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A Comparative Study between Atropine and Tropicamide as Cycloplegic Agents for a Sample of Iraqi Children

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Abstract

Background The ideal cycloplegic drug that is effective, safe, and convenient allowing accurate measurement of the refractive errors by both subjective and objective means is not yet available.

Objective This study was designed to compare the cycloplegic activity and adverse effects of two cycloplegic agents (atropine vs. tropicamide) for children with hyperopia. The response to cycloplegia in different age groups, with or without strabismus, was also compared.

Methods Tropicamide 1% eye drops (Regimen 1) and atropine 1% eye drops (Regimen 2) was evaluated in thirty children with different ages. Cycloplegic refractions and adverse effects were assessed. The results expressed refractions and presented as mean ± SD. A *P*-value of less than 0.05 was considered statistically significant.

Results Tropicamide refraction mean value (+3.60 ± 2.25 D) didn't differ significantly in comparison with that of atropine (+3.92 ± 2.50 D); ($P > 0.05$). Children during regimen 2 (atropine drops) suffered from more frequent and statistically significant side effects ($P < 0.05$), represented by blurred vision, fever; flushing and tachycardia, compared with regimen 1 (tropicamide drops).

Conclusion Tropicamide applied to younger or older children is sufficient to produce good cycloplegia, with an effect approach to and safer than atropine, even in children with a high degree of hypermetropia, and with or without strabismus.

Keywords Cycloplegia, hyperopia, atropine, tropicamide.

List of abbreviation: D = diopter, RT = right, LT = left, SD = standard deviation.

Introduction

As a definition, the accommodative power of the eye is the variable force of accommodation that alters the path of light rays by causing the ciliary body to change the curvature of the lens [(1)].

Muscarinic receptors of the parasympathetically innervated smooth muscle fibers are present in the ciliary body. Cycloplegia inhibits the accommodative power of the eye by blocking the action of the ciliary muscle, allowing the static or objective refractive error of the eye to be measured. This anticholinergic action inhibits cholinergic stimulation (muscarinic receptors) of the iris sphincter and ciliary muscle, which results in mydriasis and cycloplegia [(2)].

Cycloplegic examinations not only allow refractive error to be determined, they also dilate the pupil, preparing the patient for an ophthalmoscopic examination. Cycloplegic refraction is necessary for the evaluation of patients with decreased vision or ocular deviation. It also helps detection of full hyperopia in patients with accommodative esotropia and prevents overcorrection in myopic patients [(3)].

After the discovery of modern laser refractive surgery, cycloplegic refraction has become a valuable preoperative test for accurately determining the refractive error. In older children and young adults, cycloplegic refraction can confirm the diagnosis of accommodative spasm, which is a constant or intermittent involuntary increase in ciliary contraction. Patients with low hyperopia may be presented as myopic during the examination; this so-called pseudomyopia can be identified by cycloplegic evaluation [4,5].

Cycloplegia can be used in pharmacologic occlusion therapy when the nonamblyopic eye is sufficiently hypermetropic where the effective blurring of vision can be obtained by instilling a cycloplegic drug in that eye alone. If under test conditions the patient switches from using the good eye to the amblyopic one, chances are excellent that he or she will also do so during treatment and that penalization will force the amblyopic eye to be used [6].

Medical uses for cycloplegic refraction are limited in adults. As the amplitude of accommodation gradually decreases with age, a closer agreement between cycloplegic and manifest refraction findings takes place [7].

The three most commonly used cycloplegic drugs, atropine, tropicamide and cyclopentolate, act by competing with the physiological muscarinic agent "acetylcholine", resulting in inhibition of ciliary muscle contraction [8]. Numerous studies have documented the efficacy of these cycloplegic drugs. Some authors have shown a significant and others showed no significant cycloplegic effect for some of these agents [9,10].

Most clinicians agree that cycloplegia is necessary when performing refraction in young children, high hyperopia, and patients with strabismus [11]. Fogging and other techniques cannot replace cycloplegic method for preciseness in determining refractive errors in early childhood because it does not depend on patient cooperation or fixation distance [12,13].

The unpleasant nature of instilling eye drops especially in children can prevent completion of the examination and is so important that sprays have been suggested instead of eye drops by some authors. Inadequate cycloplegia can cause inaccurate refraction and lead to inappropriate diagnostic and therapeutic approaches. On the opposite side, over dosage of cycloplegics may cause drug reactions or lead to patient discomfortable feeling [14].

