

Prior Topical Anesthesia Reduces Time to Full Cycloplegia in Chinese

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Purpose: To investigate the effect of prior anesthesia on the time to full cycloplegia in young Chinese subjects.

Methods: The amplitude of accommodation was monitored over a 50-minute interval after the application of 1% cyclopentolate hydrochloride with a pretreatment of 0.4% benoxinate (oxybuprocaine) or 0.9% saline solution (control). Using a nonlinear mathematical model, the rate of accommodative loss (k) and the time required for 95% of total cycloplegia ($T_{95\%}$) were determined.

Results: Statistical analysis revealed a significantly faster rate of accommodative loss ($P < .0001$) after prior anesthesia (0.129 ± 0.05) compared with the controls (0.103 ± 0.04). $T_{95\%}$ was noted at 26.43 ± 10.22 minutes after prior anesthesia, which was significantly shorter ($P < .0001$) than that after the saline treatment (35.28 ± 16.51 minutes).

Conclusions: Prior application of topical anesthetic can shorten the time to full cycloplegia for people, such as the Chinese, with dark irides. **Jpn J Ophthalmol 1999;43:466–471**
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Key Words: Chinese, cyclopentolate, cycloplegia, local anesthesia.

Introduction

Accommodation is known to confound the types of refractive anomalies, such as latent hyperopia¹ and pseudomyopia.^{2,3} Whenever accommodation is suspected to play a role in causing visual problems, a cycloplegic refraction is mandatory.⁴

Cycloplegia is normally accomplished by topical administration of a diagnostic ophthalmic agent that paralyzes the ciliary muscle. The most commonly used agents are 0.5% and 1% cyclopentolate, and 1% tropicamide.⁵ Comparing the efficacy of these diagnostic agents for cycloplegic refraction, 1% cyclopentolate led to a lower amount of residual accommodation than 1% tropicamide.^{6,7} However,

these authors claimed that the differences were not clinically significant.

Cyclopentolate hydrochloride is a muscarinic antagonist that paralyzes the actions of the ciliary muscle.⁸ The drug is administered to the eye as a topical ophthalmic agent and it penetrates to the receptor sites through the cornea. When it is absorbed by the eye, it binds to the postganglionic muscarinic receptors of the parasympathetic nervous system. After this, the action of ciliary muscles is reversibly inhibited by the competitive binding of the drug to the muscarinic receptors. A latent period (the time between drug application and full cycloplegia) exists, and the inhibitory effect is commensurate with the availability of the drug.⁹ The latency is important information for clinicians, as it defines the time when measurement can begin. The accuracy of cycloplegic refraction is affected by the time of measurement. It is of utmost importance to understand the time course of cycloplegia to ensure a valid finding.

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Topical anesthesia is sometimes used together with cyclopentolate, either to alleviate the unpleasant drug sensation of cyclopentolate¹⁰ or to shorten the waiting time before the measurement is conducted.¹¹ It is believed that topical anesthesia shortens the time¹² to maximum cycloplegia. While prior anesthesia has been widely practiced before cycloplegic refraction,^{11,12} its effect on cycloplegia has not been documented.

Cycloplegic refraction is normally conducted when the amplitude of accommodation has ceased to decrease or when a full-sized pupil is observed.¹³ When the second criterion is adopted, practitioners should be aware that a full-sized pupil does not necessarily warrant complete cycloplegia.^{14,15} If refraction is conducted on patients with active accommodation before cycloplegia is completed, the accuracy of the refraction might be questioned.

It has been reported that the time required to achieve full cycloplegia was longer in subjects with deeply pigmented irides.^{16,17} Lovasik¹⁶ compared the accommodative loss in subjects with light-blue and brown irides under cycloplegia. The results showed that the brown irides group lost accommodation slower than the blue irides group. Chan and Edwards¹⁷ showed that people with heavily pigmented irides required more time to achieve full cycloplegia. In the literature, the recommended waiting time varies considerably between 20 and 45 minutes.^{5,18} Whereas these data describe the clinical performance in Caucasians, these studies^{16,17} also indicated a possible difference in cycloplegic performance among ethnic groups.

