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Factors Affecting Pupil Reactivity After Cycloplegia in Asian Children

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Purpose: The aim of this study was to evaluate the factors affecting cycloplegia, as determined by pupil reactivity, in Asian children.

Design: Prospective observational study.

Methods: Two-hundred sixty-eight children, aged 2 to 12 years, requiring cycloplegic refraction, were recruited. Nurses instilled 2 to 3 cycles of eye drops consisting of cyclopentolate 1%, tropicamide 0.5%, and phenylephrine 2.5%, and recorded the child's level of cooperation. Optometrists recorded pupil reactivity after the last cycle. Multivariate analysis determined factors affecting pupil reactivity including age, sex, race, number of eye drop cycles, pupil sizes before and after cycloplegia, and child's cooperation during eye drops instillation.

Results: The pupils in 36 children (13.4%) were found to be still reactive. On univariate analysis, children with reactive pupils also had smaller pupils after cycloplegia (6.27 ± 1.16 mm vs 7.42 ± 0.81 mm, $P < 0.001$). On multiple logistic regression analysis, for every 1-mm increase in the pupil size after cycloplegic eye drop administration, the odds of having reactive pupils decreases by 65% (odds ratio = 0.35, 95% confidence interval 0.25–0.51, $P \leq 0.001$). Those who were uncooperative during administration of eye drops were 3.13 times more likely to have reactive pupils (95% confidence interval 1.21–8.13, $P = 0.019$), whereas age ($P = 0.904$), sex ($P = 0.355$), the number of cycles of eye drops ($P = 0.462$), and other psychological factors were not relevant in affecting pupil reactivity.

Conclusions: Pupil reactivity, which was used as a measure of cycloplegia, was more likely to be affected by children's level of cooperation during instillation of eye drops, rather than age and sex. Two cycles of eye drops were as effective as 3 cycles in producing cycloplegia.

Key Words: cycloplegic refraction, dilation, pediatric, pupil reactivity

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Cycloplegia is an essential component of the pediatric ocular examination for accurate refraction.[1,2] It involves administering topical agents to paralyse the pupillary sphincter and/or stimulate the pupillary dilator to achieve maximal pupillary dilation and cycloplegia. Pupil size has been shown or presumed to correlate with adequate cycloplegia,[3–5] and use of cyclopentolate and tropicamide eye drops for cycloplegia result in dilated pupils that do not react even to intense light.[6,7] Unreactive pupils may, therefore, be used as a proxy to assess the effectiveness of cycloplegia.

Studies suggest that the success of cycloplegia may be associated with genetic factors, where pupil size after mydriasis is strongly heritable, and to a lesser extent, environmental factors (eg, variation in dosage of drug, unique environmental circumstance).[1] The roles of age, sex, and race have also been explored, and were found to have little impact on dilated pupil size post-cycloplegia.[1,8]

Our last study investigating the impact of psychological distress of eye drop administration in children showed that the experience can be very stressful,[9] resulting in poor cooperation of children during administration. Younger children, males, and those who had a previous bad experience with eye drop administration were more likely to be uncooperative. To the best of our knowledge, the effect of psychological factors on cycloplegia and pupil reactivity in children has not been reported so far.

Our aim was to assess the factors which influence the failure of cycloplegia, as measured by the presence of pupil reactivity, in young Asian children.

METHODS

In this prospective study, 268 children, aged 2 to 12 years requiring cycloplegic refraction, were recruited from a pediatric ophthalmology clinic. Children who had learning disabilities, developmental delay, syndromes or other chronic medical conditions, and whose parents were unable to speak or read English, were not included. The study was approved by the Singhealth-Centralized Institutional Review Board.

Children and parents were invited to take part in the study by the attending doctors. Written informed consent was obtained from parents after explaining the nature of the study. In addition, verbal assent was obtained from children aged 6 to 12 years. Demographic information, such as age, sex, and race, was collected. Parents completed a questionnaire about their child's baseline anxiety state; whether they were usually anxious (ie, often or very anxious), or not anxious (not, rarely, sometimes anxious). Pupil size was measured by ophthalmologists before instillation of eye drops using a pupil size ruler, where pupil diameter was measured to the nearest millimeter, in a mesopic environment.

