Clinical investigation of the effect of topical anesthesia on intraocular pressure

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Background/Aims: Contact tonometry is generally considered more accurate than non-contact tonometry in the assessment of intraocular pressure (IOP). This study was designed to investigate the effect of ocular anesthesia, a pre-requisite for contact tonometry, on the IOP in a sample of visually normal subjects.

Method: In a random sample of 120 young visually normal subjects (divided equally among three groups), the Topcon CT80 non-contact tonometer was used to measure IOP before, at the second minute and at the fifth minute following instillation of one drop of one of three eyedrops – carboxymethylcellulose sodium 0.5% (control), oxybuprocaine hydrochloride 0.4% and proparacaine hydrochloride 0.5%.

Results: The IOP measured before instilling the ophthalmic drops did not vary significantly among the three groups of subjects ($p > 0.05$). In the control group, the average IOP of 15.1 ± 2.6 mmHg did not vary significantly ($p > 0.05$) 2 minutes and 5 minutes following instillation of one drop of Carboxymethylcellulose sodium. There were statistically significant reductions of IOP 2 minutes ($p < 0.01$) and 5 minutes ($p < 0.001$) after the instillation of one drop of oxybuprocaine hydrochloride. One drop of proparacaine hydrochloride caused significant reductions in the average IOP after 2 minutes ($p < 0.001$) and after 5 minutes ($p < 0.001$).

Conclusions: One drop of topical proparacaine or oxybuprocaine may cause a small but a statistically significant reduction in IOP which could lead to lower IOP readings.

Keywords: tonometry, topical anesthesia, oxybuprocaine, proparacaine

Introduction

Goldmann applanation tonometry remains the method of choice the assessment of intraocular pressure (IOP), which is one of the important clinical signs monitored for the diagnosis and management of glaucoma. The advent of non-contact tonometry has enabled easier and quicker screening of IOP.

Non-contact tonometers have as their main advantage, the ability to reliably estimate IOP without coming into contact with the anterior ocular surface. This negates the need for topical anesthesia and eliminates the risk of cross-contamination leading to transmission of ocular infections between patients.

Though non-contact tonometers have gained widespread acceptance, the consensus is that contact (specifically Goldmann) tonometry is more accurate and should be employed to confirm readings of intraocular pressure. Thus contact tonometry is the preferred method of assessing IOP.

The continued use of contact tonometry to evaluate IOP raises the question whether or not topical anesthesia influences the measured IOP. More to the point, Goldmann applanation tonometry is the gold standard for the clinical assessment of IOP and any new technique for measuring IOP must be compared with the Goldmann tonometer for accuracy and reliability. In the event that this new technique does not require topical anesthesia (as is the case with non-contact tonometers), the reliability and

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accuracy indices will be biased if topical anesthetics have a significant effect on the measured IOP. Previous studies (Carel et al 1979; Jose et al 1983; Leys et al 1986; Meyer et al 1987; Baudouin and Gastaud 1994) investigated the effects of topical anesthetics on IOP. However these studies mixed normal, glaucomatous and/or ocular hypertension populations, were poorly controlled, employed too few subjects or were carried out in conditions that were markedly different from conventional applications of clinical tonometry.

This study was undertaken to investigate the effects of two topical anesthetics (0.5% proparacaine hydrochloride and 0.4% oxybuprocaine hydrochloride) on the IOP of a randomly selected group of young visually normal subjects, in conditions identical to those in which assessments of intraocular pressure are made in the clinical setting.

Subjects and methods

This prospective clinical study was carried out on the right eyes of 120 randomly selected routine refraction patients, divided equally between men and women, visiting the King Saud University Optometry clinics. The subjects were divided into three groups of 40 each (divided equally between men and women). One group was treated with 0.5% carboxymethylcellulose sodium eyedrops (Refresh Tears, Allergan, USA), a second group with 0.4% oxybuprocaine hydrochloride eyedrops (Novesin, Novartis, Switzerland) and a third group with 0.5% proparacaine hydrochloride eyedrops (Alcaine, Alcon, USA).