How long should the wait be before the measurements are made for the Chinese? To what extent does prior anesthesia affect the performance of cycloplegic refraction? The answers to these questions remain unclear. More information is required to understand the effects of prior anesthesia on cycloplegia.

The purpose of this study was to investigate the pharmacological response of the accommodative system to cycloplegics in a Chinese population when a prior topical anesthetic is administered. Our aim was to determine the minimum waiting time for cycloplegic refraction, with and without prior anesthesia of the cornea. The rate of accommodative loss, with and without a prior local anesthesia, was also compared.

Materials and Methods

Twenty-eight subjects were invited to participate in this study. They were all Chinese with dark brown

irides and were recruited from the student community of the Hong Kong Polytechnic University; and their ages varied between 19 and 25 (mean = 21.14, SD = 1.98) years. Their spectacle refractions, with a back vertex distance of 12 mm, were determined before the commencement of the experiment. Subjects with high refractive errors (greater than -6.00 DS or -1.50 DC), and those having manifest ocular and vergence-accommodation abnormalities were excluded from this study. All subjects had a corrected distant visual acuity of 6/6 or better. Human ethics approval was granted by the University, and signed informed consent was obtained from each subject before the study.

Distant refraction was measured by the standard subjective technique. The end-points were obtained by adjusting the spherical lens powers until the neutral point in the duochrome test was attained. After the refraction, fully corrected trial lenses were carefully fitted before the left eye (right eye occluded), with a pinhole aperture of 3 mm in diameter in front of the pupil. The artificial pupil controlled the retinal illuminance and depth of focus throughout the experiment. The back vertex distance of the trial frame was maintained at 12 mm throughout the measurements.

The amplitude of accommodation was measured by the subjective push-up method. A white card with a line of letters (equivalent acuity of 6/9 at 40 cm) was used. The card was mounted vertically on a movable rail-track alongside a measuring rule. It was illuminated continuously by two fluorescent lamps (6V DC) fixed to the top and bottom of the card. The average luminance of the card was maintained at 120 candela (cd)/m². The subject was properly restrained by a headrest facing the reading card. Baseline amplitude of accommodation was determined by the method of limits. The average distance (m) from the "clear-to-blur" and "blur-to-clear" was taken as the near point of accommodation. The determination was repeated three times and the mean value recorded. The amplitude of accommodation in diopters (D) was determined by the numeric reciprocal of the near point (1/m).

After the baseline measurement, one drop (15 μ L) of either 0.9% saline (control) or 0.4% benoxinate (oxybuprocaine; Dr. Thilo and Company, Freiburg, Germany) solution was instilled into the left eye followed by another drop (15 μ L) of 1% cyclopentolate hydrochloride solution (Dr. Thilo and Company), with an interval of 1 minute. The solution was measured and dispensed by a micropipette (Biohit Proline, Helsinki, Finland) fitted with disposable tips. The instillation of saline or benoxinate was

randomized and the subject was not informed of which solution was applied. The subjects were told that the applied solution may cause a slightly unpleasant feeling. Subsequently, the amplitude of accommodation was measured three times and the average value recorded at 2.5-minute intervals for the following 50 minutes.

The subject returned to the laboratory at least 4 days after the first session. The baseline amplitude of accommodation was determined and compared with that recorded on the first visit. Saline solution was instilled if the subject had been given a drop of benoxinate solution in the initial visit, or vice versa. The measurement of the amplitude of accommodation was repeated as described.

Results

Baseline Amplitude of Accommodation

The baseline amplitudes of accommodation measured on the first and second visits were compared. The mean baseline amplitude of accommodation was 10.89 ± 1.47 D (mean \pm 1 SD) and 10.93 ± 1.53 D for the first and second visit, respectively. The slightly higher mean amplitude of accommodation on the second visit was not significant (paired *t*-test, $P = .78$).