Eye drops for cycloplegia were instilled by a team of staff nurses, and refraction was performed by 1 of 4 trained optometrists. Drops were administered in 3 cycles, except for 1 doctor, who routinely prescribed eye drops for 2 cycles. Each cycle was spaced 5 to 10 minutes apart. In the first cycle, children received 1 drop each of proparacaine 0.5% (Alcaine, Alcon Couvreur, Belgium), tropicamide 0.5% (Mydriacyl, Alcon Laboratories Ltd., UK), and cyclopentolate 1% (Cyclogyl, Alcon Couvreur, Belgium). The second cycle consisted 1 drop each of

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phenylephrine 2.5% (Mydfrin, Alcon Laboratories, Inc) and cyclopentolate 1%, and the third cycle consisted 1 drop of cyclopentolate 1%. This drop regimen is used to maximize the dilation and cycloplegia in Asian eyes with darker and thicker irides.[10] Nurses assessed the child's reluctance (ie, not, slightly, reluctant, or very reluctant) upon entering the room for eye drops administration, and graded the child's reaction after each eye drop (ie, no problem, minor sulking <20 seconds, cried but allowed drops, or cried and struggled). Children were classified as being "uncooperative" when nurses graded child's reaction toward the first drop as "cried and struggled." After the last cycle of eye drops, the optometrists recorded the dilated pupil size using pupil size rulers, and assessed pupil reactivity clinically, using a bright torchlight, in the following grades of "reactive," "slightly reactive," or "nonreactive." Children whose pupil reactivity was deemed to be either reactive or slightly reactive by the optometrists were classified as having "reactive pupils."

Statistical Analysis

A sample size of 300 was found to have enough power (of >90%) to allow a desired difference to be detected between the 2 groups (nonreactive vs reactive pupils). Thirty-two were excluded due to incomplete questionnaires. The children's characteristics were described as frequencies, percentages, and mean ± SD. Categorical variables were compared and analyzed by chi-square test for proportions. Continuous variables were analyzed by *t* test for 2 independent samples. A multiple logistic regression was performed to determine the factors associated with having reactive pupils after cycloplegia, that is, age, sex, race, number of eye drop cycles, pre- and post-eyedrop pupil sizes, reluctance of child upon entering room, and level of cooperation of children with eye drop administration. Statistical significance was set at $P \leq 0.05$. Data were analyzed using SAS version 9.4 for Windows (SAS, Inc., Cary, NC).

RESULTS

Of the 268 children, the mean age was 5.9 ± 2.0 years, with the majority (83.6%) being younger than 8 years. Most of the children were of Chinese ethnicity (80.2%), with an almost equal male to female ratio (Table 1). Indications for receiving cycloplegic eye drops were mostly for refractive errors (77.0%), followed by for evaluations of strabismus associated with refractive errors (10.4%).

In 36 children (13.4%), pupils were noted to be still reactive by optometrists after receiving cycloplegic eye drops, and were deemed to have failed to achieve cycloplegia.

Pupils were noted to be reactive in 16.7%, 13.1%, and 6.8% of children aged 2.0 to 4.9, 5.0 to 7.9, and 8.0 to 12.0 years, respectively. Children with reactive pupils also had a smaller final pupil size after cycloplegia (6.27 ± 1.16 mm vs 7.42 ± 0.81 mm), and were less cooperative with eye drops instillation (19.4% vs 7.3%) (Table 1).

TABLE 1. Demographic Variables and Clinical Features of Children Receiving Cyclopegic Eye Drops (Nonreactive Versus Reactive)

		Mean ± SD/Freq (%)		
Category	**Unit/Level**	**Whole Cohort (n = 268)**	**Not Reactive (n = 234)**	**Reactive (n = 36)**
Demographics				
Age	y	5.91 ± 1.96	5.94 ± 1.99	5.69 ± 1.76
Age groups	2.0–4.9 y	102 (38.1)	85 (36.6)	17 (47.2)
	5.0–7.9 y	122 (45.5)	106 (45.7)	16 (44.4)
	≥8.0 y	44 (16.4)	41 (17.7)	3 (8.3)
Sex	Male	150 (56)	131 (56.0)	19 (52.8)
Race	Chinese	215 (80.2)	184 (79.3)	31 (86.1)
	Malay	24 (9.0)	23 (9.9)	1 (2.8)
	Indian	20 (7.5)	16 (6.9)	4 (11.1)
	Others	9 (3.4)	9 (3.9)	0 (0.0)
General level of anxiety of children	Not or sometimes anxious	233 (86.9)	201 (86.6)	32 (88.9)
	Often or very anxious	35 (13.1)	31 (13.4)	4 (11.1)
No. of eye drop cycles instilled	2	58 (21.6)	48 (20.7)	10 (27.8)
	3	210 (78.4)	184 (79.3)	26 (72.2)
Pre-eye drop administration pupil size				
Pre-eye drop pupil size	3 mm	192 (71.6)	168 (72.4)	24 (66.7)
	4 mm	67 (25.0)	57 (24.6)	10 (27.8)
	5 mm	9 (3.4)	7 (3.0)	2 (5.6)
Pre-eye drop pupil size	mm	3.32 ± 0.53	3.31 ± 0.52	3.39 ± 0.6
Post-eye drop administration (final) pupil size				
Post-eye drop (final) pupil size	4 mm	3 (1.1)	2 (0.9)	1 (2.8)
	5 mm	15 (5.6)	4 (1.7)	11 (30.6)
	6 mm	31 (11.6)	24 (10.3)	7 (19.4)
	7 mm	77 (28.7)	66 (28.5)	11 (30.6)
	8 mm	142 (53.0)	136 (58.6)	6 (16.7)
Post-eye drop (final) pupil size	mm	7.27 ± 0.95	7.42 ± 0.81	6.27 ± 1.16
Post-eye drop (final) pupil size	<7 mm	49 (18.3)	30 (12.9)	19 (52.8)
	≥7 mm	219 (81.7)	202 (87.1)	17 (47.2)
Nurse's perception of child during administration of drops				
Reluctance of child upon entering room	Reluctant or very reluctant	28 (10.5)	22 (9.5)	6 (16.7)
Level of cooperation during eye drop administration at first drop cycle	Uncooperative	24 (9.0)	17 (7.3)	7 (19.4)

