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A Comparison of Two Drug Combinations for Dilating Dark Irides

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Abstract

Purpose—Two combinations of dilation drops (1% Tropicamide & 2.5% Phenylephrine [TP] versus 1% Tropicamide & 1% Cyclopentolate [TC]) were compared to determine time course and magnitude of dilation for patients with dark irides.

Methods—45 subjects, 4–32 years of age, with dark irides were enrolled. Photographs were taken prior to dilation and at 5, 10, 15, 20, 40, & 60 minutes after instillation of drops. Subjects received TP in one eye and TC in the fellow eye with eyes randomized to the combination received. An examiner masked to drug combination and time used digital analysis to calculate pupil diameter for each photograph. TP and TC were compared to determine the time to reach both 6 and 7 mm pupil diameter, and the percentage of subjects reaching these diameters.

Results—98% of pupils reached 6 mm with either combination; however, 80% reached 7 mm with TP and only 58% with TC ($p = 0.0062$ McNemars Exact Test). Time at which 50% of pupils reached 6 mm was not significantly different between drug combinations (TP 11 min vs. TC 12 min, Kaplan-Meier survival analysis). However, time at which 50% reached 7 mm was statistically and clinically significant (TP 32 min vs. TC 52 min, $p = 0.0325$). For subjects ≤ 10 years versus > 10 years, there was no significant difference in time at which 50% reached a 6 mm or 7 mm pupil with TP or TC; however, in every case the younger group took longer.

Conclusions—A 6 mm pupil dilation may be obtained with either TP or TC; however, more subjects achieved a 7 mm pupil with TP than TC and had a faster time course to attain that size.

Keywords

pupil dilation; phenylephrine; tropicamide; cyclopentolate; dark iris

Sympathomimetic and anticholinergic drops are commonly used for performing pupil dilation in the clinical setting. Numerous studies have investigated the time course and maximal effect of dilation for different drugs in these categories in an attempt to determine which drugs provide a quick, adequate dilation with the least potential for adverse side effects in patients.^{1–11} In individuals with light irides, these drugs typically perform well with relatively short time courses of dilation; however, in individuals with dark irides the results differ between drugs with some yielding inadequate or slower dilation.^{3–5,8} One study in particular reported that a small sample of subjects with dark irides achieved greater magnitude dilation when a combination of drugs with two different mechanisms of action was used (ephedrine combined

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with homatropine) rather than one drug alone.⁴ In addition to differences in iris color, studies have also suggested that age may play a role in the speed and magnitude of dilation achieved with younger subjects demonstrating faster and greater magnitude dilations.^{2,11}

This study aims to compare two commonly used combinations of dilation drops, Tropicamide 1% (anticholinergic) and 1% Cyclopentolate (anticholinergic)¹² versus Tropicamide 1% (anticholinergic) and 2.5% Phenylephrine (sympathomimetic)¹², in subjects with dark irides to identify the combination which provides the shortest time course and greatest magnitude dilation for improving exam efficiency in patients with dark irides. These specific drug combinations are commonly used clinically, but have yet to be compared directly for dilating patients with dark irides. In addition, subject age will be compared to identify any potential relationship between age, time course, and magnitude of dilation.

METHODS

This study followed the tenets of the Declaration of Helsinki and was approved by the University of Houston Committee for the Protection of Human Subjects. Informed consent was obtained from all adult participants and parental consent and child assent obtained for all participants <18 years of age.

Forty-five subjects 4 to 32 years of age were recruited from the clinic at the University of Houston College of Optometry for participation in the study. Subjects varied in ethnicity, although the majority were Hispanic (53.3%), followed by African American (28.9%), Asian (11.1%), and Caucasian (6.7%).

As a recruitment criterion, all subjects had dark irises of grade 4 or 5 (brown or dark brown) as determined by comparison with standardized iris photographs from Seddon, et al. (1990).¹³ To grade the iris color, two examiners independently assessed the subject's iris through a slit lamp at low illumination and graded the color on a scale of 1 to 5, matching to photographs from Seddon, et al.¹³ If the two examiners did not agree on the iris color, a third examiner graded the iris and the color was documented as the grade level for which two of the three examiners agreed.

Two common clinical combinations of drugs were compared in this study: one drop each of 1% tropicamide and 2.5% phenylephrine (TP) versus one drop each of 1% tropicamide and 1% cyclopentolate (TC). Each subject received both combinations of drugs, TP in one eye and TC in the fellow eye, with the eyes randomized to the drug combination received. The drops were instilled by one of the two study investigators who were not involved in data collection or analysis. All subsequent study measurements were conducted by an examiner who was masked as to which eye received each drug combination. Prior to the instillation of any dilation drops, von Herrick angle measurements were performed with a slit lamp to ensure subjects did not have narrow angles which would contraindicate dilation, and one drop of 0.5% proparacaine anesthetic was instilled in each eye.

