Tropicamide has limited clinical effect on cycloplegia and mydriasis when combined with cyclopentolate and phenylephrine

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PURPOSE To examine the cycloplegic and mydriatic effect of tropicamide omission from a common pediatric eye drop combination.

METHODS Consecutive children examined at the Ann & Robert H. Lurie Children's Hospital of Chicago from June 8, 2017 to September 6, 2017 were enrolled prospectively. Tropicamide, cyclopentolate, and phenylephrine (TCP) was instilled in one eye; cyclopentolate and phenylephrine (CP), in the other. Spherical equivalent, maximum pupil size, and pupillary constriction in response to photostimulation were measured before and 30 minutes after instillation using an autorefractor and pupillometer. Iris pigmentation was examined as a between-subjects variable.

RESULTS A total of 75 children 4-11 years of age were included. Mean differences in spherical equivalent between TCP and CP were not statistically significant ($P = 0.95$). Significant interactions between eye drop regimen and iris pigmentation were observed for pupil size ($P = 0.001$) and constriction percentage ($P = 0.02$). Among only patients with dark irides, TCP yielded slightly larger pupils (7.70 vs 7.31 mm [$P < 0.001$]) that were less responsive to light (5.75% vs 8.07% [$P = 0.002$]). All pupils dilated to ≥6.0 mm, with equivalent proportions achieving ≥7.0 mm for TCP and CP ($P = 0.18$).

CONCLUSIONS TCP and CP elicited equivalent cycloplegic effects. Mydriatic differences between the regimens, although statistically significant in dark irides, were of limited clinical magnitude, and all pupils achieved sufficient dilation for funduscopy. (J AAPOS 2019;23:30.e1–5)

Cycloplegic refraction is an essential component of the pediatric eye examination. Practitioners routinely rely on cycloplegic agents when performing funduscopy, assessing refractive error under conditions of reduced accommodation, and diagnosing and treating disease. An ideal cycloplegic agent possesses rapid onset, maximal effect, brief accommodative recovery, and the absence of ocular and systemic side effects.[1] Atropine, the gold standard, is poorly tolerated and has been associated with severe adverse effects, including prolonged blurry vision, tachycardia, delirium, and convulsions.[2,3] It has largely been replaced by less potent, short-acting parasympatholytic agents.[4] In particular, cyclopentolate has been shown to be a reliable alternative, with faster onset and shorter duration of action, fewer complications, and nearly equivalent cycloplegic effect.[2,5,6] There have been reports, however, of central nervous system reactions (eg, hallucinations, seizures, ataxia), making the drug contraindicated in children with epilepsy and other neurologic disorders.[7,8] In contrast, tropicamide possesses negligible systemic toxicity[9] and the fastest onset of action and recovery,[6] but it elicits inferior, and potentially inadequate, cycloplegia on its own, particularly in children with dark irides.[4,10,11]

Many clinicians have turned to combinations of cyclopentolate and tropicamide, often in synergy with phenylephrine, a sympathomimetic, for maximal mydriatic effect.[12-14] Still, there remains no consensus as to the optimal regimen for use in children.[10,15] According to a survey of 522 pediatric ophthalmologists, the most common mixture appears to be tropicamide-cyclopentolate-phenylephrine (TCP), followed by cyclopentolate-phenylephrine (CP).[16] While many continue to recommend TCP,[15,17] the added benefit of tropicamide remains dubious.[18,19] One study found no significant difference in accommodative amplitude or pupil diameter between a TCP solution and CP control, suggesting that any effect induced by tropicamide was negligible in comparison to that of cyclopentolate and phenylephrine.[20] It is important to note, however, that this

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study was conducted in adults and may, consequently, not be generalizable to children, who possess greater amplitudes of accommodation and require more potent cycloplegic agents.[2,14] Accordingly, we sought to examine the differences between TCP and CP in a pediatric population. We hypothesized that tropicamide would be superfluous in combination with cyclopentolate and phenylephrine and, thus, its omission would not significantly affect cycloplegia or mydriasis. Given that eye drops, in particular, tropicamide, are associated with painful burning and stinging,[21-23] use of a CP regimen would help to minimize ocular discomfort and make the administration of eye drops a less traumatic experience for patients. It would also make ophthalmic exams more facile for practitioners, reduce costs, and represent good practice in medical stewardship.

