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# Changes in central corneal thickness values after instillation of oxybuprocaine hydrochloride 0.4%

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ABSTRACT

*Purpose:* To assess the variation in central corneal thickness (CCT) following the instillation of oxybuprocaine hydrochloride (0.4%), in normal subjects.
*Methods:* This was a randomized, prospective study of CCT measurements (before and after the instillation of topical anaesthesia) obtained with the Topcon SP-3000P noncontact specular microscope, in 60 eyes of thirty subjects. The subjects' mean age was 20 ± 1 years (mean ± SD). In each subject, one eye was treated with one drop of oxybuprocaine hydrochloride (HCl) and the fellow eye with one drop of normal saline (control). The SP-3000P CCT readings were first obtained before instillation (baseline) and monitored every 30 s after instillation of each eye drop for a period of 10 min.
*Results:* The mean baseline CCT for oxybuprocaine was 526 ± 23 μm. Ten minutes after, it was 526 ± 24 μm. In the control, the mean CCT was 526 ± 27 μm, 10 min after it was 526 ± 28 μm. The mean variation in CCT measurement was −0.7 ± 3.1 (5.5 to −6.8 μm, 95% CI) for oxybuprocaine and −0.6 ± 4.1 μm (7.5 and −8.6 μm, 95% CI) for the fellow eyes ($P > 0.05$). There was no significant variation among the 20 CCT columns for either oxybuprocaine or the control group ($P > 0.05$ for both).
*Conclusions:* One drop of topical oxybuprocaine 0.4% did not cause a significant change in CCT at up to 10 min following instillation. However, higher differences were observed at 2.30 min and 4.30 min after instillation.



## 1. Introduction

Corneal anaesthesia is required to perform applanation tonometry, ultrasound pachymetry, cataract surgery, diagnostic ultrasound, corneal refractive surgery, contact lens fundus examination, and other ophthalmic examinations. Assessment of corneal thickness is important in deciding which patients may undergo corneal refractive surgery and the monitoring of patients after surgery [1,2] to confirm the values of intraocular pressure with Goldmann applanation tonometry [3] and to determine the function of the endothelial cells [4]. Accurate measurement of central corneal thickness (CCT) has become an essential factor for the diagnosis and treatment of many ocular diseases [5,6].

The corneal thickness can be measured by ultrasound pachymetry or by noncontact devices such as the specular microscope, the Oculus Pentacam, and the Orbscan, etc. Even though ultrasound pachymetry is the most common method in CCT assessment [7], it requires anaesthesia, so cannot be used to determine corneal changes induced by anaesthetic eye drops. For this reason, noncontact devices have been employed in studies on the effects of topical anaesthetics on measured corneal thickness. One such device, which has rapidly become a method of choice because of its speed, reliability, ease of use, non-invasive nature, and its ability to obtain an endothelial cell count [8] is, the Topcon SP-3000P noncontact specular microscope.

The effects of various topical anaesthetics on corneal thickness measurements made with several pachymetry devices unclear. In some cases the patients exhibited a temporary increase in CCT [9–13], while others did not find significant variations [11,14–17]. There is some confusion in the literature as to why anaesthetics significantly affect corneal thickness and IOP measurements. Some authors have attributed the changes to the structural/functional damage to both the corneal epithelium and endothelium caused by the preservatives used in the preparation of these anaesthetics [17–19] whereas, others have reported that, the diffusion of the topical anaesthetic into the deep stroma layers, causes an inhibition of the endothelial cell metabolism which results in corneal oedema and subsequent increase in corneal thickness [9,11]. However, most of the previous studies were not randomized, poorly randomized, poorly controlled and/or used different devices. We therefore designed this randomized, placebo-controlled study to evaluate the variations, if any, in central corneal thickness measured by the SP-3000P over a period of 10 min after instillation of oxybuprocaine.