Atropine, the strongest cycloplegic known used frequently in children, has its own advantages, and disadvantages in the form of prolonged action. Several investigators have shown atropine to be more effective in blocking accommodation in young esotropic children. In most cases of esotropia with hypermetropia in children less than 5 years of age, atropine or scopolamine preferably is used to ensure that no residual accommodation goes unrecognized [15,16].

Atropine is the gold standard for complete cycloplegia but it needs at least 3 hours to reach peak effect and must be used for 3 days to produce full cycloplegia. It takes 8-14 days for its effect to wash out from the pupil and ciliary body. Tropicamide, on the other hand, has a faster onset of action and reaches peak effect after 30-45 minutes; its cycloplegic effect washes out after 6-8 hours and has fewer complications [17].

Almost all ocular drugs have undesirable side effects, dividing into those of an ocular and systemic in nature. However, the complications from mydriatic and cycloplegic drugs are rare, compared with their extensive uses [18].

The toxic effects of atropine may be summarized by saying: "blind as a bat, dry as a bone, red as a beetroot and mad as a hatter". Atropine users are "blind" owing to the induced cycloplegia; "dry" due to the inhibition of the sweat and salivary glands; "red" because of peripheral vasodilation to lose heat and overcome the lack of function of the sweat glands; and "mad" owing to the effects on the CNS [19]. Atropine may lead to complications such as fever, tachycardia, convulsions, and even death [20].

The ideal cycloplegic drug that is effective, safe, and convenient allowing accurate measurement of the dioptric error by both subjective and objective means is not yet available. This study was designed to compare the cycloplegic activity and adverse effects between 1% eye drops of atropine versus 1% eye drops of tropicamide for a sample of Iraqi children with hyperopia.

Methods

This study involved 30 children (16 males/ 14 females) their ages were (2-9 years), with hyperopia of more than 1.0 Diopter (unit of refraction power) in at least one eye, enrolled in a prospective fashion among patients attending Ibn AL-Haitham Teaching Hospital and private eye clinics, during January to April of 2014 under supervision of professional ophthalmologists and approval of ethical committee in the College of Pharmacy, Al-Mustansiriyah University, after taking an oral consent from the parents of the participated children.

The primary goal of this study involved a comparison between tropicamide and atropine in cycloplegic effect, onset and duration of action, and their safety. The influence of age, sex, and iris color on the completeness of cycloplegia was considered as a secondary goal.

Because of the expected atropine pharmacokinetic profiles and long half-life, its onset and duration of action were detected by an accurate follow up for mydriatic and cycloplegic effects with the traditional slit lamp by giving a restricted appointment of the enrolled children for ophthalmic investigation depending on the doctor instructions.

The selection of the sample was based on the inclusion criteria which involved children below ten years, with approximate male/female ratio, suffering from hypermetropia with or without strabismus, and having different iris colors. Children excluded from this study involve those with a known cardiovascular disease, ophthalmic disease other than refractive error and/or strabismus, history of allergy to atropine or tropicamide, and inability to comply with the treatment regimen. All children underwent a routine ophthalmic evaluation.

Each child was given two regimens of eye drops, regimen 1 (tropicamide as mydriacyl® / Alcon Lab.), and then after one week, regimen 2 (atropine as isopto® atropine/ Alcon Lab.). Tropicamide 1% eye drops instilled at the hospital or eye clinic in the conjunctival sac two times at intervals of 5 minutes on the day of examination; refraction was performed 30 min after the last drop by mean of retinoscopy. Atropine 1% eye drop instilled at the home twice daily for 3 days prior to and on the day of examination. Post-instillation of drops, the lacrimal puncti was closed by pressure on the medial canthus for 3 minutes, to minimize systemic absorption. Parents were informed about the signs of local and systemic toxicity due to the drugs used and they were instructed to return the children to the clinic if adverse events were noted.

The results of refractive error were expressed as mean ± SD. Student t-test and chi- square test were used for statistical analysis, applying the Microsoft Office Excel Program-2007. A *P*-value of less than 0.05 was considered statistically significant.

Results

A total of 30 children (60 eyes) with age mean of (5.47 ± 1.44 years), range (2-9 years), were enrolled prospectively. Whole refractions were recorded after cycloplegia with tropicamide 1% (regimen 1) and atropine 1% (regimen 2) (Table 1). The mean of tropicamide refraction values (+3.60 ± 2.25 D) did not differ significantly in comparison with that of atropine (+3.92 ± 2.50 D); ($P > 0.05$) (Table 2).

