• Clinical Research •

Different administration regimens of compound tropicamide eyedrops for pupil dilation for children with dark iris: a randomized clinical trial

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Abstract

• **AIM:** To compare the efficacy of different administration regimens of compound tropicamide eyedrops (CTE) for pupil dilation for children with dark iris.

• **METHODS:** A prospective, comparative, randomized interventional study was conducted. Children in Group 1 received CTE 3 times with a 3min interval between each application. Children in Group 2 received CTE 4 times with a 5min interval between each application. We measured their pupil diameters at baseline (pre-drug instillation) and 30min and 60min post-drug instillation and assessed the pupillary light reflex at 60min post-drug instillation.

• **RESULTS:** In total, 194 eyes of 101 children were enrolled. The changes of pupil diameter at 30min and 60min post-drug instillation were 1.2±0.6 mm and 2.3±1.0 mm in Group 1, and 2.3±0.9 mm and 3.7±1.0 mm in Group 2, respectively. Group 2 showed a larger change in pupil size than Group 1 at 30min (P<0.01) and 60min (P<0.01). The effect of pupil dilation in Group 2 was 1.25 times that in Group 1. The change in pupil size was positively associated with age. A higher proportion of children in Group 1 had smaller pupil diameter and reactive pupils at the final time point, with only 33 children (33.7%) had final pupil size ≥6.5 mm, and only 9 children (9.2%) had non-reactive pupils. Children in Group 2 achieved larger pupil diameter and more non-reactive pupils at the final time point, with 84 children (87.5%) had final pupil size ≥6.5 mm, and only 22 children (22.9%) had reactive pupils.

• **CONCLUSION:** Increasing the frequency of compound tropicamide and lengthening the interval between eye drop applications can produce stronger mydriatic effects.

• **KEYWORDS:** pupil dilation; mydriasis; compound tropicamide; dark iris; children
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INTRODUCTION

Pupil dilation (mydriasis) is the most common procedure for pediatric ophthalmology examination or preoperative preparation. The pupil size of children should be dilated enough, so as to provide favorable condition for subsequent observation and operation. Inadequate pupil size would affect the observation during fundus examination and retinal laser photocoagulation. For cataract surgery, poor pupil dilation also increases the incidence of intra-operative complications, such as vitreous loss and capsule rupture. The intense light of surgical microscope or indirect ophthalmoscope may lead to pupil contraction. It is usually considered that pupil diameter exceeding 6.5 mm or absence of pupillary reaction to light is sufficient for observation or safe operation[1].

The three most widely used mydriatic drugs in clinical settings are atropine, cyclopentolate, and tropicamide. Atropine has a strong cycloplegic effect, inducing prolonged blurry vision and long recovery time, which limits its application in children's mydriasis. Previous studies showed cyclopentolate is related to some systemic effects such as drowsiness, ataxia, disorientation, incoherent speech, restlessness, and visual hallucinations. Compared with cyclopentolate, tropicamide has a relatively faster onset of cycloplegic effect and shorter recovery time[2]. Therefore, tropicamide is the most widely accepted and used mydriatic drug due to its short time course of action and low incidence of adverse effects[3]. In addition, a combination of drugs with two different mechanisms of action has been proved to be faster with greater magnitude

of dilations than one drug only[4]. The most commonly used compound dilation eyedrop in China is the combination of 0.5% tropicamide and 0.5% phenylephrine.

In different clinical centers in China, there is no standard regimen for the administration of mydriatic drugs. Our common clinical impression is that Chinese children need multiple dosages of compound tropicamide to achieve adequate pupil size for fundus examination. The most common iris color among Chinese is dark brown. In this study, we investigated the different administration regimens of compound tropicamide eyedrops for pupil dilation, in order to better guide the usage of this drug in clinical setting for Asian children with dark iris.

PARTICIPANTS AND METHODS

Ethical Approval The study is approved by the Institutional Review Board of Beijing Children's Hospital (2022-E-110-Y). All procedures and data collection were conducted in compliance with the tenets of the Declaration of Helsinki. In addition, informed consent was obtained from all the children and their parents/legal guardians. Trial registration: Chinese Clinical Trial Registry (ChiCTR2300067669).