Subjects and Methods

This prospective within-subjects study was approved by the Institutional Review Board of Ann & Robert H. Lurie Children's Hospital of Chicago in accordance with the US Health Insurance Portability and Accountability Act of 1996 and Declaration of Helsinki. The sample consisted of children who presented consecutively to an ophthalmology clinic for routine examinations independent of the study between June 8, 2017, and September 6, 2017. All participants were return patients for whom past medical histories were known. Patients with cardiovascular, neurological, or anterior segment disease, as well as those with vision loss unrelated to refractive error (eg, blindness, enucleation, other significant ocular pathology), were excluded. Additionally, children with allergies to tropicamide, cyclopentolate, or phenylephrine were not permitted to participate. Written parental informed consent and verbal patient assent were obtained prior to enrollment.

Eye drops were administered by ophthalmic nurses and technicians as a part of routine examination. For each participant, one drop of 1% tropicamide, one drop of 1% cyclopentolate, and one drop of 2.5% phenylephrine (TCP) were instilled in one eye and only one drop of 1% cyclopentolate and one drop of 2.5% phenylephrine (CP) in the other. Drops were instilled individually and applied directly to the eye, not as a preexisting mixture. Participants were initially assigned TCP to their right eyes and CP to their left eyes. Midway through data collection, eye assignment was reversed to control for nurse dexterity and counterbalance any potential interocular confounds.

All ophthalmic measurements were recorded by the researchers. Iris color was categorized as either light (blue, green, grey, hazel) or dark (brown, dark brown). Sphere, cylinder, and axis were measured using a Topcon KR-8900 AutoRefractor Keratometer (Topcon Medical Systems Inc, Paramus, NJ). Three readings were taken for each eye, and mean values were used to calculate spherical equivalent (SE). A NeurOptics PLR-200 Pupillometer (NeurOptics Inc, Irvine, CA) was used to assess pupil size and reactivity. Maximum pupil diameter (MAX) was measured in a dark room, and minimum pupil diameter (MIN) was measured at the peak of constriction following photostimulation by the pupillometer. All measurements were taken twice: before and 30 minutes after eye drop instillation.

Cycloplegia was defined as the difference, in SE (D), between pre- and post–eye drop autorefraction measurements. Participants were also compared according to type of refractive error: myopia (SE $<$ 0.00 D), emmetropia (SE = 0.00 D), mild hyperopia (0.00 D $<$ SE $\leq$ +3.00 D), and high hyperopia (SE $>$ +3.00 D). MAX (mm) at 30 minutes was used to assess mydriasis. Similarly, the proportion of pupils achieving MAX $\geq$6.0 and $\geq$ 7.0 mm, previously established minimum and ideal cutoffs for funduscopic examination,[4] were calculated. Constriction percentage, defined as the percent change in pupil size induced by photostimulation ([MAX–MIN]/MAX), was calculated as an additional measure of mydriatic efficacy.

Data Analysis

All data were entered into REDCap (Vanderbilt University, Nashville, TN) and analyzed using SPSS version 23.0 (IBM Corp, Armonk, NY). A value of $\alpha = 0.05$ was used as the criterion for statistical significance. The t test and repeated measures analysis of variance were used to examine within-subjects differences in cycloplegia, MAX, and constriction percentage between TCP and CP. Iris color was also included as a between-subjects factor. In addition, the proportions of pupils achieving MAX $\geq$6.0 and $\geq$ 7.0 mm for each regimen were compared using the χ^2 or the Fisher exact test. Post hoc analyses, where warranted, were performed using Bonferroni correction.

Results

A total of 150 eyes of 75 children 4-11 years of age were included. Sample demographics and predilation measurements are displayed in Table 1. Participants ranged in age from 4.08 to 11.87 years (mean, 7.51 $\pm$ 2.09 [standard deviation]). There was a slight male predominance and a 1:1.88 ratio of light-to-dark irides. At baseline, there were no statistically significant differences between the TCP and CP groups for SE (t[68] = −0.48; P = 0.63), MAX (t[74] = 0.48; P = 0.63), or constriction percentage (t[74] = −0.59; P = 0.56).

