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Optimal dosage of cyclopentolate 1% for complete cycloplegia: A randomized clinical trial

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PURPOSE. *To determine the optimal dosage of cyclopentolate for adequate cycloplegia with minimal side effects.*

METHODS. *A prospective randomized clinical trial of patients 3.5 to 20 years of age referred to a strabismus clinic during a 1-year period. Eligible patients were randomly divided into three groups. In Group 1, the cycloplegic effect of one drop of cyclopentolate was compared with two drops; in Group 2, the effect of two drops was compared with three drops; and in Group 3, the effect of one drop was compared with three drops.*

RESULTS. *This study includes 192 eyes of 96 patients with a mean age of 11.0±5.7 years. Strabismus was present in 43 patients (44.8%). A total of 146 patients (76%) were hyperopic, 33 (17.2%) were myopic, and 13 (6.8%) were slightly hyperopic or myopic at the two stages of the study. Overall, only 16 eyes, including 9 eyes in Group 1 (16.4%), 2 eyes in Group 2 (3.2%), and 5 eyes in Group 3 (8.6%), had ≥0.5 D difference in spherical equivalent refractive error at two stages of the study; however, intergroup differences were not statistically significant (p=0.16, chi-square test). Within each group, the percentage of eyes with <0.5 D difference was significantly greater than those with ≥0.5 D difference (p<0.001 in all three groups, binomial test). Side effects were more prevalent using more frequent drops.*

CONCLUSIONS. *A single drop of cyclopentolate 1% suffices for cycloplegic refraction. There were less frequent side effects using one drop of cyclopentolate, compared to two or three drops. (Eur J Ophthalmol 2007; 17: 294-300)*

KEY WORDS. *Autorefraction, Cyclopentolate, Cycloplegics, Refraction*

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INTRODUCTION

Cycloplegic refraction is invaluable in the evaluation of patients with decreased vision or ocular deviation. The rationale for cycloplegic refraction is that patients have different levels of accommodation at different times (1). Cycloplegic refraction helps determine full hyperopia in patients with accommodative esotropia and prevents overcorrection in myopic patients. It is also useful in prescribing correction in patients with limited cooperation during subjective refraction and amblyopic patients who have chaotic accommodation (1, 2).

The two drugs routinely used for cycloplegic refraction include atropine and cyclopentolate. 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 complete cycloplegia. It takes 8–14 days for its effect to wash out from the pupil and ciliary body. Atropine may lead to complications such as fever, tachycardia, convulsions, and even death, and is contraindicated

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in patients with Down syndrome and albinism (3). On the other hand, cyclopentolate has a faster onset of effect and reaches peak effect after 30–45 minutes; its cycloplegic effect washes out after 6–8 hours. It incurs fewer complications and has become the drug of choice for cycloplegia (4). Some authors have shown no significant difference between the cycloplegic effect of cyclopentolate and atropine (5, 6).

No consensus exists on the optimal dosage of cyclopentolate for adequate cycloplegia. Havener recommends three drops with 10-minute intervals 1 hour prior to refraction (7). Apt believes two drops with a 10-minute interval is enough in all patients other than neonates (8). Repka recommends two drops of cyclopentolate with a 5-minute interval 40–45 minutes before refraction (9). Vitale et al state that a single drop of cyclopentolate suffices 25–75 minutes before performing refraction (10).

Inadequate cycloplegia can cause inaccurate refraction and lead to inappropriate diagnostic and therapeutic approaches; on the other hand, overdosage of cycloplegics may cause drug reactions or lead to undue patient discomfort. The unpleasant nature of instilling eyedrops especially in children can prevent completion of the examination and is so important that sprays have been suggested instead of eyedrops by some authors (11).

This study compares the effect of once, twice, and three times instillation of cyclopentolate in producing cycloplegia and also evaluates the effect of factors such as age, sex, iris color, and pigmentation on cycloplegia.