This prospective, comparative, randomized interventional study was performed on 194 eyes of 101 children. All children were Chinese children with dark iris and were recruited between July 2022 and December 2022 at our institution. Children who needed mydriasis for fundus examination or retinal laser photocoagulation were included. Exclusion criteria included children with leucoma, uveitis, persistent pupillary membrane, posterior synechia, congenital iris dysplasia, and other diseases that affect iris contractility. Children with significant developmental delays or any other known neurological diseases were also excluded. Data collection included the patient's age, sex, and medical history.

Subjects were randomly divided using a random number generator into 2 groups. Specifically, a random number of 0 or 1 was generated for every subject by an independent technician, and subjects with the number of 0 and 1 were assigned to Group 1 and Group 2, respectively. All the children used compound tropicamide eye drops containing 0.5% tropicamide and 0.5% phenylephrine. Children in Group 1 received the eye drop 3 times with a 3-min interval between each application. Children in Group 2 received the eye drop 4 times with a 5-min interval between each application. A single drop of compound tropicamide was instilled in the lower cul-de-sac of each eye, beginning with the right eye. Care was taken to ensure that only a single, bubble-free drop from each minim dispenser was instilled into the lower conjunctival cul-de-sac. The timing began after the installation of the first drop. The entire procedure was conducted in a dark room.

Spot Vision Screener (Welch Allyn Inc., Skaneateles Falls, NY, USA), a portable, handheld, and infrared photo-screener, was used to measure pupil diameter. We measured all the eyes at baseline (pre-drug instillation) and then 30min and 60min post-drug instillation. Data was taken from a distance of 1 m. Random visual patterns were shown on the device, and an audible sound was emitted to attract the child's attention. It can measure pupil size ranging from 4 mm to 9 mm. For children who could not complete the measurement by Spot Vision Screener, we measured their pupil sizes with a modified metric ruler by direct observation. We assessed the pupillary light reflex with a pen torch (light) at 60min post-drug instillation.

Table 1 Clinical characteristics of children enrolled in this study

Variable	Group 1	Group 2	*P*
Number of children	51	50	-
Number of eyes	98	96	-
Age (mean±SD; mo)	39.0±36.9	32.0±32.3	0.31
Sex (male/female)	29/22	29/21	0.91
Baseline pupil size (mean±SD; mm)	3.7±0.5	3.8±0.4	0.31

SD: Standard deviation.

Statistical Analysis Data were analyzed using the statistical software Stata (version 15.1). The continuous variables were compared between the study groups using the independent samples *t*-test. The Pearson Chi-square test was used to compare non-continuous variables between groups. Regression analyses were performed to determine whether or not there was a greater change in pupil size after dilation with age. *P*-values of less than 0.05 were considered statistically significant.

RESULTS

Overall, 194 eyes of 101 children were enrolled in this study. Children were randomly divided into two groups. Group 1 included 98 eyes of 51 children who received compound tropicamide eye drop 3 times with a 3-min interval between each application. Group 2 included 96 eyes of 50 children who received compound tropicamide eye drop 4 times with a 5-min interval between each application. Their clinical characteristics were described in Table 1. There were no statistically significant differences in the mean age, sex, or baseline pupil size.

There was an increase in pupil size after dilatation for both Group 1 and Group 2. The change of pupil diameter for Group 1 at 30min and 60min post-drug instillation were 1.2±0.6 mm and 2.3±1.0 mm, respectively; the change of pupil diameter for Group 2 at 30min and 60min post-drug instillation were 2.3±0.9 mm and 3.7±1.0 mm, respectively (Figure 1). Group 2 showed a larger change in pupil size than Group 1 at 30min (P<0.01) and 60min (P<0.01).

We found that the change in pupil size was positively associated with age. Figure 2 showed the relationship between the change in pupil diameter and age at 30min and 60min post-drug instillation. It is shown that an older age results in a significantly larger change in pupil size after dilation for both Group 1 (R^2_{30min}=0.2, P_{30min}=0.00; R^2_{60min}=0.2, P_{60min}=0.00) and

Group 2 (R^2_{30min}=0.3, P_{30min}=0.00; R^2_{60min}=0.2, P_{60min}=0.00), respectively.