Cycloplegia

Six participants were unable to complete the autorefraction task because of distraction and were excluded from analyses. Mean differences between pre- and post–eye drop SE measurements were not statistically significant for TCP compared to CP (F[1, 67] = 0.01; P = 0.95). See Table 2. In addition, there was no significant interaction between eye drop regimen and iris color on cycloplegia, (F[1, 67] = 1.22; P = 0.27). See Figure 1A. This trend was observed across all types of refractive error (myopia, emmetropia, mild hyperopia, and high hyperopia) (F[3, 67] = 0.81; P = 0.50). Iris color did not have a statistically significant between-subjects main effect on cycloplegia (F[1, 67] = 1.74; P = 0.19).

Table 1. Sample demographics and baseline (before dilation) measurements (N = 75)

Study parameter	Result
Age, years, mean ± SD	7.51 ± 2.09
Sex, no. (%)	
Male	41 (54.7)
Female	34 (45.3)
Eye Color, no. (%)	
Light	26 (34.7)
Dark	49 (65.3)
Refractive error, no. (%)	
Myopia (SE < 0.00 D)	25 (36.2)
Emmetropia (SE = 0.00 D)	3 (4.3)
Mild hyperopia (0.00 D < SE ≤ +3.00 D)	30 (43.5)
High hyperopia (SE > +3.00 D)	11 (16.0)
SE, D, mean ± SD	
TCP	−0.47 ± 3.18
CP	−0.23 ± 2.62
MAX, mm, mean ± SD	
TCP	6.00 ± 0.89
CP	5.93 ± 0.90
Constriction %, mean ± SD	
TCP	28.58 ± 7.31
CP	29.34 ± 7.91

D, diopter; *CP*, cyclopentolate and phenylephrine; *SD*, standard deviation; *SE*, spherical equivalent; *TCP*, tropicamide, cyclopentolate, and phenylephrine.

Mydriasis

All participants were compliant with pupillometry. All pupils dilated to ≥6.0 mm in both the TCP and CP groups (Table 2). Although a greater proportion of pupils achieved ≥7.0 mm dilation with TCP (66/75 = 88.0%) compared with CP (60/75 = 80.0%), this difference was not statistically significant ($\chi^2[1] = 1.78$; $P = 0.18$). Furthermore, among dark irides, TCP was not more effective at achieving ≥7.0 mm dilation ($\chi^2[1] = 2.78$; $P = 0.10$). Similarly, no significant difference was observed in light irides ($P > 0.99$).

On the other hand, there was a significant interaction between eye drop regimen and iris color on MAX ($F[1, 73] = 11.80$; $P = 0.001$). See Figure 1B. In dark irides, TCP resulted in pupils that were, on average, 0.39 mm larger than those administered CP; this difference was statistically significant ($t[48] = 4.93$; $P < 0.001$). In contrast, TCP and CP yielded statistically equivalent pupil diameters in light irides ($t[25] = -0.69$; $P = 0.50$). As expected, dark irides were associated with inherently smaller pupils at 30 minutes when compared to light irides, irrespective of eye drop regimen ($F[1, 73] = 19.25$; $P < 0.001$).

Constriction Percentage

There was a statistically significant interaction between eye drop regimen and iris color on constriction percentage at 30 minutes ($F[1, 73] = 6.06$; $P = 0.02$). See Figure 1C. In dark irides, TCP resulted in less pupillary constriction in response to light when compared to CP ($t[48] = -3.30$; $P = 0.002$), whereas in light irides, the regimens had equivalent efficacy ($t[25] = -0.43$; $P = 0.67$).