Effects of Local Anesthetics on Cycloplegia

After the drug administration, the accommodation clearly decreased with time and the results are represented in Figure 1. The diagram depicts the time course of the reduction in amplitude of accommodation over 50 minutes at 2.5-minute intervals. The results showed that accommodation declined dramatically in the initial 10–15 minutes and then continued to decrease slowly until it reached a relatively constant value. Statistical analysis revealed a significant reduction in accommodation with time after the application of cyclopentolate hydrochloride (analysis of variance [ANOVA]; $df = 20$, $P = .0001$).

The amplitude of accommodation was found to be significantly lower when the subjects had received the local anesthetic (ANOVA; $df = 1$, $P = 0.0001$). The results also showed that the amplitude of accommodation stopped decreasing significantly from 27.5 minutes onward (Tukey test, $P > .05$). The data indicated that the accommodative loss might be different over the time course in the presence of local anesthetics, although both treatments resulted in the same amount of residual accommodation eventually. However, statistical analysis failed to identify a significant interaction effect (ANOVA; $df = 20$, $P = .742$) between time and types of solution instilled (benoxinate and saline).

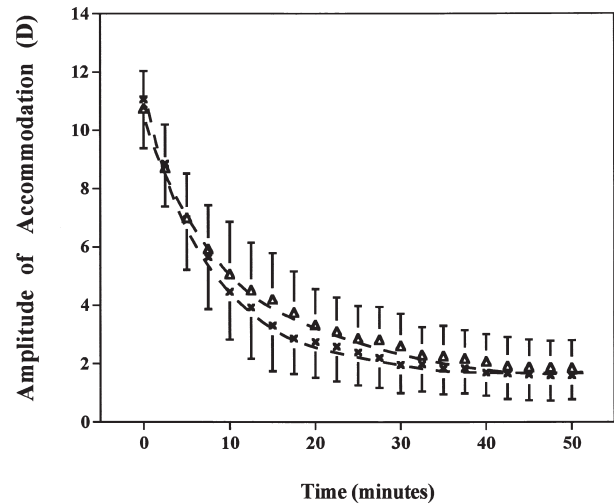


Figure 1. Reduction in amplitude of accommodation after instillation of 1% cyclopentolate hydrochloride, with prior application of 0.4% benoxinate (x) or 0.9% saline (Δ) in Chinese eyes. Mean \pm SD are plotted ($n = 28$).

Rates of Accommodative Loss

To quantify the effect of local anesthetics on cycloplegia, the individual rate of accommodative loss, with and without the instillation of benoxinate, was calculated. The amplitudes of accommodation were analyzed using the following nonlinear exponential mathematical model (Eq. 1):

$$\text{Acc}(t) = \frac{\text{Acc}(b) \cdot \exp(-k \cdot t) + \text{Acc}(r)}{1 + \exp(-k \cdot t)} + \text{errors}, t \geq 0, k \geq 0 \quad (1)$$

In Eq. 1, $\text{Acc}(t)$ is the amplitude of accommodation at time t (minutes) after the instillation of cyclopentolate hydrochloride, $\text{Acc}(b)$ and $\text{Acc}(r)$ are the baseline and residual amplitude of accommodation, respectively. The rate of accommodative loss is represented by the exponential constant, k . A higher k value denotes a faster rate of declination.

After prior anesthesia, the mean k value was 0.129 ± 0.05 (± 1 SD), whereas the mean k value for the control was 0.103 ± 0.04 (± 1 SD). Figure 2 depicts the mean k values, and statistical analysis revealed that the rate of accommodative loss was significantly faster after the subjects received a prior treatment of benoxinate solution (paired *t*-test; $df = 27$, $P = .0001$).