Quadruplicate measurements of IOP were taken with the Topcon CT80 non-contact tonometer (Abdulrehman Al-Gosaibi GTB, Riyadh, Saudi Arabia) before a single drop of any of the three eyedrops was instilled. Repeat quadruplicate measurements of IOP were taken two minutes after and five minutes after instillation of any of the three drops. The average of the last three of the quadruplicate measurements was used for statistical analyses. This procedure was adopted to suit the principle of IOP measurement used by the Topcon CT80 non-contact tonometer in which, after the first pulse is fired at the cornea, subsequent pulses are automatically adjusted to the IOP of the subject to minimize the risk of excessive air pressure.

All the measurements of IOP were made by one clinician (KO) and the subjects were randomly assigned to groups in a masked fashion by the other clinician (TA). Subjects who were less than 18 years old, those with a best-corrected acuity less than 20/20, or those with a positive history for ocular disease, contact lens wear, ocular surgery, ocular trauma or ocular dysgenesis were excluded from this study. Each subject underwent the following ophthalmic examinations: auto refractokeratometry, subjective refraction, slit-lamp biomicroscopy of the anterior segment and monocular direct ophthalmoscopy. The subjects were patients in the routine refraction clinics, their spherical subjective refraction was within ±4.00D and neither corneal nor total astigmatism exceeded −2.50D in any subject. Subjects gave informed consent to participate in this investigation and the study was designed to conform to the tenets of the Helsinki Declaration.

All IOP measurements were made between 14:00 hrs and 16:00 hrs to ensure that the IOP was assessed at the period of the day when it is known to be most stable (Liu et al 1999).

Single-factor ANOVA was used to compare the average age of the subjects and the initial IOP between groups. Repeated-measures ANOVA was used to examine the effect of each eyedrop on IOP. All values are given as mean ± SD. The level of statistical significance for this study was set at 5%.

Statistical analyses were conducted with the Graphpad Instat for Windows program, version 3.00 (Graphpad Software Inc., San Diego California USA, http://www.graphpad.com).

Results

The three groups were age-matched so that the average age did not differ significantly ($p = 0.6044$) between groups. The average age and standard deviation of each group are listed in Table 1.

Table 1 Age and IOP characteristics of subject groups

	Age	IOP before drops	2 mins after	5 mins after
Refresh (Control)				
Eyedrops				
Average	21.0	15.1	15.3	15.1
Std Dev	2.0	2.6	2.5	2.5
p *values*			$p > 0.05$	$p > 0.05$
Novesin				
Eyedrops				
Average	21.1	15.7	15.1	14.9
Std Dev	2.0	3.6	3.1	3.0
p values			$p < 0.01$	$p < 0.001$
Alcaine				
Eyedrops				
Average	21.4	16.1	15.3	15.1
Std Dev	1.9	3.0	3.2	3.0
p values			$p < 0.001$	$p < 0.001$

p values are from repeated-measures ANOVA comparisons of IOP 2 minutes and 5 minutes after eyedrop instillation, with the baseline IOP measured before the eyedrop was instilled.

Table 2 Effect of 0.5% carboxymethylcellulose sodium on IOP – number of subjects (% of total subjects)

Change in IOP	2 minutes post-eyedrop instillation	5 minutes post-eyedrop instillation
2 mmHg increase	3 (7.5%)	3 (7.5%)
1 mmHg increase	15 (37.5%)	7 (17.5%)
No Change	10 (25%)	20 (50%)
1 mmHg decrease	10 (25%)	8 (20%)
2 mmHg decrease	2 (5%)	1 (2.5%)
3 mmHg decrease	0 (0%)	1 (2.5%)

There was no change in measured IOP with one drop of 0.5% carboxymethylcellulose sodium (Table 1). An analysis of the effect of carboxymethylcellulose sodium is given in Table 2. Most of the subjects (88% two minutes and five minutes after eyedrop instillation) presented with an IOP change evenly distributed within ±1 mmHg (of the initial IOP).

There were significant reductions in measured IOP two minutes and five minutes after 0.4% oxybuprocaine hydrochloride was instilled. The difference between the IOP measured at two minutes and that measured at five minutes was not statistically significant. Most of the oxybuprocaine subjects presented with an IOP change within ±2 mmHg (of the initial IOP) after instillation of the eyedrops, with approximately 87% (two minutes and five minutes post eyedrop instillation) showing an IOP change that ranged from +1 mmHg to –2 mmHg.