METHODS

This clinical trial was performed after conducting a pilot study on 28 patients. Only patients 3.5–20 years of age were included because of adequacy of accommodative amplitude and cooperation for completion of the study (12). Exclusion criteria were insufficient cooperation interfering with instillation of drops or autorefraction. Patients with history of ocular trauma, inflammation, infection, or any emergent condition and patients with systemic metabolic disorders such as diabetes mellitus, which could affect accommodation, were excluded from the study. Institutional review board (IRB) and ethics committee approval was obtained. Ninety-six consecutive cases meeting the inclusion and exclusion criteria were selected from subjects referred to the strabismus clinic at Labbafinejad Medical Center, Tehran, Iran, from February 2004 to June 2004 and divided randomly into three groups.

Group 1

Group 1 consisted of 32 patients in whom one and two drops of cyclopentolate were compared. In the first session, one drop of cyclopentolate was instilled 5 minutes after application of tetracaine 0.5% in both eyes; 30 minutes later, autorefraction was performed three times and the average value was documented. One week later, in the second session, a similar procedure was repeated using two drops of cyclopentolate 5 minutes apart.

Group 2

In this group of 33 patients, we compared two and three drops of cyclopentolate. In the first session, two drops of cyclopentolate were instilled 5 minutes apart after application of tetracaine. After 30 minutes, autorefraction was performed three times and the average value was documented. One week later, a similar procedure was repeated; however, cyclopentolate was instilled three times 5 minutes apart. Autorefraction was performed in a similar manner 30 minutes after the last drop.

Group 3

This group consisted of 31 patients in whom one and three drops of cyclopentolate were compared. The procedures were similar to those described above and the sessions were also spaced 1 week apart.

History

History included age, sex, and history of systemic or ocular disorders. A comprehensive ocular examination was performed paying attention to deviation, amblyopia, and iris color and pigmentation. Two trained nurses who were familiar with the goals of this study instilled the drops and measured oral temperature. Ocular examinations and refraction were performed by one of the authors (A.B.). To enhance the quality of measurement, refraction at each stage in each patient was repeated three times and the average was documented. Any drug complication including palpitation, flushing, nausea and vomiting, or lightheadedness was documented. Oral temperature was taken before instilling the drop and 30 minutes after the last

drop; any increase >0.3 °C from basal temperature was regarded as significant. Spherical equivalent refractive error and drug complications at each stage were documented and compared.

Medications and devices

Medications and devices used in this study were cyclopentolate 1% (Tubilux, Pharma Co, Italy), the RM-A 2300 autorefractometer (Topcon, Japan), and oral mercury type thermometer (Meheco Ltd., Iran). The objective was to compare cycloplegic effect after once, twice, and three times instillation of cyclopentolate in order to determine the optimal dosage and prevent complications of overdosage.

Statistical analysis

To have a 90% chance of detecting as significant (at two sided 5% level) a 0.25 D difference in mean spherical equivalent between any two groups with an assumed standard deviation of 0.4 D, 56 eyes (28 patients) were required in each group (a total of 84 patients). For random allocation patients were assigned on an individual basis to Group 1, 2, or 3. Patients had equal probability of assignment to each group. Randomization was performed using a computer number generator to select random permuted blocks. This study was conducted as an open label trial without blinding methods.

Data analysis was performed according to a pre-established plan. Proportions were compared by the chi-square test with continuity correction or Fisher exact test when appropriate. Quantitative variables were compared using analysis of variance (ANOVA) with Scheffe post hoc method for multiple comparisons. Multivariate analyses were conducted with multivariate analysis of variance (MANOVA) test assessing the effect of potential confounders one at a time.