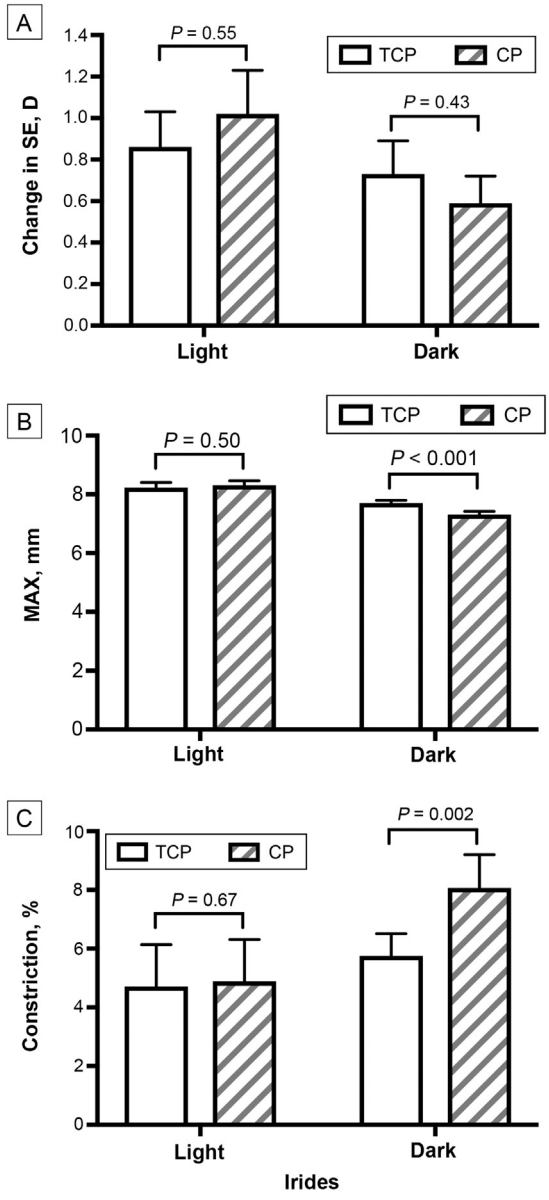

FIG 1. Tropicamide, cyclopentolate, and phenylephrine (TCP) versus cyclopentolate and phenylephrine (CP) in light and dark irides. A, Cycloplegia. B, Maximum pupil size at 30 minutes. C, Constriction percentage at 30 minutes.

Discussion

Balancing thoroughness of clinical examination with patient comfort is particularly challenging for children undergoing refraction with TCP, the most common combination.[16] Instillation of eye drops may be traumatic for some patients and may consequently limit cooperation with the examination. Moreover, in children who poorly tolerate eye drops, lacrimation can dilute or flush out the agents, reducing ocular penetration. For these reasons, we sought to examine whether tropicamide, the weakest and usually the most irritating of the agents, could be omitted from TCP while maintaining sufficient cycloplegia and mydriasis.

Table 2. TCP versus CP in light and dark irides at 30 minutes

Study parameter	Light irides		Dark irides	
	TCP	CP	TCP	CP
Change in SE, D, mean ± SD	+0.86 ± 0.86	+1.02 ± 1.05	+0.73 ± 1.15	+0.56 ± 0.94
≥6.0 mm, no. (%)	26/26 (100)	26/26 (100)	49/49 (100)	49/49 (100)
≥7.0 mm, no. (%)	25/26 (96.2)	26/26 (100)	41/49 (83.7)	34/49 (69.4)
MAX, mm, mean ± SD	8.23 ± 0.86	8.31 ± 0.91	7.70 ± 0.69[a]	7.31 ± 0.80[a]
Constriction %, mean ± SD	4.71 ± 7.27	4.89 ± 7.23	5.75 ± 5.29[b]	8.07 ± 7.89[b]

D, diopter; *CP*, cyclopentolate and phenylephrine; *MAX*, maximum pupil diameter; *MIN*, minimum pupil diameter; *SD*, standard deviation; *SE*, spherical equivalent; *TCP*, tropicamide, cyclopentolate, and phenylephrine.
[a]TCP vs CP; $P < 0.001$.
[b]TCP vs CP; $P < 0.01$.