TABLE 2. Summary of Univariate and Multiple Logistic Regression Analysis of Factors Associated With Having Reactive Pupils After Receiving Cyclopegic Eye Drops (Versus Nonreactive)

			Univariate		Multiple*	
Factor	**Event Level/Unit**	**Reference Level**	**OR (95% CI)**	***P* Value**	**OR (95% CI)**	***P* Value**
Age	Year	—	0.94 (0.78–1.13)	0.499	1.01 (0.83–1.23)	0.904
Sex	Female	Male	1.16 (0.58–2.34)	0.672	1.42 (0.68–2.96)	0.355
Race	Chinese	Non-Chinese	1.51 (0.57–3.96)	0.407	1.59 (0.6–4.23)	0.353
General level of anxiety of children	Not or sometimes anxious	Often or very anxious	1.13 (0.39–3.29)	0.824	1.13 (0.38–3.31)	0.828
No. of eye drop cycles instilled	—	—	0.66 (0.3–1.46)	0.307	0.74 (0.33–1.65)	0.462
Pre-eye drop pupil size	mm	—	1.34 (0.73–2.46)	0.349	1.37 (0.74–2.54)	0.323
Post-eye drop (final) pupil size	mm	—	0.35 (0.24–0.5)	<0.001	0.35 (0.25–0.51)	<0.001
Reluctance of child upon entering room	Reluctant or very reluctant	Not reluctant or seldom reluctant	1.99 (0.76–5.24)	0.162	0.5 (0.07–3.39)	0.478
Level of cooperation during eye drop administration at first drop cycle	Uncooperative	Cooperative	3.13 (1.21–8.13)	0.019	3.13 (1.21–8.13)	0.019

CI indicates confidence interval; OR, odds ratio.

*Adjusted for level of cooperation during eye drop administration at first drop cycle.

On univariate logistic regression (Table 2), children with reactive pupils had a smaller pupil size after cycloplegia [odds ratio (OR) = 0.35, 95% confidence interval (CI) 0.24–0.5, $P < 0.001$], were more reluctant to enter the room [although this was not significant ($P = 0.162$)], and were less cooperative during instillation of the first cycle of the eye drops (OR = 3.13, 95% CI 1.21–8.13, $P = 0.019$). In the multiple logistic regression analysis, stepwise selection approach was used to adjust for potential confounders, and the level of cooperation at the first eye drop cycle was found to be the only confounder. The adjusted ORs were reported in Table 2. The odds of having reactive pupils were found to decrease by 65% (OR = 0.35, 95% CI 0.25–0.51, $P < 0.001$) for every 1-mm increase in pupil size (Table 2). Age, sex, and number of cycles of eye drops appeared to be less relevant based on multiple logistic regression analysis.

DISCUSSION

In this study, we found that 13.4% of children persisted with reactive pupils at the time of cycloplegic refraction. Children with reactive pupils were noted to have smaller pupils after cycloplegia, and were more likely to be uncooperative with the instillation of the eye drops. Age, sex, race, anxiety level, and the number of cycles of drops were not associated with reactive pupils.

Cycloplegia was used mainly to enable optometrists to ascertain the refractive error in young children with high levels of accommodation. Without cycloplegia, inaccuracies in classification of refractive errors may occur, with an underestimation of hyperopia especially in very young children.[11,12] Manny et al[3] reported that adequate cycloplegia appears to occur when the pupil reaches 7 mm in diameter, and in a study by Ebri et al[4] looking at the effectiveness of cycloplegic agents, it was noted that 100% of children who received atropine for cycloplegia had a dilated pupil size of ≥6 mm, and 97% showed no pupillary response to light. Additionally, Mordi et al[13] found that the time course of the change in accommodation was similar to that of pupil dilation. Although our study's definition of success of cycloplegia was based on the reactivity of children's pupils to bright light rather than pupil size, we found that the mean pupil diameter in the reactive group (6.3 ± 1.2 mm) was much smaller than those with nonreactive pupils (7.4 ± 0.8 mm). However, some pupils in the nonreactive group (12.9%) were <7 mm, whereas some in the reactive group (47.2%) were ≥7 mm in size. If a more stringent definition of full cycloplegia (ie, pupils which are nonreactive and ≥7 mm) was applied, then success of cycloplegia would have fallen from 86.6% to 75.4%.