Table 1. Cycloplegic refractions and their difference values

Pt. No.	Tropicamide drops Rt/Lt eye	Atropine drops Rt/Lt eye	Difference Values	Age (years)
1	+2.5/+2.5	+2.5/+2.5	0.0/0.0	2
2	+4.75/+4.75	+5.25/+5.25	0.5/0.5	4.5
3	+6.0/+6.0	+7.0/+7.0	1.0/1.0	3
4	+3.25/+3.25	+4.0/+4.0	0.75/0.75	7
5	+8.0/+8.5	+8.5/+8.5	0.5/0.0	5
6	+1.5/+1.5	+1.5/+1.5	0.0/0.0	9
7	+4.0/+4.0	+4.0/+4.0	0.0/0.0	6
8	+2.75/+2.75	+3.0/+3.0	0.25/0.25	5.5
9	+2.5/+2.5	+2.5/+2.5	0.0/0.0	5
10	+4.25/+5.0	+4.50/+5.50	0.25/0.50	9
11	+1.0/+1.0	+1.0/+1.0	0.0/0.0	5
12	+3.0/+3.0	+3.5/+3.5	0.5/0.5	5
13	+2.75/+2.50	+3.0/+3.0	0.25/0.50	8
14	+4.0/+4.5	+4.5/+5.0	0.5/0.5	6
15	+4.5/+4.5	+5.0/+5.0	0.5/0.5	6
16	+3.0/+3.0	+3.25/+3.25	0.25/0.25	5
17	+3.0/+3.25	+3.0/+3.50	0.0/0.25	7.5
18	+3.25/+3.25	+3.25/+3.25	0.0/0.0	5
19	+3.75/+3.75	+4.0/+4.0	0.25/0.25	8
20	+3.0/+3.0	+3.5/+3.5	0.5/0.5	2.5
21	+1.0/+2.0	+1.0/+2.0	0.0/0.0	5.5
22	+7.0/+7.0	+8.0/+8.0	1.0/1.0	7
23	+3.5/+3.5	+4.0/+4.0	0.5/0.5	3
24	+3.25/+3.25	+3.5/+3.5	0.25/0.25	4
25	+3.75/+4.25	+4.0/+4.5	0.25/0.25	8.5
26	+5.0/+5.0	+6.0/+6.0	1.0/1.0	4
27	+3.5/+3.5	+4.0/+4.0	0.5/0.5	6.5
28	+4.5/+4.5	+5.0/+5.0	0.5/0.5	4
29	+2.5/+2.5	+2.5/+2.5	0.0/0.0	3.5
30	+6.0/+6.0	+6.0/+6.0	0.0/0.0	9

Data represented by Diopters (D).

Children were divided into two groups according to their age, either ≤ or > 6 years. In younger children, the cycloplegic refraction means after atropine was (+4.15 ± 2.88 D) followed by tropicamide (+3.77 ± 2.68 D); (P > 0.05). In older children, the cycloplegic refraction means after atropine was (+3.70 ± 1.87 D) followed by tropicamide (+3.37 ± 1.56 D); (P > 0.05).

In hypermetropic-strabismic children, the mean cycloplegic refraction after atropine was (+4.0 ± 2.25 D) followed by tropicamide (+3.70 ± 2.87 D); (P > 0.05). In hypermetropic children without strabismus, the mean cycloplegic refraction after atropine was (+3.82 ± 1.97 D) followed by tropicamide (+3.45 ± 1.87 D); (P > 0.05).

Regarding gender, no significant association was found between the sex and refractive error values. The effect of iris color on accommodation after instillation of cycloplegic drops was evaluated by dividing the five known iris categories into two groups: a light-iris group and a dark-iris group. Categories 1, 2,

and 3 were combined as the light-iris group and consisted of irises that were blue, gray, green, or light brown, with or without brown or yellow pigmentation. Categories 4 and 5 were brown or dark brown with minimal yellow pigmentation and were termed the dark-iris group. In this study, no association was seen between residual accommodation and iris color.

The onset of mydriatic and cycloplegic effects for tropicamide was faster than that of atropine, while the duration of mydriatic and cycloplegic effects for atropine was longer than for tropicamide (Table 3).