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## 2. Subjects and methods

A total of sixty eyes of 30 young volunteers [16 men (53%) and 14 women (47%)] were included in this prospective study. The mean age of the subjects was 20 ± 1 years (range: 20–25 years). These patients were recruited randomly from the various colleges of the University after the research protocol was explained, and informed consent obtained, from each subject. The College review board approved the study protocol and study procedures conformed to the tenets of the declaration of Helsinki (1975), as revised in Edinburgh 2000. A comprehensive ophthalmological examination including corneal topography examination was conducted on each subject before inclusion in this study. Exclusion criteria included eyes with a positive history for corneal disease (or any ocular surface disease), previous use of hard contact lenses, eyes with a positive history of glaucoma or previous anterior segment surgery. Soft contact lens wearers were included in the study only if they discontinued contact lens use 24 h prior to examination.

Triplicate CCT measurements were obtained from both eyes of each subject with a noncontact specular microscope SP-3000P (Topcon Corp., Tokyo, Japan) before instillation of the eye drops. Each subjects' eyes were randomized (using a series of random numbers generated from a Microsoft Excel spreadsheet) to receive either oxybuprocaine hydrochloride or normal saline (control). Both the subjects and the examiner were blinded to the allotted groups of the subjects' eyes.

Following the instillation of 1 drop of oxybuprocaine HCl 0.4% (Minims; Chauvin pharmaceuticals Ltd, London, UK) or saline, triplicate CCT re-measurements were made every 30 s until a 10 min period elapsed. Each measurement involved 3 readings, and an average was calculated. A total of 60 CCT measurements per eye were obtained, giving an average of 20 CCT measurements per eye, after instillation of either oxybuprocaine or normal saline. All measurements were made between 11.00 a.m. and 2.00 p.m., in order to minimize the effects of diurnal variation [20].

The SP-3000P non-contact specular microscope is a newer version of the SP-2000P with various advanced features and algorithm integrated. Aside from the improvement in quality of the captured image, the reliability and repeatability of measurements obtained in the current version has been enhanced by its ability to obtain 5 images per eye in contrast to 3 images per eye obtained by the previous version. Central corneal thickness readings are obtained using a reflection of light from the anterior and posterior corneal surfaces. Focusing on the endothelium, it provides a specular image and measures the focal distance, from which corneal thickness can be calculated.

## 3. Statistical analysis

All data were entered into a Microsoft Excel spreadsheet. The mean, standard deviation, minimum and maximum values were calculated and presented descriptively in a table. Analysis of CCT measurements was performed by subtracting each of the 20 average CCT measurements obtained after instillation (of oxybuprocaine or normal saline) from the baseline CCT measurements. For both the control eyes and experimental eyes, the resulting CCT changes in all subjects were averaged at each 30 s interval. For analysis of the influence of oxybuprocaine on CCT the Graphpad Instat software (version 3.00 – Graphpad Software Inc., San Diego, CA) was used.

To study the variation in corneal thickness during the 10 min interval (following instillation of both eye drops), a single factor repeated measures ANOVA test was conducted to compare the baseline with all the thickness values at each point. To obtain the 95% limits of variation on corneal thickness, we calculated the confidence interval (CI) as mean ± 1.96 × $SD^{mean\ difference}$.

Bland and Altman [21] recommended that both groups be compared directly and the size of differences reported. So the twenty time points following the instillation of saline were each subtracted from the baseline CCT to get twenty difference columns. The same operation was carried out for the oxybuprocaine group. Finally, the twenty difference columns from the control group were compared with the difference columns from the oxybuprocaine group using two-factor repeated-measures ANOVA. To study the corneal thickness variations during the entire 10 min after instillation of oxybuprocaine, a paired *t*-test was applied on the mean CCTs (before and 10 min after instillation). A $P$ value < 0.05 ($\alpha$) was considered statistically significant, and with 58 eyes the study had a power of 80% as calculated using the G* Power software 3.1.3 version.