Table 3 shows an analysis of the magnitude and direction of change in IOP induced by oxybuprocaine. One drop of 0.5% proparacaine hydrochloride significantly reduced IOP. The IOP measured two minutes post eyedrop instillation was not significantly different from the IOP measured after five minutes ($p > 0.05$). Almost all the subjects in this group presented with an IOP change between +1 mmHg and –3 mmHg. The proportion of subjects with an IOP reduction of 1 mmHg or greater was approximately 75% (two minutes and five minutes post eyedrop instillation) compared with approximately 28% (two minutes and five minutes post instillation) with carboxymethylcellulose sodium and approximately 65% (two minutes and five minutes post instillation) with oxybuprocaine hydrochloride. Table 4 is an analysis of the magnitude and direction of change in IOP caused by proparacaine.

Table 3 Effect of 0.4% oxybuprocaine hydrochloride on IOP – number of subjects (% of total subjects)

Change in IOP	2 minutes post-eyedrop instillation	5 minutes post-eyedrop instillation
2 mmHg increase	2 (5%)	3 (7.5%)
1 mmHg increase	7 (17.5%)	3 (7.5%)
No Change	5 (12.5%)	7 (17.5%)
1 mmHg decrease	15 (37.5%)	13 (32.5%)
2 mmHg decrease	10 (25%)	12 (30%)
3 mmHg decrease	1 (2.5%)	2 (5%)

Discussion

The Topcon CT80 non-contact tonometer provides accurate and reliable assessments of IOP in young normotensive subjects (Ogbuehi 2006). This tonometer was therefore well suited to assess the effect of topical anesthesia on the measured IOP. The assessment of IOP following topical anesthesia was made two minutes and five minutes after instillation to closely approximate conditions in which Goldmann or contact tonometry is employed in the clinical setting following topical anesthesia.

All anesthetics are weak bases, which are relatively insoluble in water and thus have to be prepared commercially as water soluble salts of hydrochloric acid (Asensio et al 2003). This makes them acidic but it also significantly improves their shelf life. The more common ocular topical anesthetics in use today are benzoate esters (of which both proparacaine and oxybuprocaine are examples) which act by reversibly stabilizing the voltage-dependent sodium ion channels, decreasing their permeability to sodium ions and thus blocking the initiation and conduction of sensory nerve impulses to the spinal cord and brain stem.

The effect of topical anesthetics on IOP remains unclear. Two studies (Herse and Siu 1992; Nam et al 2006) reported transient increases in central corneal thickness following the instillation of 0.5% proparacaine hydrochloride, a development which would be expected to induce a transient increase in IOP with the non-contact tonometer (Recep et al 2001; Ko et al 2005). Nam et al (2006) also reported a transient increase in corneal thickness after the instillation of one drop of 0.4% oxybuprocaine hydrochloride. However, a more recent study (Lam and Chen 2007) found no effect on corneal thickness with one drop 0.5% proparacaine. Yet another study (Asensio et al 2003) found no effect on corneal thickness with 0.4% oxybuprocaine. Carel et al (1979) reported an average decrease in IOP of 0.72 mmHg 10 minutes after the instillation of 2% amethocaine. Another study by Weekers (1974) concluded that topical anesthetics caused an alteration of the endothelial Na^+/K^+ pump resulting increased stromal hydration and as a consequence, increased corneal thickness. In a week-long study of 28 patients, ten of whom were

Table 4 Effect of 0.5% proparacaine hydrochloride on IOP – number of subjects (% of total subjects)

