Is Tropicamide a More Effective Cycloplegic than Cyclopentolate in Children with Dark Irides?

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ABSTRACT

Background: Cycloplegia of dark irides is commonly achieved using a combination of cyclopentolate (1%) and tropicamide (1%). To date, no studies have compared the use of a cyclopentolate/tropicamide combination with the use of tropicamide alone to determine whether the cyclopentolate is necessary in dark irides. In addition this is the first study to use the interval between drops as a variable for cycloplegic effect.

Methods: We compared 4 different drug regimens - cyclopentolate plus tropicamide with 10 second interval (cyclo/trop), tropicamide plus tropicamide with 10 second interval (trop/trop), cyclopentolate plus tropicamide with 5 minute interval (cyclo/5min/trop) and tropicamide plus tropicamide with 5 minute interval (trop/5min/trop). The different cycloplegic regimens were administered to 174 Singaporean Chinese children aged between 3 and 12 years old.

Results: The 4 treatment groups all had similar differences in autorefraction after cycloplegia (mean 0.4D), with a slightly larger (but not statistically significant) difference with the 'trop/trop' combination. Residual accommodation measured by the 'push-up' method was least in the 'cyclo/5min/trop' group, followed closely by 'trop/cyclo'. The 'trop/trop' group had an average of 0.8D more residual accommodation than 'cyclo/5min/trop'. This was statistically significant, p=0.035).

Conclusions: Tropicamide (1%) is safer and faster acting than cyclopentolate (1%). In people with dark irides it has a superior mydriatic effect and similar cycloplegic effect. The authors suggest that clinicians consider substituting cyclopentolate combinations with 2 drops of tropicamide for maximum cycloplegic effect in Chinese children and other races with dark irides in cases where atropine is not required.

Keywords: tropicamide, cyclopentolate, Chinese, cycloplegics, accommodation

INTRODUCTION

The introduction of cyclopentolate in the early 1950s ousted atropine as the drug of choice for routine cycloplegic refraction[1,2,3,4]. It produced rapid cycloplegia and mydriasis that lasted significantly less time than atropine. At the original 2% concentration it commonly caused CNS effects[5,6,7,8] but at 1% concentration the side effects were tolerable without a significant loss of effectiveness[4]. The more common side effects include However, even at the 0.5% level side effects such as unsteadiness, confusion, constipation, fast heartbeat, red face and hallucinations have been reported and it has been suggested that many side effects of cyclopentolate go unreporeted because the children do not realise that it is important to mention these effects[9,10].

The cycloplegic and mydriatic effects of cyclopentolate are not as effective in people with dark irides as they are in light irides[3,11]. Its mydriatic effect is particularly poor and so tropicamide is often added to cyclopentolate to ensure adequate mydriasis[12]. This addition of tropicamide has been found by some authors to enhance the cycloplegic effect. Miranda found that adding tropicamide to cyclopentolate resulted in similar residual accommodation in dark irides as cyclopentolate alone had on light irides[11]. Lin and co-workers compared the difference between cycloplegic refractions and found that in Chinese eyes, tropicamide was more effective and furthermore that adding cyclopentolate to tropcamide only increased the effect by 0.1D[13]. Another study similarly found (in light irides) that two drops of 1% cyclopentolate resulted in similar residual accommodation as two drops of tropicamide[14].

Atropine is often thought to be the gold standard for cycloplegia[14,15]. However, while no studies have claimed that other cycloplegics are as effective as atropine, several comparison studies (including one on dark irides) with cyclopentolate and cyclopentolate/tropicamide combinations have found approximately 0.35 D difference in post-cycloplegic refractions, with between 8 - 22% having more than 1D difference[12,16,17,18]. The suggestion arising from these studies is that atropine is preferable in hypermetropes greater than 2D and esotropes but that other children can safely be refracted with the shorter-acting cycloplegics.

In addition to the choice of drug, the other factor thought to influence the effectiveness of cycloplegia is the time between instillation of drops. Pilocarpine studies on both animals and humans have indicated that waiting at least five minutes between drops is necessary due to slow drainage of eye drops[19, 20, 21]. However, Geyer and co-workers found that there was no difference in mydriatic effect if 2 mydriatic drops were instilled 10 minutes apart or immediately following each other[22]. A later study found no difference in the mydriatic effect of cyclopentolate instilled at 1 minute compared to 5 minute intervals[23].