To measure pupil size, photographs of the subject's eyes were taken with the Tomey ViVA (Fortune Optical), an infrared photorefractor that was commercially available at the time the study was conducted. Photographs were taken at baseline and at 5, 10, 15, 20, 40, & 60 minutes following drug instillation (Figure 1) while the patient held a "visor" between their forehead and the ViVA to shield light from above and standardize the test distance for the photographs. Immediately following each photograph, pupil response was graded on a scale of 0 to 3 (0 = no response, 3 = maximum response) for each eye using a binocular indirect ophthalmoscope (BIO) set to maximum intensity while the subject sat in a dark room.

After completion of the measurements, the digital photographs were divided into right and left eyes and analyzed with Scion Image software (Scion Corporation) to determine pupil diameter (Figure 1). The examiner performing the analysis was masked to both the drug combination instilled in each eye, as well as the time of the photograph. Prior to analysis of the photographs, the image software was calibrated for the photograph test distance and pixel size equated to a metric scale. The examiner outlined the entire edge of the pupil, whether spherical or elliptical, and the Scion software calculated the pixel area over the entire pupil. Regardless of pupil shape, the pupil diameter was then calculated from the total measured area as if it were from a spherical pupil. Five independent estimates of pupil diameter were made for each photograph and the average pupil diameter and standard deviation obtained.

RESULTS

Time to Reach a 6 Versus 7mm Pupil Size

Data were analyzed with regards to two different dilated pupil diameters (6 mm and 7 mm) to allow for equal outcome comparisons between the two drug combinations. These two diameters were chosen for comparison as 6mm has previously been reported as an adequate diameter for eye examination;¹⁴ however, a pupil diameter of 7 mm would permit a more thorough examination of the fundus.¹⁵ Kaplan-Meier survival analysis was used to compare the median time to reach either a 6 mm or 7 mm pupil diameter using the two different drug combinations (Figure 2). This analysis plots a continuous function using data from the time intervals sampled in the study and identifies the predicted median time for 50% of the subject's eyes in the study to reach a given pupil diameter. Median time for 50% of subject's eyes to reach a pupil diameter of 6 mm was 12 min with TP and 13 min with TC. These times were not significantly different (log rank test, $p = 0.62$). Median time for 50% of eyes to reach a pupil diameter of 7 mm was 32 min with TP and 52 min with TC. This difference was statistically significant (log rank test, $p = 0.0325$), indicating that the time to reach a 7 mm dilation with TC is significantly longer than that with TP.

Number of Subjects Reaching a 6 Versus 7mm Pupil Diameter

Histogram analysis was then used to identify the total number of pupils reaching a 6 and 7 mm diameter with each drug combination irrespective of the time course (Figure 3). Both drug combinations successfully increased pupil diameter to 6 mm in 98% of subjects. Differences were observed for the percentage of subjects reaching a 7 mm pupil diameter; however, with TP resulting in 80% and TC only 58% of subjects with a 7 mm pupil diameter. This difference was statistically significantly different (McNemar's Exact Test, $p = 0.0062$), as well as clinically significant, indicating that TP produces a 7 mm pupil in a greater percentage of subjects with dark irides.

Age Effects

Subjects were binned into two age groups based upon the median age split of the sample: 4 to 10 years ($n = 24$ [53.3%]) and 11 to 32 years ($n = 21$ [46.7%]) to determine if age was a factor in the time it took for 50% of eyes to reach a 6 mm or 7 mm pupil diameter (Table 1). No significant age difference in the time to reach a 6 or 7 mm pupil was observed for either drug combination; however, the younger age group did take longer to reach the target pupil diameter in all cases. It should also be noted that for the TC drug combination, only 11 of 24 subjects aged 10 years and younger reached a 7 mm pupil by 60 minutes.

Pupil Reactivity

Pupil reactivity was graded on a scale of 0 to 3 at the same time intervals at which pupil diameter was judged. For the TP drug combination, pupil reactivity was eliminated in more than 90%

of subjects by 20 minutes after drug instillation. The TC drug combination was slower to eliminate pupil reactivity with more than 20% of subjects still demonstrating some level of pupil reactivity by 20 minutes after drug instillation. For TC, pupil reactivity was eliminated in more than 90% of subjects by 40 minutes after drug instillation (Figure 4).