Sixty minutes after eye drop administration is the final time point for our study. There was a significant difference in the final pupil size between Group 1 and Group 2 (6.0±1.1 mm *vs* 7.5±1.0 mm; P<0.01). The effect of pupil dilation in Group 2 was 1.25 times that in Group 1. A larger proportion of children in Group 1 had smaller pupil diameter and reactive pupils at the final time point, with only 33 children (33.7%) had final pupil size ≥6.5 mm and only 9 children (9.2%) had non-reactive pupils. Children in Group 2 obtained larger pupil diameter and more non-reactive pupils at the final time point, with 84 children (87.5%) had final pupil size ≥6.5 mm and only 22 children (22.9%) had reactive pupils (Table 2).

DISCUSSION

Iris color as a multifactorial hereditary trait varies depending on the race and ethnicity of people. The presence of melanin has been proven in the pigment epithelium and stroma layer of the iris, but the melanin in the pigment epithelium of the iris in all healthy individuals does not contribute significantly to variation in iris color or structure. Instead, the color of the iris is determined by the pigments in the stroma layer[5]. In recent years, studies found that variation in iris color is an important factor for pathological conditions[6]. The dark iris contains more melanin concentration and is thicker, which is associated with an increased incidence of angle closure glaucoma in East Asians[7]. Epidemiology studies found that age-related macular degeneration (AMD) is much more common in subjects with light-colored iris than those with dark-colored iris[8]. Previous studies have shown a slower drug response to dark iris, and mydriasis is closely related to race differences[4]. In 1977, Goldsmith *et al*[9] found that failure of dilation occurred more frequently in Aymara and Mestizo groups in Chile population with dark iris in the Multi-national Andean Genetic and Health Program. Manny *et al*[10] also found that myopic children with dark irises were less responsive to 1% tropicamide. In our study, we found that only 33 patients (33.7%) achieved ≥6.5 mm final pupil size after administration of compound tropicamide 3 times with 3min interval, and 84 patients (87.5%) achieved the same size after administering 4 times with 5min interval, which is inconsistent with the previous literature reporting that the same mydriasis effect can be achieved after a single to two doses of use[1]. The possible reason for this discrepancy is that binding of mydriatic agents with melanin evokes less response in heavily pigmented iris. German *et al*[11] investigated antimuscarinic drugs and their nonspecific binding affinity for melanin pigment. They believed that for dark iris, binding to melanin can significantly reduce and prolong the effect of mydriatics, because the melanin could act as a 'drug-reservoir'.

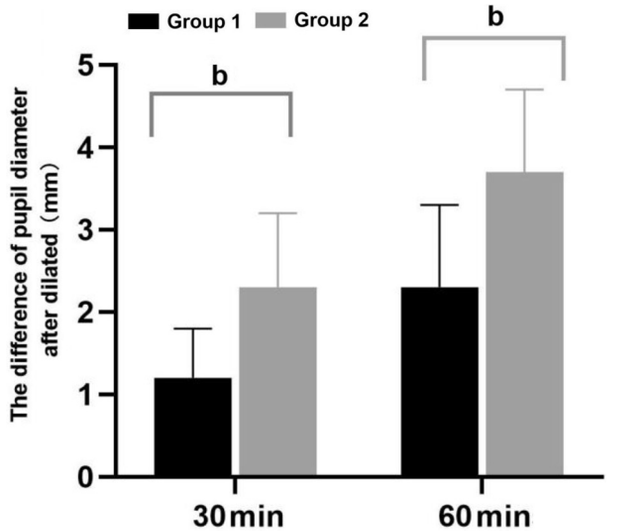

Figure 1 Comparison of pupil size differences between Group 1 (regimen: 3 times with a 3-min interval) and Group 2 (regimen: 4 times with a 5-min interval) at 30min and 60min post-drug instillation ^bP<0.01.