RESULTS

Overall, 96 patients (192 eyes) including 40 (41.7%) male and 56 (58.3%) female subjects with mean age of 11.0±5.7 years (range 3.5–20 years) were included in this study. Thirteen patients (13.5%) had no problem other than refractive errors; the remaining 83 patients (86.5%) had disorders including esotropia (27 patients, 28.1%) with mean angle of deviation of 36±11.9 PD (range 20–65 PD), exotropia (14 patients, 14.6%) with mean angle of deviation of 38±7.7 PD (range 20–55 PD), and amblyopia (39 patients, 40.6%). Fifteen patients (15.6%) had lightly pigmented irides, 49 patients (51%) had medium iris pigmentation, and 30 patients (31.3%) had dark irides. Ninety patients (93.7%) had brown irides and 4 patients (4.2%) had green irides. Iris color and pigmentation was not documented in 2 patients (2.1%).

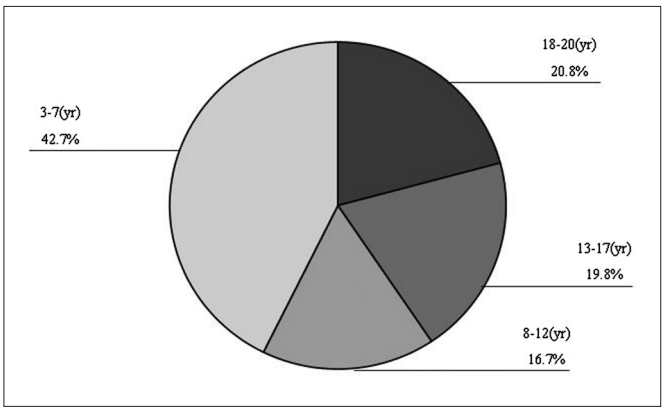

Fig. 1 - *Age distribution of patients.*

Random block analysis of variance detected significant differences between spherical equivalent refractive error at two stages among the three groups (p=0.04). In the next step, spherical equivalent refractive error in each eye was compared at two stages of the study. After adjusting for multiple comparisons mean absolute differences were statistically significantly different from zero in Group 1 (0.30 D±0.48) (p<0.001), Group 2 (0.16 D±0.17) (p<0.001), and Group 3 (0.23 D± 0.23) (p<0.001). To evaluate the clinical significance of these differences we determined the percentage of patients with less than 0.5 D difference in spherical equivalent refractive error at two stages of the study and those with ≥0.5 D difference. Overall, only 16 of 192 eyes had ≥0.5 D difference in spherical equivalent refractive error; 83.6% of patients in Group 1, 96.8% of patients in Group 2, and 91.4% of patients in Group 3 had less than 0.5 D difference in refractive error, and these percentages were statistically different from those with ≥0.5 D difference (p<0.001 in all three groups, binomial test).

The percentages of eyes with ≥0.5 D difference in spherical equivalent refractive error at two stages of the study were 16.4%, 3.2%, and 8.6% in Groups 1, 2, and 3, respectively. However, intergroup differences were not sta-