DISCUSSION

The results of this study suggest that adequate pupil dilation (6 mm) can be obtained in the majority of patients with dark irides using either the TP or the TC combination; however, if a 7 mm pupil is desired, a greater number of patients will attain this diameter with the TP combination. The time course to attain a 7 mm pupil diameter is also significantly faster when using the TP combination (32 versus 52 min). These findings support the hypothesis that using a combination of drops with two different mechanisms (sympathomimetic plus anticholinergic) results in greater dilation in patients with dark irides.⁴

Previous studies have suggested a variety of mechanisms to explain reduced effectiveness of dilation drops in persons with dark irides. These explanations include a more powerful reflex miosis in persons with dark irides⁴ and a smaller baseline pupil prior to dilation.¹ However, a more recent study of the influence of iris color on the pupillary light reflex found that baseline pupil size was the same between blue and brown eyed subjects, but that pupil contraction was in fact significantly greater in both velocity and magnitude in brown versus blue eyes.¹⁶ In light of these findings, the previous study hypothesized that brown irides may have a different number or sensitivity of adrenergic receptors compared to blue irides, making them less susceptible to the mydriatic effects of sympathomimetic drugs when administered in isolation.

In addition to differences between magnitude and time course of dilation for TP versus TC, this study also found a difference in time to eliminate pupil reactivity to light after administration of drug combinations. TP eliminated pupil reactivity in 90% of subjects by 20 minutes whereas TC took 40 minutes. However, this difference in time course to eliminate pupil reactivity may be exaggerated due to the sampling intervals of the measurements. Pupil reactivity was tested every 5 minutes up to the 20 minute measurement and then not again until the 40 minute measurement. Thus, it is unknown at what point during that 20 minute interval that pupil reactivity was eliminated with TC. However, it should be noted that the time to eliminate pupil reactivity was less than that to reach a 7mm diameter pupil for both drug combinations, indicating that pupil diameter may continue to increase after pupil reactivity is eliminated.

The protocol used in this study included the instillation of one drop of 0.5% proparacaine anesthetic in each eye prior to adding the dilation drops. Previous studies have demonstrated greater magnitude and shorter time course dilation in eyes in which anesthetic was used prior to the instillation of phenylephrine.^{7,17} The same effects have not been seen when combining proparacaine and tropicamide, except perhaps to a small degree in light eyed subjects.^{18,19} The authors are currently unaware of any studies comparing the effect of proparacaine on the magnitude and time course of dilation with cyclopentolate. Given the previous findings of an enhanced dilation effect for phenylephrine when combined with proparacaine, it is possible that the findings of this study may have differed if proparacaine were not instilled prior to the two different combinations of dilating drugs (TC & TP).

One limitation to the present study is that each subject received both combinations of drugs (one set in each eye) which may have allowed for some interocular effects if the drugs were to cross to the fellow eye. As the TP combination had the greatest and fastest course of dilation, one might argue that cyclopentolate may have crossed to the fellow eye, increasing the effectiveness of the TP drug combination. However, a previous study in rabbits has shown

interocular effects of cyclopentolate are only present when the drug is administered systematically, and that no effects on pupil diameter were observed in the fellow eye with monocular topical administration,²⁰ and thus the authors do not feel that the observed differences in the present study were due to drug transfer to the fellow eye.

The present study did not find any significant differences in magnitude or time course of dilation related to subject age. This information is useful for the examination of older patients in whom practitioners may not require or desire full cycloplegia. For younger patients in whom practitioners may desire full cycloplegia, the findings of this study suggest that TC results in adequate pupil dilation (6 mm in the majority of patients) and may reach 7 mm if given adequate time.

CONCLUSIONS

Both 1% tropicamide combined with 2.5% phenylephrine and 1% tropicamide combined with 1% cyclopentolate produced a 6 mm pupil diameter in 98% of subjects with dark irides. However, the combination of tropicamide and phenylephrine was capable of producing a 7 mm pupil in a greater percentage of subjects (80% vs. 58%) and with a shorter time course (32 vs. 52 min.). These results suggest that using a combination of dilation drugs with two different mechanisms produces a greater pupil diameter with a faster time course in subjects with dark irides.

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Figure 1.
Infrared photograph taken with the ViVA-Tomey at 40 minutes following drug installation.
White ring indicates the area used to calculate the pupil diameter.

Figure 2. Kaplan-Meier survival analysis showing the percent of subjects to reach a 6 mm (A) or 7 mm (B) pupil for TP and TC.

Figure 3.
Maximum pupil diameter obtained with TP (A) versus TC (B)

Figure 4.
Time course of change in pupil reactivity for TP (A) versus TC (B)

Table 1
Median time for 50% of eyes to reach a 6 or 7 mm pupil for either drug combination.

TP			TC		
Pupil Diameter	Age (yrs)	Median Time (min)	p – value	Median Time (min)	p – value
6 mm	≤ 10	13	0.1407	14	0.9023
	> 10	10		13	
7 mm	≤ 10	37 ⁺	0.3431	60 [*]	0.0780
	> 10	29		34	

* Only 11 of 24 subjects ≤ 10 years of age reached a 7 mm pupil by 60 minutes with TC

⁺ 19 out of 24 subjects ≤ 10 years of age reached a 7 mm pupil by 60 minutes with TP