Adverse effects of these cycloplegic agents were summarized in table (4). Children using regimen 2 (atropine drops) suffered from more frequent and statistically significant side effects ($P < 0.05$), represented by blurred vision, fever; flushing and tachycardia, compared with regimen 1 (tropicamide drops).

Table 2. Means of refractive error for each subgroup

Stratification	No.	Tropicamide drops	Atropine drops	*P* value
All participants	30	+3.60 ± 2.25	+3.92 ± 2.50	0.071
Children ≤ 6 years	20	+3.77 ± 2.68	+4.15 ± 2.88	0.096
Children > 6 years	10	+3.37 ± 1.56	+3.70 ± 1.87	0.085
Hypermetropic with strabismus	18	+3.70 ± 2.87	+4.0 ± 2.25	0.073
Hypermetropic without strabismus	12	+3.45 ± 1.87	+3.82 ± 1.97	0.094

Data represented by mean ± SD of refractive errors (Diopter).
P value > 0.05 was considered statistically non-significant.

Table 3. Onset and duration of action for the studied cycloplegic drugs

	Onset of action		*Duration of action*	
Drug	**Mydriasis**	**Cycloplegia**	**Mydriasis**	**Cycloplegia**
Tropicamide	15-30 min	25-30 min	4-6 hr	5-6 hr
Atropine	30-40 min	1-1.5 day	7-10 day	12-14 day

Discussion

The ideal cycloplegic agent should produce complete cycloplegia with minimal complications or morbidity and allow rapid recovery of accommodation. For children who are at the critical age of visual maturation and have higher amplitudes of accommodation acting as an obstacle against accurate refraction, full cycloplegia is a basic procedure in the diagnosis and treatment of those patients [21].

With atropine, a prolonged cycloplegia during a sensitive period might, in some cases, potentiate stimulus deprivation and contribute to amblyopia. Moreover, the parents often have difficulties in applying the drops in a correct manner and doubts often arise whether a full cycloplegic effect has been achieved [22].

Table 4. Adverse effects for the studied cycloplegic drugs

Adverse effects	Tropicamide drops (1%)	Atropine drops (1%)	*P* value
Stinging	2 (6.6)	3 (10)	0.087
Blurred vision	1 (3.3)	4 (13.3)	0.046
photophobia	3 (10)	2 (6.6)	0.079
Fever	0 (0.0)	3 (10)	0.041
Dryness of skin	0 (0.0)	1 (3.3)	0.092
Flushing	1 (3.3)	5 (16.7)	0.026
Headache	2 (6.6)	2 (6.6)	0.065
Tachycardia	0 (0.0)	3 (10)	0.037

Data represented by numbers (%).
P value < 0.05 was considered statistically significant.

Many ophthalmologists believe that other cycloplegic agents like cyclopentolate, tropicamide, and homatropine alone are not enough in children 2 to 5 years old, especially in esotropic children with hyperopia greater than 2.0 diopters who must be repeatedly refracted with atropine to detect latent hyperopia [(23)]. Others have demonstrated that the cycloplegic effect of these agents is comparable to atropine [(24)].

So many authors consider atropine as the drug of choice for complete cycloplegia and believe that other mydriatic agents cannot be an appropriate substitute. However, due to its complications, the difficult regimen, and prolonged impairment of near vision, atropine gradually may replace by other cycloplegic agents which have fewer complications, easier to administer, and has a shorter duration of action [(25)]. Comparisons of combinations of these drugs have also failed to detect the ideal regimen. Possible causes for the variable results could be the differences in drug combinations, therapeutic regimens, and patient populations [(26)].

In the present study, the mean of tropicamide refraction values (+3.60 ± 2.25 D) didn't differ significantly in comparison with that of atropine (+3.92 ± 2.50 D); ($P > 0.05$). The two drugs in this study appear remarkably similar; even in children with a high degree of hypermetropia. Therefore, it may possible to replace atropinization at home with the instillation of tropicamide in the hospital or eye clinic.

For drugs like tropicamide and cyclopentolate, a precaution should be taken as they tend to be less cycloplegic than atropine in young children with high hypermetropia. However, atropine should be reserved for children (less than 6 years) with a large amount of accommodative esotropia and those with a history of tropicamide allergy [(27)]. Observations of this study revealed that 1% eye drops of tropicamide, 5 minutes apart, provide considerable cycloplegia sufficient for refraction in most children.