Our results demonstrated no differences in spherical equivalent between TCP and CP, confirming that any additional cycloplegic effect exerted by tropicamide was trivial compared with that of cyclopentolate.[18] Further, this trend was observed among all types of refractive error, including high hyperopia in excess of +3.00 D. These findings are consistent with Zetterström,[19] who argued that the use of two different short-acting parasympatholytic drugs would be unnecessary, given that cyclopentolate and tropicamide block the action of acetylcholine at the same receptors. Recognizing cyclopentolate's well-documented efficacy as a cycloplegic on its own,[2,5] it is logical to expect any further influence from the less potent tropicamide to be negligible.

On the other hand, tropicamide did appear to have a discernable mydriatic effect when combined with cyclopentolate and phenylephrine. TCP resulted in pupils that were larger and less responsive to light compared with CP. The clinical implications of this effect, however, may be limited. First, it is important to note that all pupils successfully dilated to 6.0 mm, a well-established minimum diameter for funduscopic examination,[4] and both regimens achieved 7.0 mm, the ideal diameter, with proportional statistical equivalence. Furthermore, the added mydriatic effect of tropicamide was only observed in dark irides; thus, patients with blue, green, gray, or hazel eyes did not benefit from its inclusion. Research has demonstrated that patients with dark irides require higher doses of mydriatic agents because the increased pigmentation absorbs and reduces the efficacy of the drugs.[3,4,10] However, even in our subsample of patients with dark irides, all pupils dilated to 6.0 mm, with equivalent proportions achieving 7.0 mm. Lastly, the mean differences in MAX and constriction percentage between TCP and CP were only 0.39 mm and 2.32%, respectively. These differences, although statistically significant, typically cannot be ascertained by practitioners without the deliberate use of a pupillometer. Thus, the omission of tropicamide from TCP would not preclude the level of mydriasis needed for a complete ophthalmic examination.

Tropicamide omission would also have financial implications for eye care professionals. The present cost of TCP at our institution is $27.87 per patient, of which tropicamide comprises $8.04. Further, tropicamide is purchased in individual 15 mL bottles, and because of infection control and patient safety protocols, an entire bottle must be discarded after single use (less than 1 mL). Even at institutions that permit the reuse of tropicamide bottles, switching to a CP regimen would substantially reduce costs given the large volume of patients that undergo cycloplegic refraction as part of routine eye examinations.

We believe this study offers a compelling argument for the omission of tropicamide from TCP. Of particular strength, its within-subjects design enabled participants to serve as their own controls, allowing us to compare the two regimens without the influence of pharmacodynamic confounders that may exist between patients of various refractive errors, pupil reactivities, and iris shades. A limitation of this design, however, is the possibility of tropicamide exerting a contralateral effect on the eye receiving CP, which has been demonstrated in rats.[24] To our knowledge, this phenomenon has not been studied in the human literature; nonetheless, given the significantly weaker nature of tropicamide in comparison to cyclopentolate,[11] we would expect the magnitude of such a contralateral effect to be minimal.

Another limitation to this study is the fact that post–eye drop measurements were only taken at 30 minutes. Although ideally patients in clinic are seen as soon as cycloplegic refraction is complete, examinations involving irritable children and other setbacks may result in delays. It could be informative to compare the time courses of TCP and CP to see whether their onset and duration of actions differ. Doing so would provide clinical insight into the appropriate timing of the ophthalmic examination as well as practical implications for children seeking to resume activities that would otherwise be precluded by blurry vision.

Regarding the issue of patient discomfort during eye drop instillation, some have advocated for the use of proparacaine, a topical anesthetic not used in this study. Although it is associated with mild stinging, proparacaine is thought to improve patient compliance by reducing the pain elicited by subsequent drops.[23] It has even been shown to potentiate the mydriatic effects of tropicamide and

phenylephrine.[25] It is unclear, however, whether proparacaine's anesthetic properties would have any net effect on patient discomfort, which may be due to a multitude of factors in addition to pain, such as unfamiliarity with the instillation process, prior negative experiences, or blurry vision induced by cycloplegic refraction. Future research could examine the role of proparacaine as a potential mitigating agent in the instillation of TCP or CP.

Literature Search

PubMed was searched most recently on July 20, 2018, without date or language restriction, using the following terms: *cycloplegia* OR *cycloplegic*, *mydriasis* OR *mydriatic*, *pediatric*, *cyclopentolate*, and *tropicamide*.

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