A line graph of time point variation in CCT (following instillation of eye drops) as a function of mean CCT difference (pre minus post), was also plotted. Levels of CI were indicated by error bars. Pearson's correlation analysis was performed to assess agreement between oxybuprocaine eyes and saline eyes before and after instillation.

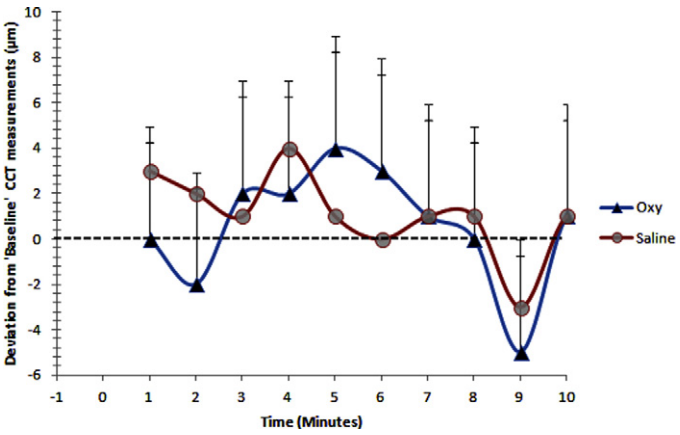


**Fig. 1.** Variation in central corneal thickness measured by noncontact specular microscope (Topcon SP-3000P) every 30 s over a period of 10 min after instillation of 1 drop of normal saline on one eye and 1 drop of oxybuprocaine hydrochloride 0.4% on the fellow eye. Arrow bars represent limits of confidence interval, while dotted straight line represent mean baseline CCT value.

## 4. Results

The mean CCT measurements obtained at baseline, 10 min after instillation of one drop of oxybuprocaine HCl and one drop of normal saline respectively were: 526 + 23 μm, 526 + 23 μm ($P$ > 0.05) and 526 + 27 μm, 526 + 28 μm ($P$ > 0.05). There was also no significant difference in corneal thickness measurements obtained at baseline between eyes (paired *t*-test: $P$ = 0.8539).

The graphical representation of the time point variations in CCT (baseline – after instillation) of oxybuprocaine and saline is shown in Fig. 1.

After averaging the CCT measured at the twenty time points up to 10 min post-instillation of the eye drops, the mean variation in oxybuprocaine and saline treated eyes were −0.7 ± 3.1 μm and −0.6 ± 4.1 μm, respectively, with 95% of the differences ranging from +5.5 to −6.8 μm for oxybuprocaine and from +7.5 to −8.6 μm for the saline (control group). In the oxybuprocaine treated eyes, the largest increase (5 μm) and decrease (4 μm) in thickness values were observed at 2.30 and 4.30 time points respectively (Fig. 1). The difference between means of corneal thickness measurements at baseline, after instillation of saline and oxybuprocaine were not statistically significant (repeated measures ANOVA: $P$ = 0.9988).

The analysis of thickness variations in central corneal thickness during the 10 min interval showed that variations in corneal thickness were not statistically significant compared with the baseline values in the oxybuprocaine treated eyes (repeated measures ANOVA: $P > 0.05$) and in the saline treated eyes (repeated measures ANOVA: $P > 0.05$). The 95% CI of these variations ranged from +4 μm to −5 μm and +4 to −3 μm for the oxybuprocaine and saline groups, respectively.

Between oxybuprocaine and control eyes, neither the average CCT measurements obtained 10 min after instillation (paired *t*-test: $P = 0.8707$) of eye drops, nor the differences between eye drops (paired *t*-test: $P = 0.9188$) differed significantly. The differences in CCT ranged from +12 μm to −13 μm, with only one eye showing an increase of more than 11 μm, and 2 eyes showing a decrease of more than 12 μm. Also, at no point in time was there a significant difference between variations in corneal thickness obtained after instillation of oxybuprocaine and normal saline (repeated measures ANOVA: $P > 0.05$).