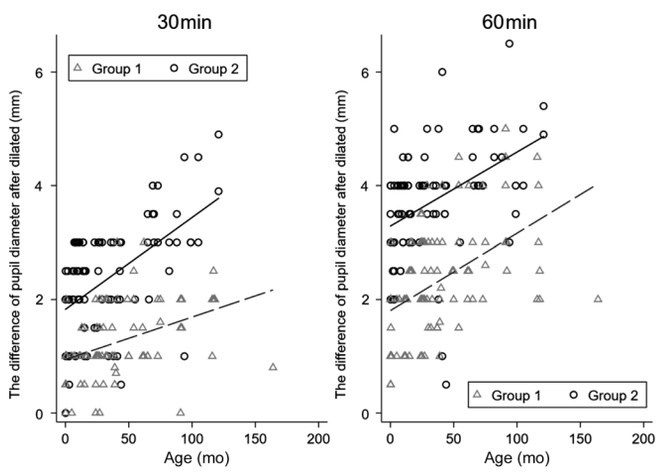

Figure 2 Relationship between the change of pupil diameter and age at 30min and 60min post-drug instillation The fitted lines are estimated from OLS regression models.

Table 2 Comparison of the pupil dilation between Group 1 and Group 2 at 60min post-drug instillation (final time point)

Variable	Group 1 (*n*=98 eyes)	Group 2 (*n*=96 eyes)	*P*
Final pupil size (mm)	6.0±1.1	7.5±1.0	<0.01
Final pupil size			<0.01
<6.5 mm	65 (66.3%)	12 (12.5%)	
≥6.5 mm	33 (33.7%)	84 (87.5%)	
Pupillary light reflex			<0.01
Not reactive	9 (9.2%)	74 (77.1%)	
Reactive	89 (90.8%)	22 (22.9%)	

There are few studies on whether longer intervals are needed for mydriatic drugs. Stolovitch *et al*[12] showed that the time interval between the instillation of the two drops of 1% cyclopentolate had no significant influence on pupil dilation in children, and instilling eye drops 1min apart is as effective

as instilling them 5min apart. The research by Geyer *et al*[13] showed that even after a 10min interval, mydriatic drugs are not more effective than those instilled immediately after one another. Denion *et al*[14] found 5min interval between two dilating eye drops can yield a 5.6% relative pupil surface gain. In our research, children in Group 2 who were administered 4 times of eye drops with 5min intervals showed a larger change in pupil size at 30min and 60min than children in Group 1, who were administered 3 times of eye drops with 3min intervals. Such a significant difference has not been reported in previous studies. Lim *et al*[15] assessed 268 young Asian children with dark iris. After 2-3 cycles of cycloplegic eye drops with 5 to 10min interval, a failure of cycloplegia were found in 36 children (13.4%), as measured by the presence of pupil reactivity. However, for the same race, in our study, the presence of pupil reactivity was more common, as failure of cycloplegia were found in 89 children (90.8%) after administering 3 cycles of eye drops, and 22 children (22.9%) still had presence of pupil reactivity even after administering 4 cycles of eye drops. In terms of methodological differences, Lim *et al*[15] used longer intervals than us. This may suggest that in dark iris, extending the time interval of administration appropriately can achieve a better pupil dilation effect. In addition, in Lim *et al*'s[15] research, age was not associated with the presence of reactive pupils, which is inconsistent with the finding in our study that the change in pupil size was positively associated with age. We speculate that this may be related to the younger mean age of the study population we included. The subjects recruited in our study included a large proportion of children under 2y of age, but in Lim *et al*'s[15] study, the individuals were all greater than 2 years old. Wang *et al*[16] measured the corneal diameter of 432 infants and found that corneal diameter positively correlates with age from 0 to 36mo. This may suggest that a larger corneal diameter is associated with a larger diameter of the iris, allowing dilating drugs to bind to more receptors. In other studies, the effect of age on pupil dilation was hardly noted[17], because the changes in corneal diameter tend to flatten out after one year of birth[18]. To conclude, increasing the frequency of compound tropicamide and elongating the interval between eye drops can produce stronger mydriatic effects. It would be possible to consider mydriatic effect in relation to age. Nevertheless, more research is warranted in the future.

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Conflicts of Interest: Xu X, None; **Zhang LX,** None; **Jiang JJ,** None.

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