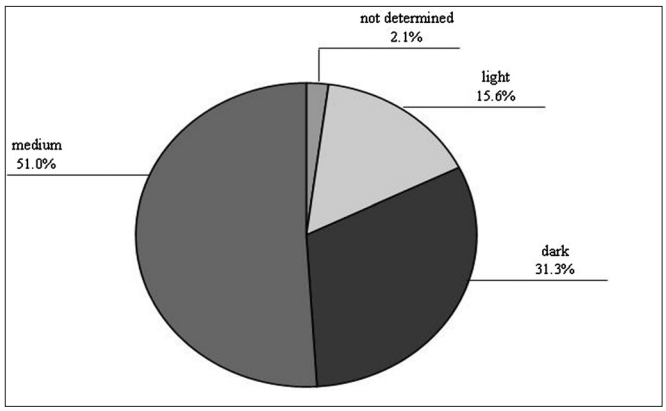

Fig. 2 - *Frequency of different levels of iris pigmentation.*

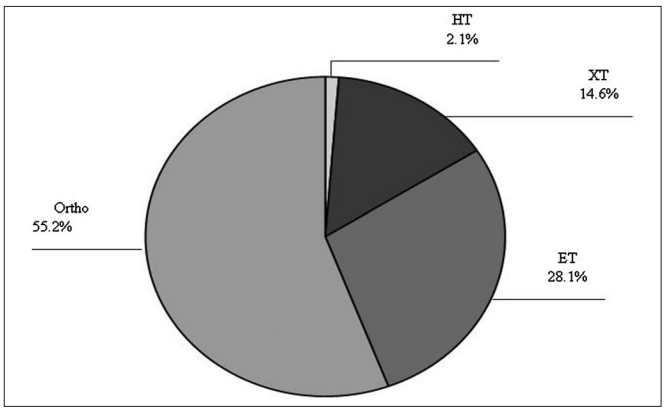

Fig. 3 - *Distribution of different alignments.*

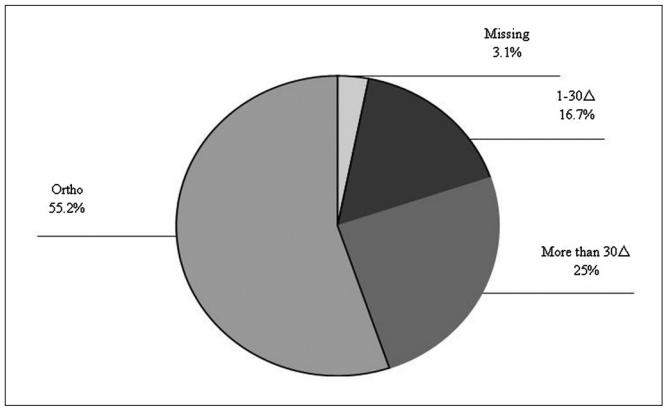

Fig. 4 - *Distribution of different angles of deviation.*

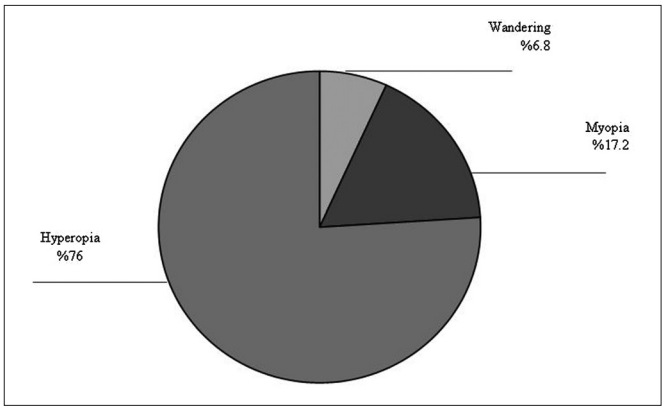

Fig. 5 - *Distribution of different refractive errors.*

tistically significant (p=0.16, chi-square).

We used the Manova test to evaluate whether age or sex could be potential confounders. We divided the patients into four age groups (Fig. 1). It was shown that neither age nor sex was a confounder in the evaluation of spherical equivalent in any of the three study groups (p>0.9 and p=0.6, respectively). Moreover, different age groups and sex were equally distributed in the three study groups (p=0.4, Anova test for age and p>0.8, chi-square test for sex).

Patients were divided into three groups with light and medium and dark irides (Fig. 2). Manova test showed that iris darkness was not a confounder in measurements of refractive error in the study subgroups (p>0.5). Furthermore, iris color and pigmentation were equally distributed in all three groups (p=0.8, chi-square test).

As previously mentioned, out of a total of 96 subjects, 27, 14, and 2 patients had ocular deviation including esotropia, exotropia, and pure hypertropia (HT), respectively (Fig. 3). MANOVA test showed that the presence and type of deviation had no effect on spherical equivalent refractive error in the three subgroups (p=0.08). Moreover, different types of strabismus were equally distributed in the groups (p=0.5, chi-square test).