Children with reactive pupils tended to be uncooperative during eye drop administration. Pediatric distress during eye drop administration can lead to unsuccessful instillation[14] and efficacy of eye drops. This could be due to a struggling child resulting in difficulty in the instillation of eye drops, or an anxious child who is tearful, or who may have a higher blink rate,[15] resulting in higher tear dilution and increased solution drainage. These can cause inadequate cycloplegia, consequently affecting the accuracy of cycloplegic refraction. Implementing interventions to allay distress during the eye drop experience may help to increase cooperation. Such strategies could include providing parents and children with adequate pre-procedural information (eg, verbally or through pamphlets or videos),[16,17] having a calm and pleasant place to administer drops; and training of staff to use distraction techniques or coping-promoting behaviors.[16,18,19]

In our study, age and sex were not associated with having reactive pupils. Our findings were similar to few other studies done in adults to assess the factors affecting pupillary size after cycloplegia. Age was noted to have limited effect on pupil size after cycloplegia, and presumably reactivity, in an adult twin eye study.[1] Another study on different mydriatic eye drops combinations in adults found that sex made no difference to the amount of pupillary dilation obtained.[20] Furthermore, Bagheri et al,[8] in a study assessing the optimal dosage of cyclopentolate 1%, found that age and sex had no effect on the extent of cycloplegia.

Previous studies in adults reported that races with dark irises were less responsive to cycloplegics.[21,22] Possible reasons include mydriatic agents binding to melanin evoking a lesser response in heavily pigmented irises,[23] and presence of a more powerful reflex miosis.[24] In our study in children, race was not found to be associated with reactive pupils between different Asian ethnicities ($P = 0.353$). This could mainly be due to the top 3 races in our study (Chinese, Malay, Indian) having similarly dark-colored irises. Likewise, Obianwu and Rand[24] also reported a lack of association between iris color and pupil dilation among Asians. Some studies reported a greater variability of response to

cycloplegics in dark brown eyes due to different corneal sensitivity.[10] Iris color was not documented in our study, but only 3.4% of children belonged to the racial group "others" who may have had lighter-colored irises. In addition, Hammond et al[1] looked at the factors affecting pupil size after dilatation on a population with blue, green, hazel, and brown eyes, and also found that iris color had no clinically significant effect on pupil size.

Our study revealed that undergoing 2 cycloplegic drop cycles is as effective as undergoing 3 drop cycles in achieving pupillary nonreactivity. There has been no consensus on the optimal dosage regimen for adequate cycloplegia. However, multiple studies have noted that reducing the number of drops or medications used in a cycloplegic drop regimen can still provide adequate pupil dilation.[5,8,25,26] Gadioux-Madern et al,[25] in particular, showed that instilling 2 drops of cyclopentolate 0.5% 10 minutes apart was as effective for cycloplegic refraction as 3 drops 5 minutes apart in white children. Reducing the number of drops may remedy the time-consuming and inconvenient aspects of cycloplegia in pediatric outpatient clinics. However, randomized clinical trials are required in future to study the effect of the number of eye drops instillations in an Asian population.

The strengths of our study lie in its sample size, and obtaining input from various sources (parents, ophthalmologists, nurses, and optometrists). There are also limitations. Although there is literature strongly suggesting that lack of pupil reactivity and a large dilated pupil correlate with adequate cycloplegia,[3–5,13] we cannot be absolutely certain that lack of reactivity equates to full cycloplegia. Pupil reactivity was not measured objectively, for example, with a pupillometer, but as the outcome of pupil reactivity was dichotomized into 2 categories only (reactive and not reactive), we felt that clinical assessment by experienced optometrists would suffice. Although the team of 5 nurses administering drops was briefed as to how to rate cooperation of child, some inter-rater variability may exist. The manner in which each nurse administered drops may also vary. Very few parents of children declined to be involved in the study, however, those that did, may have responded differently to eye drops. Results from this study may not be applicable to studies elsewhere because of procedural differences.

In summary, our study showed that 13.4% of children undergoing cycloplegia still persisted with reactive pupils after receiving dilating eye drops. Poor cooperation during eye drop administration was associated with a reactive pupil and inadequate cycloplegia. The number of drop cycles, age, sex, and race were not associated with having a reactive pupil. Implementing strategies to improve cooperation during eye drop administration is recommended to ensure accurate refraction.

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