## 5. Discussion

Our results show that oxybuprocaine 0.4% in its non-preserved form does not induce any significant variations in CCT (as compared with a saline control group) measured by the SP-3000P, at up to 10 min after instillation of one drop.

Anaesthetics are weak bases, which are relatively insoluble in water and as such has to be prepared commercially as water soluble salts of hydrochloric acid [11] so as to be clinically effective. In this form, they are made acidic, become more stable, and exhibit an improved shelf life. Oxybuprocaine hydrochloride and proparacaine hydrocholride are examples of benzoate-linked esters and are currently the commonly used agents for topical anaesthesia. Oxybuprocaine HCl is used in 0.4% solution and produces a rapid onset of corneoconjuctival anaesthesia, 15–20 s, and last 15–20 min.

Although the effect of anaesthetics on the corneal epithelium, stroma and endothelium is well known [14,22], their influence on the measured CCT still remains unclear. In this study, the instillation of 1 drop of oxybuprocaine hydrochloride (0.4%) resulted in no significant effect on the CCT, measured with the SP-3000P. These results are in agreement with three other studies [11,12,15] that have evaluated the effects of topical anaesthesia on CCT measurements obtained with the specular microscopes. Lam and Chen [15] found no effect on corneal thickness obtained in forty healthy Chinese subjects with one drop proparacaine hydrochloride (0.5%). Asensio et al. [11] reported no statistically significant differences in mean corneal thickness of 26 eyes after instillation of 2 drops of oxybuprocaine. Another study [12] on a smaller sample utilizing SP-2000P, observed a transient increase in corneal thickness of 7.7 μm (3.6–11.2 μm, 95% CI) 40 s after instilling one drop of 0.4% oxybuprocaine hydrochloride, which recovered to baseline CCT after 80 s. They further observed that the corneal thickness was unstable during the 5 min after instilling proparacaine as a second temporary increase occurred, this did not occur with oxybuprocaine. Our study also disagrees with the findings of various other studies that have assessed the influence of different topical anaesthetics on other CCT measuring devices. Herse and Siu [9] observed that one drop of proparacaine hydrochloride (0.5%) resulted in a slight, statistically insignificant, increase in CCT obtained by an optical pachymeter, which recovered after 2 min. This effect became statistically significant when two drops of proparacaine hydrochloride were instilled, resulting in an increase in CCT of about 15 μm. The CCT returned to baseline values between 7 and 8 min later. They attributed this increase to a temporary cornea stromal oedema. Utilizing the Orbscan corneal topographer, Aleman et al. [10] reported an insignificant increase in corneal thickness of 9 μm, following the instillation of tetracaine hydrochloride (0.5%). Diaz-Rey et al. [14] utilizing the Orbscan II optical scan pachymetry also noticed a non-significant difference (about 5 μm) in mean CCT measured 6 min after instilling 1 drop of Colircusi (a dual anaesthetic with 0.1% tetracaine clorhydrate and 0.4% oxybuprocaine clorhydrate) on a smaller group of subjects. A more recent study [17] utilizing the Oculus Pentacam showed that, the instillation of oxybuprocaine (0.4%) did not induce any statistically significant CCT changes in the seventy eyes studied. While these studies evaluated the effects of different topical anaesthetics on CCT using various devices, none as yet has been a well self-controlled study to monitor the effects of topical anaesthetics on the CCT measured by SP-3000P.