Change in IOP	2 minutes post-eyedrop instillation	5 minutes post-eyedrop instillation
3 mmHg increase	1 (2.5%)	1 (2.5%)
2 mmHg increase	0 (0%)	1 (2.5%)
1 mmHg increase	9 (22.5%)	2 (5%)
No Change	1 (2.5%)	6 (15%)
1 mmHg decrease	17 (42.5%)	16 (40%)
2 mmHg decrease	8 (20%)	10 (25%)
3 mmHg decrease	4 (10%)	4 (10%)

glaucomatous, Leys et al (1986) found no effect of topical anesthesia on IOP in patients receiving oxybuprocaine three times a day for a week. In the most comprehensive study in the literature, Baudouin and Gastaud (1994) found significant decreases in IOP with two topical anesthetics (0.4% oxybuprocaine and 0.2% betoxycaine) but no effect with 0.6% metipranolol or with 1% indomethacin, both of which served as control drugs. Although with metipranolol there was a significant decrease in IOP recorded fifteen minutes after the drug was instilled.

The results of this study showed a significant reduction in IOP with one drop of 0.4% oxybuprocaine and with one drop of 0.5% proparacaine, which was absent in the control subjects in whom 0.5% carboxymethylcellulose sodium was administered. This effect was observed as early as two minutes and was not significantly altered after five minutes. The average reduction of IOP was approximately 0.8 mmHg with oxybuprocaine and approximately 0.9 mmHg with proparacaine. In contrast, the IOP did not change with the instillation of 0.5% carboxymethylcellulose sodium. Although most subjects in all three groups had IOP changes between −1 mmHg and +3 mmHg, there was a significant number of subjects in the anesthetics' groups that had IOP reductions of 2 mmHg or 3 mmHg (approximately 30% after 2 minutes in both the oxybuprocaine and proparacaine groups and approximately 35% after five minutes in both groups). This was in contrast to the carboxymethylcellulose group in which only 5% had a decrease of 2 or 3 mmHg. The largest IOP increase after eye drop instillation in all three groups was 3 mmHg and the largest decrease was also 3 mmHg.

The findings of this study agree with those of Baudouin and Gastaud (1994) in which there were average reductions in IOP of 0.76 mmHg (0.7 mmHg, after two minutes, in this study) after one minute and 1.19 mmHg (0.9 mmHg, after five minutes, in this study) after five minutes, with oxybuprocaine. A smaller but significant reduction was also found by these authors with betoxycaine. Another agreement between the findings of both studies is the fact that the IOP reduction was constant after the first minute. We found no significant difference between the IOP decrease after two minutes and that after 5 minutes in agreement with Baudouin and Gastaud (1994) who found no significant difference in the IOP reduction at up to 15 minutes with oxybuprocaine. Unlike Baudouin and Gastaud, we also measured IOP at two time points with a second anesthetic (0.5% proparacaine hydrochloride) and found no significant difference between the IOP reduction after two minutes and that after five minutes, confirming their observation that the IOP stabilizes in the first minute following the instillation of a topical anesthetic.

The results from the current study can not be explained by a transient increase in corneal thickness as such an increase should lead to an overestimation of IOP not an underestimation. A possible explanation could be the destabilization of the tear film which is known to be caused by the preservatives in topical anesthetics (Cho and Brown 1995; Blades et al 1999). This destabilization could minimally alter the biomechanical properties of the precorneal tear layer leading to a decrease in IOP. The biomechanical properties of the cornea seem to have at least as profound an effect on IOP as the corneal thickness (Pepose et al 2007; Shah et al 2007). This may also be true of the precorneal tear film though to a lesser extent.

In our study we found that the majority of the subjects showed small IOP changes. However the results of a lot of studies in the literature, which compared newer non-contact IOP measurement techniques with the gold standard Goldmann applanation tonometry, showed that the non-contact tonometers return IOP values which are 2 to 4 mmHg higher than those returned by the Goldmann tonometer. Our results suggest that topical anesthesia may account for a part of this reduction. The results also raise the question of just how much the repeated applanation of the cornea with the Goldmann tonometer contributes to the lowered IOP measured with the Goldmann tonometer compared with the non-contact tonometer.

In conclusion, we found a small but statistically significant reduction of IOP with topical anesthesia in normotensive subjects. The IOP reduction varied with the anesthetic used but the effect was stable within the first two minutes after eyedrop instillation. These results have implications for studies in which contact tonometry is compared with non-contact tonometry because the error introduced by topical anesthesia is likely to bias for higher IOP values with non-contact tonometers.

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