From these studies it can be seen that cyclopentolate and tropicamide are effective cycloplegic agents, though with slightly reduced effect in patients with dark irides. There is an increasing body of evidence suggesting that in dark irides, when cyclopentolate/tropicamide combinations are used, the cyclopentolate may be having less cycloplegic effect than the tropicamide[11,13,14]. However, the best combination of drops has yet to be determined. This is important to resolve because there are potentially more severe side effects with cyclopentolate, particularly with increased dosage. In addition this is the first study to use the interval between drops as a variable for cycloplegia.

The aim of this study was to determine whether tropicamide alone was superior to a cyclopentolate/tropicamide combination and to determine whether a 5 minute interval has a greater benefit that a 10 second interval.

METHOD

This prospective study was conducted in an outpatient clinic in Singapore. We studied consecutive children sent for cycloplegic refraction. To be included, the child needed to be responsive for subjective refraction and capable of doing autorefraction. Many could not understand the accommodation test but these patients were still included, as we were interested in their autorefraction data as these children represent a large proportion of our patients for cycloplegic refraction. The majority of Singapore's population is Chinese with smaller groups of Malays and Indians. For ease of data analysis we only studied the Chinese children. Patients or their parents were asked to self-designate race.

The study included 132 children aged between 3 and 12 years old with refractive error between +3D and -10D, refracted between 30 and 60 minutes after the last drop was instilled. Children with anisometropia of more than 2.5D or with strabismus were excluded. There were 17 exclusions - 10 were due to high refractive error, 5 due to anisometropia, and 2 to strabismus. 55% were males and 45 % females. Only data from the right eye was used. See Table 1.

Table 1. Demographics

regimen	mean autorefraction (range)	age (range)	mean time†	excl ‡
cyclo / trop 45 eyes	-1.9 (+3.8 to -8.4)	6.0 (3 -12)	41 min	6.5%
cyclo/5min/trop 42 eyes	-1.2 (+1.25 to –6.4)	5.5 (3 -10)	40 min	4.7%
trop / trop 45 eyes	-1.7 (+3.4 to –6.1)	5.8 (4 -10)	43 min	4.8%
trop /5min/ trop 42 eyes	-1.7 (+0.63 to -7.5)	5.7 (3 -10)	42 min	5.5%

† mean time between instillation of last drop and autorefraction
‡ percentage of patients excluded

Patients were given combinations of Alcaine (Alcon Laboratories - proparacaine 0.5%), Cyclogyl (Alcon Laboratories - cyclopentolate 1%) and Mydriacyl (Alcon Laboratories - tropicamide 1%). We uniformly used proparacaine for all patients, because even though there is some doubt whether it aids absorption, it makes the test more comfortable and reduces crying[24].

Four experienced optometrists and orthoptists measured autorefraction and accommodation. The difference in autorefraction after cycloplegia provides the most objective and clinically relevant indication of cycloplegic effect. Autorefraction was measured on the Canon RK5. Five or more measurements were taken and the suggested refraction by the machine was recorded. Spherical equivalent of this result was used for comparisons.

Accommodative amplitude was measured using the RAF rule by the push-up method with the patient wearing best-corrected distance correction after subjective refraction with fogging. The near point was recorded as the point where the patient first noticed that the reduced Snellen 6/12 line was blurred.

There were four regimens designed to determine whether drug combination or time between drugs would effect cycloplegic effect. Each drug regimen was used during a period of two months corresponding to school vacation times. The patients were not randomised and the examiners were not blinded due to insufficient time and resources. However, as autorefraction is an objective test it should not be biased by these factors. The accommodation tests could potentially be biased but the investigators thought it still important to attempt to quantify the depth of cycloplegia. By using strict protocols this bias was minimised.