In one controlled study on 30 subjects, using the Orbscan pachymetry measurements were carried out prior to (by one examiner), and 3 min after instillation of two drops of either saline solution or two drops of 0.4% oxybuprocaine HCl (by a second examiner) [11]. They found a significant increase in corneal thickness measurements 3 min after instillation of the anaesthetics. However, it is known that conventional ultrasound corneal thickness studies have detected significant differences between observers when corneal thickness measurements are carried out by two different observers on the same sample [23] which could therefore explain their results. In the current study, one drop of oxybuprocaine was instilled (which is usually enough to produce the anaesthetic effect required during clinical measurements of CCT) and measurements carried out by same examiner to minimize any inter-examiner bias. Nevertheless, between-groups (saline and topical anaesthetic) the variability though not statistically significant, was wide, ranging from +13 to −13 μm. Rosa et al. [17] used a Pentacam for CCT measurements on 78 young patients. In their study, the control eye received no treatment, while two drops of oxybuprocaine were instilled in the fellow eye. Although their result showed no significant difference in CCT measurements obtained before and after instillation of oxybuprocaine, the absence of an appropriate placebo control limits the interpretation of their results [24].

The results of the current study show that the instillation of one drop of oxybuprocaine HCl does not significantly affect CCT measured by the SP-3000P. The current study differed from other studies in the materials and methods used.

The reliability of the SP-3000P in obtaining measurement of corneal thickness was also confirmed in this study. On each eye of each subject, one examiner measured corneal thickness 3 times to obtain an average baseline value, and 60 times to obtain 20 average values after instillation of each drop; the mean standard deviation was within 5 μm for baseline, and 6 μm each, for saline and oxybuprocaine HCl after instillation. This is slightly better than the 7.1 μm reported by Nam et al. [12] who used an earlier version of noncontact specular microscope (SP-2000P) but with a smaller sample size (18), and similar to that of ultrasound pachymetry [25,26].

This study is limited by the narrow range of the subjects' ages; and the non-inclusion of subjects affected by diseases such as ocular hypertension, glaucoma, dry eyes and diabetes where precise measurement of CCT is also very important. Therefore, studies on a subject sample with a wider age range, and in patients with ocular anomalies would be useful in confirming this finding.

In conclusion, the findings of this placebo-controlled study suggest that one drop of topical oxybuprocaine hydrochloride (0.4%) has no significant effect on the measured CCT up to 10 min following instillation.

## Disclosure statement

No conflict of interest nor financial disclosure for this study.