The angle of deviation was evaluated next and patients were categorized into the following three groups: no deviation, including 53 patients (55.2%); deviation ≤30 PD, including 16 patients (16.7%); and deviation >30 PD, including 24 patients (25%). The angle of deviation was not documented in 3 patients (3.1%) (Fig. 4). The angle of deviation did not affect spherical equivalent refractive error in any study group (p=0.4, Manova test). Moreover, the angle of deviation was also equally distributed in the three groups (p=0.4, chi-square test). Group 1 included 32 patients, 15 of whom had strabismus with mean deviation of 38.1±8 PD (range 20–50 PD). Group 2 included 33 cases,

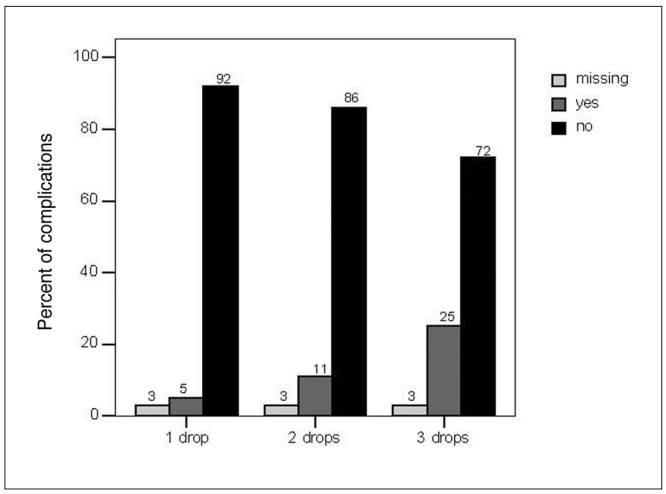

Fig. 6 - *Frequency of complications after one, two, and three times drop instillation.*

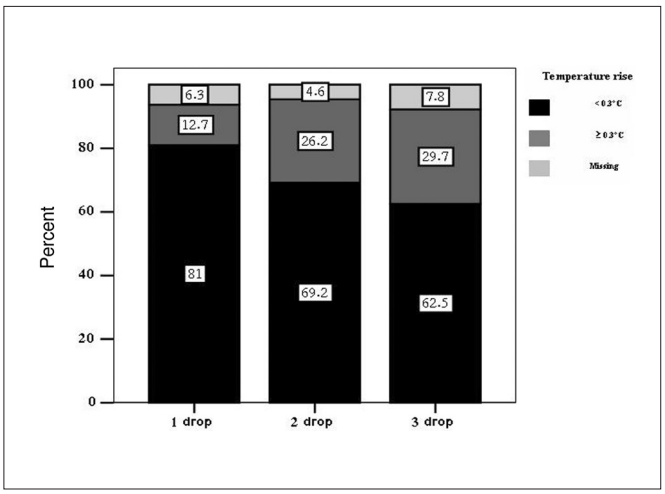

Fig. 7 - *Temperature rise after one, two, and three times drop instillation.*

16 of whom had strabismus with mean deviation of 36.7±12.5 PD (range 18–60 PD). Group 3 included 31 cases, 12 of whom had strabismus with mean deviation of 30.5±11.6 PD (range 15–50 PD).

Considering refractive error, patients were divided into three groups of myopia (33 eyes), hyperopia (146 eyes), and wandering group (13 eyes), in which spherical equivalent refractive error was slightly myopic, hyperopic, or emmetropic at different stages of the study (Fig. 5). The distribution of myopia and hyperopia in the three groups was not statistically different (p=0.3, chi-square test).

After excluding 13 eyes in the wandering group and 3 more eyes (2 from the myopic group and 1 from the hyperopic group, which were categorized in two different groups of refractive error at two stages of the study), the amount of refractive error (spherical equivalent [SE]) was divided into the following four groups:

- High myopia: SE ≤–6 D, 4 eyes (2.1%)
- Low myopia: SE –0.25 to >–6 D, 27 eyes (14.1%)
- Low hyperopia: SE 0.25 to <4 D, 129 eyes (67.2%)
- High hyperopia: SE ≥4 D, 16 eyes (8.3%).

These different subgroups were distributed similarly within the three study groups (p=0.3, chi-square test). The amount of refractive error was not a potential confounder (p=0.24, Mantel-Haenszel test).