Time Required for 95% of Total Cycloplegia

To interpret the results clinically, the k values can be converted to represent the time required to reach 95% of total accommodative loss ($T_{95\%}$). Statistically, $T_{95\%}$ can be considered as the minimum time required to achieve complete cycloplegia with a 5%

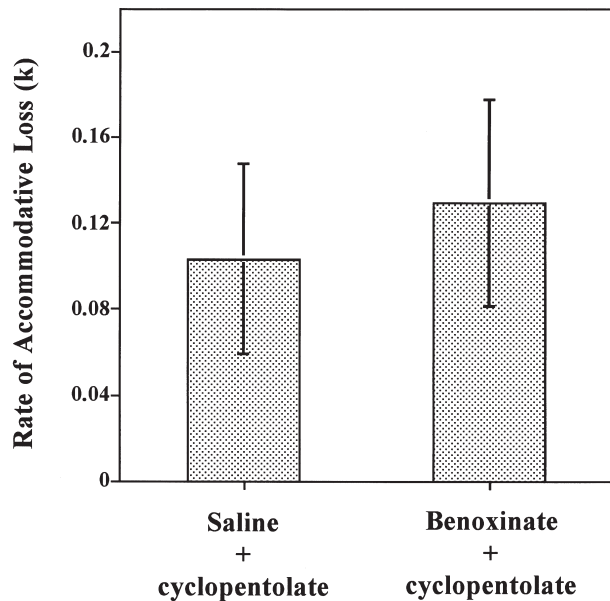


Figure 2. Rate of accommodative loss induced by cyclopentolate hydrochloride, with and without prior instillation of benoxinate solution. Rate (k) was calculated by fitting individual data to exponential model. Diagram shows sample means \pm 1 SD ($n = 28$).

probability of uncertainty. It was computed by the following conversion formula (Eq. 2):

$$T_{95\%} = [\ln(0.05)]/k \quad (2)$$

Figure 3 shows the mean $T_{95\%}$ values obtained after the two treatments. Without the application of benoxinate, $T_{95\%}$ was found to be 35.28 ± 16.51 minutes (mean \pm 1 SD) after the application of 1% cyclopentolate hydrochloride. The time, however, was reduced to 26.43 ± 10.22 minutes (mean \pm 1 SD) with 0.4% benoxinate. These results showed that prior anesthesia reduced the time required to achieve 95% of total cycloplegia by an average of 8.85 minutes, and the difference was statistically significant (paired t -test; $df = 27$, $P < .0001$).

Discussion

Our data showed that the mean baseline amplitude of accommodation was 10.90 D in this young Chinese population. Edwards et al¹⁹ reported a lower but comparable value of 10.64 D for a similar age group. The slight difference could be attributed to the different experimental procedures: our mean chart luminance was set at 120 cd/m^2 and their luminance was between 50 and 120 cd/m^2 . It is well known that a higher luminance level would enhance the visual performance,²⁰⁻²² which might lead to a

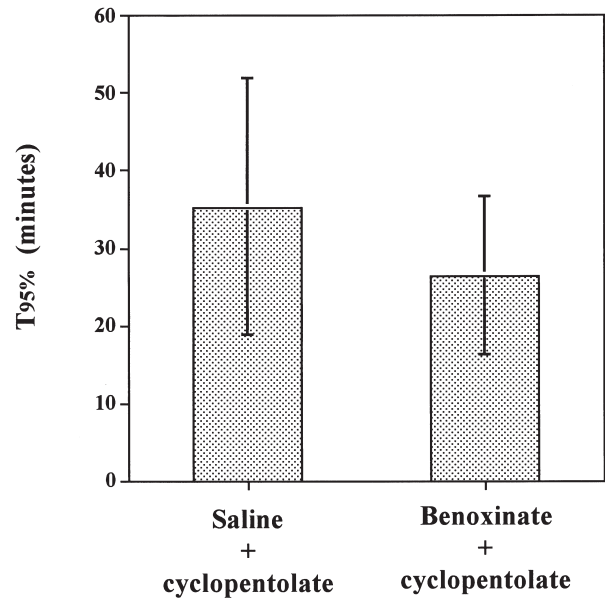


Figure 3. Time required for 95% reduction from baseline amplitude of accommodation. Diagram shows sample means \pm 1 SD ($n = 28$).

higher amplitude of accommodation as measured by the subjective push-up method. It should also be noted that the difference might be due to inter-subject variability.