## References


[1] Price Jr FW, Koller DL, Price MO. Central corneal pachymetry in patients undergoing laser in situ keratomileusis. Ophthalmology 1999;106:2216–20.
[2] Tekwani NH, Huang D. Risk factors for intraoperative epithelial defect in laser in situ keratomileusis. American Journal of Ophthalmology 2002;134:311–6.
[3] Doughty MJ, Zaman ML. Human corneal thickness and its impact on intraocular pressure measures: a review and meta-analysis approach. Survey of Ophthalmology 2000;44:367–408. Review.
[4] Waring 3rd GO, Bourne WM, Edelhauser HF, Kenyon KR. The corneal endothelium. Normal and pathologic structure and function. Ophthalmology 1982;89:531–90.
[5] Miglior S, Pfeiffer N, Torri V, European Glaucoma Prevention Study (EGPS) Group. Predictive factors for open-angle glaucoma among patients with ocular hypertension in the European Glaucoma Prevention Study. Ophthalmology 2007;114:3–9.
[6] Kwon RO, Price MO, Price Jr FW, Ambrósio Jr R, Belin MW. Pentacam characterization of corneas with Fuchs dystrophy treated with Descemet membrane endothelial keratoplasty. Journal of Refractive Surgery 2010;26:972–9.
[7] Bovelle R, Kaufman SC, Thompson HW, Hamano H. Corneal thickness measurements with the Topcon SP-2000P specular microscope and an ultrasound pachymeter. Archives of Ophthalmology 1999;117:868–70.
[8] Ogbuehi KC, Almubrad TM. Repeatability of central corneal thickness measurements measured with the Topcon SP2000P specular microscope. Graefes Archive for Clinical and Experimental Ophthalmology 2005;243(8):798–802.
[9] Herse P, Siu A. Short-term effects of proparacaine on human corneal thickness. Acta Ophthalmologica Scandinavica 1992;70:740–4.
[10] Alemán DVT, Fernández-Baca G, Abreu González R, Varela DL, Gómez-Camacho MJA, Estévez AJJ, et al. Estudio comparativo de dos sistemas de paquimetría. Efecto de las gotas anestésicas sobre el espesor corneal. Archivos de la Sociedad Canarias de Oftalmologia 2003;14:7–10.
[11] Asensio I, Rahhal SM, Alonso L, Palanca-Sanfrancisco JM, Sanchis-Gimeno JA. Corneal thickness values before and after oxybuprocaine 0.4% eye drops. Cornea 2003;22:527–32.
[12] Nam SM, Lee HK, Kim EK, Seo KY. Comparison of corneal thickness after the instillation of topical anaesthetics. Proparacaine versus oxybuprocaine. Cornea 2006;25:51–4.
[13] Mukhopadhyay DR, North RV, Hamilton-Maxwell KE. Effect of a proparacaine 0.50%-sodium fluorescein 0.25% mix and contact ultrasound pachymetry on central and midperipheral corneal thickness measured by noncontact optical pachymetry. Journal of Cataract and Refractive Surgery 2011;37:907–13.
[14] Diaz-Rey JA, Giraldez MJ, Garcia-Resua C, Yebra-Pimentel E. Effect of double anaesthetic colicursi (Tetracaine 0.1% and oxibuprucaine 0.4%) on central and paracentral corneal thickness. Archivos de la Sociedad Española de Oftalmología 2009;84:23–30.
[15] Lam AK, Chen D. Effect of proparacaine on central corneal thickness values. An evaluation using noncontact specular microscopy and pentacam. Cornea 2007;26:55–8.
[16] Montero JA, Ruiz-Moreno JM, Fernandez-Munoz M, Rodriguez-Palacios MI. Effect of topical anesthetics on intraocular pressure and pachymetry. European Journal of Ophthalmology 2008;18:748–50.
[17] Rosa N, De Bernardo M, Borrelli M, Filosa ML, Lanza M. Effect of oxybuprocaine eye drops on corneal volume and thickness measurements. Optometry & Vision Science 2011;88:640–4.
[18] Carel RS, Korczyn AD, Boyman R. Amethocaine and intraocular pressure. Ophthalmic Research 1979;11:212–5.
[19] Almubrad TM, Ogbuehi KC. Investigation of the effect of topical anesthesia on intraocular pressure. Clinical Ophthalmology 2007;1:305–9.
[20] Lattimore Jr MR, Kaupp S, Schallhorn S, Lewis RIV. Orbscan pachymetry: implications of a repeated measures and diurnal variation analysis. Ophthalmology 1999;106:977–81.
[21] Bland JM, Altman DG. Comparisons against baseline within randomized groups are often used and can be highly misleading. Trials 2011;12:264.
[22] Cho P, Brown B. The effects of benoxinate on the tear stability of Hong Kong-Chinese. Ophthalmic and Physiological Optics 1995;15:299–304.
[23] Bovelle R, Kaufman SC, Thompson HW, Hamono H. Corneal thickness measurements with the Topcon SP-2000P specular microscope and an ultrasound pachymeter. Archives of Opthalmology 1999;117:868–70.
[24] European Medicines Agency. Choice of control group in clinical trials: note for guidance on choice of control group in clinical trials; 2001 CPMP/ICH/364/96. <http://www.emea.europa.eu>.
[25] Korah S, Thomas R, Muliyil J. Comparison of optical and ultrasound pachometry. Indian Journal of Ophthalmology 2000;48:279–83.
[26] Miglior S, Albe E, Guareschi M, Mandelli G, Gomarasca S, Orzalesi N. Intraobserver and interobserver reproducibility in the evaluation of ultrasonic pachymetry measurements of central corneal thickness. British Journal of Ophthalmology 2004;88: 174–7.