Certain study was achieved on esotropic children younger than 5 years with atropine versus other cycloplegic agents, and showed that atropine was probably unnecessary [(28)]. In contrast, another study found that atropine uncovered (0.3-0.4) diopter more hyperopia in children younger than 6 years old [(27)]. For cycloplegic refraction, an allowance (or under correction) has to be made for abolished ciliary tone, this tonus allowance is taken as 1.0 diopter in the case of atropine. Some researchers recommended an equal tonus allowance for both atropine and any other cycloplegic; while others suggested that a tonus allowance for any other cycloplegic, with the exception of atropine, is inappropriate [(29)]. In children with a high degree of hypermetropia, cycloplegic drugs other than atropine did not produce a complete

cycloplegia, where 22% of the children had an additional hyperopia of (+1.0) diopter or more which was uncovered by atropine [30].

In this study and for younger children, the cycloplegic refraction mean after atropine (+4.15 ± 2.88 D) didn't differ statistically from that of tropicamide (+3.77 ± 2.68 D); ($P > 0.05$). Considering older children, the cycloplegic refraction mean after atropine (+3.70 ± 1.87 D) also didn't differ statistically from that of tropicamide (+3.37 ± 1.56 D); ($P > 0.05$). There were only four eyes, all of them younger than 6 years of age, which had 1.0 diopter hyperopia uncovered by atropine but not by tropicamide.

The importance of atropine cycloplegia in the evaluation of strabismic children has been mentioned in earlier reports [4]. The current study showed that, for children with or without strabismus, cycloplegic refraction values after atropine and tropicamide was comparable (+4.0 ± 2.25 D and +3.82 ± 1.97 D vs. +3.70 ± 2.87 D and +3.45 ± 1.87 D, respectively). Thus, tropicamide might be considered as the choice for cycloplegic refraction for children with or without strabismus.

Although investigators have reported an association between residual accommodation and iris color, which is related to the ethnicity, no such association was found in this study. A statistically significant association between residual accommodation and ethnicity was found in the previous studies, where a significant difference in residual accommodation between the white and Hispanic populations was reported [25].

In spite that atropine provides adequate cycloplegia, the adverse effects and persistent duration of action have encourage a search for alternate cycloplegic agents. Patients should be caution about the transient acute psychosis, which may occasionally occur even with few drops of atropine. Other neurological toxicities, including seizure and delirium, can also occur with atropine [31]. The incidence of adverse events for diagnostic ocular agents was reported to be less than 1%, where the researchers included a wide range of dilating eye drops, from mild to strong agents. However, significant side effects have also been reported, including tachycardia, tremor, and mental confusion [32].

In the present study, children who received tropicamide (regimen 1) did not show significant side effects when compared with that of atropine (regimen 2), where 13.3 %, 10%, 16.7 %, and 10% of children during atropine drops suffering from blurred vision, fever, flushing, and tachycardia, respectively. The small sample size used may effect on the incidence of these anticholinergic problems.

To achieve complete cycloplegia and to avoid the complications and morbidity of atropine, different combinations and concentrations of cycloplegic agents have been prepared. The possible reason for using a reduced concentration of atropine in younger children was to reduce the incidence of atropine toxicity in those patients. This appeared paradoxical because younger children have a greater accommodative response [33].

From the pharmacokinetic point of view, and as an advantage over atropine, tropicamide instillation has a rapid onset, short duration of action, and can be given at the time of examination in the eye clinic or hospital. The maximum cycloplegic effect is attained after 30 minutes and remains stable for more than 120 minutes [34]. As disadvantages with atropinization at home, compliance is often unsatisfactory, the drug effects are long acting, and it is often difficult to decide whether a complete cycloplegic effect has been achieved [35]. Results of the current study were consistent with this fact, where tropicamide was faster in onset, while atropine was longer in its duration of action.

From above, and due to its complications, difficult regimen, and prolonged impairment of near vision, atropine should be gradually replaced by other cycloplegic agents which have fewer complications, easier to administer, and has a shorter duration of action.

In conclusion, tropicamide applied to younger or older children is sufficient to produce good

cycloplegia, with an effect approach to and safer than atropine, even in children with a high degree of hypermetropia, and with or without strabismus. In addition, the residual accommodation was not associated with age, gender, and iris color, suggesting that these factors may be of no concern when using tropicamide or atropine as a cycloplegic agent in those children.

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Conflict of interest

The author declares no conflict of interest.

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