Zetterstrom²³ studied the pharmacological effect of cyclopentolate and reported that maximum cycloplegia was achieved 40 minutes after drug instillation. The effect was then maintained for the following 6 hours. Manny et al¹⁵ monitored the time course of cycloplegia in patients with light and dark irides. They found that 1% cyclopentolate solution was less effective in persons with dark irides than in those with light irides. Maximum cycloplegia was detected at 10 minutes or at 30–40 minutes after drug instillation for individuals with light or dark irides, respectively. In our Chinese sample, $T_{95\%}$ was recorded at 35.28 minutes for the controls; this result agreed with these previous findings.

In an attempt to determine the effect of proparacaine on tropicamide-induced mydriasis, Siderov and coworkers²⁴ found no significant difference in either the rate of pupillary dilation or the time required to attain peak mydriasis for subjects with dark-colored irides with prior anesthesia. However, Mordi et al²⁵ reported that prior anesthesia significantly prolonged the mydriatic and the cycloplegic effects of tropicamide by 3 or 4 minutes. Similarly, the present study also showed that prior anesthesia reduces the time required to achieve complete cyclo-

plegia. The apparent discrepancy suggests that a topical anesthetic agent may play different pharmacokinetic roles in the processes of cycloplegia and mydriasis.

Under our experimental conditions, a prior instillation of local anesthetics clearly decreased the mean $T_{95\%}$ by 8.85 minutes (from 35.28 minutes to 26.43 minutes). When the amplitude of accommodation was compared between treatment with saline and local anesthetic, the latter resulted in a weaker amplitude of accommodation by 0.50 D at 26.43 minutes. It then follows that potential measurement errors could be associated with cycloplegic refraction if it is conducted without a prior instillation of local anesthetics and when complete cycloplegia has not been achieved. The small difference, however, is not clinically significant.

The mechanism of such a reduction is not fully understood, but it had been suggested that topical anesthetics reduced basal tear production²⁶ and increased corneal permeability to water.²⁷ Because of the increase in corneal permeability and a reduction in pre-corneal tear turnover rate, the availability of cyclopentolate to the eye might be increased. This would shorten the time of drug penetration and thus result in a faster action. However, the question of whether the local anesthetic interacts with cyclopentolate at the receptor sites requires further investigation.

The instillation of a local anesthetic is useful in preventing the unpleasant feeling associated with the cyclopentolate solution.¹⁰ The effective time of local anesthetics normally lasts 20–30 minutes before the cornea begins to regain its normal sensitivity. During this time, there is a risk of acquiring corneal abrasions should any foreign bodies remain on the desensitized cornea. Given that the refraction is not completed for at least 10 minutes, the cornea should have recovered partially from total anesthesia after the procedures (if it is conducted 30 minutes after drug instillation). Although our study did not address the issue of recovery in accommodation, the relatively low risk of ocular side effects from local anesthetics used in ophthalmic dosage²⁸ supports the proposition that prior anesthesia might be considered before cycloplegic refraction, especially for people with dark irides. In such cases, the patients should receive a careful corneal assessment and be advised not to rub their eyes in the following hour before being discharged by the doctor.

Cycloplegic refraction is a useful clinical technique for infants, children, and patients with suspected accommodative anomalies. We compared the efficacy of cycloplegia with and without a prior instillation of

local anesthetics. The results showed that prior anesthesia significantly reduced the mean $T_{95\%}$ to 26.43 minutes in the eyes of young Chinese subjects. At $T_{95\%}$, the amplitude of accommodation was still 0.50 D higher when the subjects did not receive prior anesthesia.

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