values after topical corneal anaesthesia may be corneal oedema (Herse and Siu, 1992).

Our results revealed that there was a significant increase in CCT values after the instillation of both anaesthetic eye drops protocols used. Thus, these results seem to confirm that anaesthesia by means of oxybuprocaine eye drops and by means of a combination of tetracaine and oxybuprocaine eye drops can affect CCT values.

Nevertheless, while one study (Herse and Siu, 1992) reported a significant increase in CCT values about two minutes after 0.5 % proparacaine eye drops, and another described a significant increase in CCT values after the instillation of a combination of tetracaine and oxybuprocaine eye drops (Asensio et al., 2004), the authors of a third study that analysed the effect of 0.4% oxybuprocaine failed to find any significant increases in mean CCT values after corneal anaesthesia (Asensio et al., 2003).

One important aspect of the third study is that analysis of interindividual variations in corneal thickness revealed that variations in CCT values were higher than the mean precision of the Orbscan pachymetry following the instillation of anaesthetic eye drops. The present study obtained similar results, in part, because when comparing the CCT differences between the *baseline oxybuprocaine* and the *baseline combination of tetracaine and oxybuprocaine* we found no variations higher than 10 microns. Nevertheless, we obtained significant increases in mean CCT values after both anaesthetics, our results being similar to those reported by Herse and Siu (1992) and Asensio et al., (2004). However, as occurred in the study by Asensio et al. (2003), we found higher variations in corneal thickness than the mean precision of the Orbscan pachymetry after anaesthesia with oxybuprocaine eye drops. Moreover, Asensio et al. (2003) found interindividual responses to anaesthetic eye drops; the changes in CCT values were not the same in all the eyes. The same occurred in the present study although the increases in CCT values were higher after the combination of oxybuprocaine and tetracaine. Nevertheless, Asensio et al. (2003) found that several eyes had increases in CCT values similar to those obtained in the present study. In sum, the individual in-depth eye-by-eye analysis shows similarities in the results of the studies.

Our results prompt us to wonder wheter the effect of anaesthetic eye drops on corneal thickness should be ignored when carrying out quantitative anatomic studies of the CCT. Our results have shown that the anaesthetic eye drops used in ultrasound pachymetry may cause changes in CCT values. Thus, when interpretating the results researchers who use ultrasound pachymetry in quantitative anatomic studies should take into account that different anaesthetic eye drops may cause different increases in CCT values. In sum, we believe CCT measurements should be carried out without anaesthetic eye drops when possible in order to avoid the effect of such drops on CCT values.

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