The 4 groups were:

1. **cyclo/trop** (45 eyes): 1 drop proparacaine, 1 drop cyclopentolate, 10 seconds, 1 drop tropicamide
2. **cyclo/5min/trop** (42 eyes): 1 drop proparacaine, 1 drop cyclopentolate , 5 minutes, 1 drop tropicamide
3. **trop/trop** (45 eyes): 1 drop proparacaine, 1 drop tropicamide , 10 seconds, 1 drop tropicamide
4. **trop/5min/trop** (42 eyes): 1 drop proparacaine, 1 drop tropicamide, 5 minutes, 1 drop tropicamide

RESULTS

The difference in autorefraction was similar for all regimens. The trop/trop combination showed the biggest difference (0.44D), with 33% of their eyes having more than 0.5D difference. The least difference was the trop/5min/trop group (0.32D). There was no statistical significance between groups with ANOVA test. See Table 2

Table 2. Means of the Differences in Autorefraction Before and After Cycloplegia and Percentage of Eyes with a Mean Difference Greater than +0.5D or +1.0D.

drug regimen	mean difference (+/- SD)	difference > +0.5D	difference > +1.0D
cyclo / trop 45 eyes	+0.36 (+/- 0.56)	27%	7%
cyclo/5min/trop 42 eyes	+0.41 (+/- 0.59)	29%	10%
trop / trop 45 eyes	+0.44 (+/- 0.41)	33%	2%
trop /5min/ trop 42 eyes	+0.32 (+/- 0.38)	21%	2%

Residual accommodation did not follow the trends of autorefraction. The cyclo/5min/trop group showed the least residual accommodation (2.8D), with 32% of these eyes having more than 3D of residual accommodation. Interestingly, the trop/trop group, which had the biggest difference in autorefraction, had the largest amount of residual accommodation (4.0D) and 57% of these eyes had more than 3D of accommodation. See Table 3.

Table 3. Mean Accommodation Before and After Cycloplegia and Percentage of Children with more than 3D Residual Accommodation.

drug regimen	mean accommodation		mean post-cyclo accommodation >3D
	pre-cycloplegia	post-cycloplegia (range)	
cyclo / trop 22 eyes	12.5	3.2 (1.5 – 8)	27%
cyclo/5min/trop 25 eyes	13.4	2.8 (1.5 – 6)	32%
trop / trop 23 eyes	13.8	4.0 (2 – 9)	57%
trop /5min / trop 22 eyes	13.3	2.9 (1.5 – 6)	32%

There was a significant difference in residual accommodation between the cyclo/5min/trop group and the trop/trop group (ANOVA p=0.035) but not between any other groups.

DISCUSSION

This study supports previous research indicating tropicamide alone is as effective combinations of tropicamide and cyclopentolate for cycloplegic refraction13. It also supports the contention that for cycloplegic refraction, the time between drops is not clinically significant[22,24].

The results raise some questions as to why we are using cycloplegia and our methods for measuring how deep the cycloplegia is. The two most common measures of cycloplegic effect - autorefraction and residual accommodation did not correlate in this study and in a previous study actually showed a negative correlation[14].

When compared on the basis of difference in autorefraction, the combination that historically would be regarded as least effective (2 drops of tropicamide with 10 second interval) was at least as effective as the other combinations. However the difference between this combination and the poorest performing combination (trop/5min/trop) was only 0.12D and not statistically significant. This result does not suggest that a better cycloplegic result can be achieved with a smaller time interval but rather that increasing the time interval is of questionable usefulness.

When residual accommodation was used as a measure of cycloplegic effectiveness, the trop/trop regimen performed most poorly and was the only combination to have a statistically significant difference when compared with the most effective regimen (cyclo/5min/trop).

The results of this study could now be used in the determination of drug regimens for eye clinics. In contrast with other studies, this study has compared the most commonly used drug regimens by varying the drug type and time interval. In Chinese children with dark irides there is no evidence that drug combinations involving cyclopentolate are more effective than tropicamide alone. In addition, this paper adds weight to several other studies that indicate that it may not be necessary to wait more than a few seconds between eye drops to achieve satisfactory cycloplegia.

In summary, two drops of tropicamide 10 seconds apart seems to provide an effective, practical, safe, faster-acting and more comfortable alternative to the more traditional regimens used for cycloplegia of children with pigmented irides. However, the authors also support the contention that atropine is preferable for cycloplegic refraction of hypermetropes greater than 2D and esotropes.

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