Sixty-three patients (126 eyes) were evaluated after once, 65 patients (130 eyes) were evaluated after twice, and 64 patients (128 eyes) were evaluated after three times instillation of cyclopentolate. We refer to these patients as one drop, two drops, and three drops.

The rate of drug complications after once, twice, and three times instillation is shown in Figure 6. Significant oral temperature rise (more than 0.3 °C) occurred in 8 patients (12.7%) after one drop, 17 patients (26.2%) after two drops, and 19 patients (29.7%) after three drops of cyclopentolate (Fig. 7). Mean temperature rise after once, twice, and three times drop instillation was 0.04, 0.12, and 0.15 °C, respectively.

DISCUSSION

Full cycloplegia is a basic procedure in the diagnosis and treatment of a number of important ophthalmic disorders, particularly in children who are at the critical age of visual maturation and have higher amplitudes of accommodation acting as an obstacle against accurate refraction.

The ideal cycloplegic agent should produce complete cycloplegia with minimal complications or morbidity and allow rapid recovery of accommodation. Some cycloplegic drops like tropicamide and homatropine are not reliable for complete cycloplegia. Atropine has been used as the gold standard for cycloplegia for many years. Many authors consider it as the drug of choice for complete cycloplegia and believe that cyclopentolate cannot be an appropriate substitute (13-15). Atropine is the gold standard for producing cycloplegia; however, due to its complications, the difficult regimen, and prolonged impairment of

near vision, it has gradually been replaced by cyclopentolate, which has less complications, is easier to administer, and has a shorter duration of action. Many authors have demonstrated that the cycloplegic effect of cyclopentolate is comparable to atropine (5, 6, 16). Others believe that cyclopentolate alone is not enough in children 2 to 5 years old, especially in esotropic children with hyperopia greater than 2 D who must be repeatedly refracted with atropine to detect latent hyperopia (10, 14). Various products combining different combinations and concentration of cycloplegic agents have been prepared to achieve complete cycloplegia and at the same time avoid the complications and morbidity of atropine (15, 17-19).

Although cyclopentolate is accepted for cycloplegic refraction, no agreement exists on the frequency, interval of instillation, and time for peak effect (2, 6, 7, 9, 16, 17, 20, 21). Some authors believe that cyclopentolate should be instilled three times to produce complete cycloplegia while others state that two drops or one drop is enough.

Others believe that more frequent use of cycloplegics yields better cycloplegia in patients with esotropia (8, 9, 16). Fraunfelder reported that two drops of cyclopentolate within a 10-minute interval leads to complete cycloplegia in 40% of patients after 15 minutes (16). Similarly, Parfitt observed that two drops of cyclopentolate instilled within a 5- to 15-minute interval produces adequate cycloplegia after 25–75 minutes (22). Caloroso et al stated that two drops of cyclopentolate 0.5% for children under 1 year and cyclopentolate 1% for children older than 1 year within a 5-minute interval produces complete cycloplegia after 30–40 minutes (2). Other authors who favor the two drop regimen include Robb and Petersen (21), Salvasen and Kohler (23, 24), and Khurana et al (5). Some authors recommend three times cyclopentolate instillation for complete cycloplegia. Good and Hoyt recommend three times cyclopentolate 1% with 10-minute intervals (25) and Celebi and Aykan recommend three times cyclopentolate 1% with 5 minute-intervals and performing refraction 1 hour after the last drop (6). Havener also recommended three drops of cyclopentolate for complete cycloplegia after 25–75 minutes (7). Other authors recommend a single drop application of cyclopentolate for cycloplegia. Miranda and Sanjuan (17) instilled this drop only once and Vitale and Foster (10) recommended using one drop of cyclopentolate 0.5–2% for complete cycloplegia and mydriasis in light-skinned patients and noted that more drops are needed in dark-skinned patients. Some authors believe it is better to use one drop of cyclopentolate 0.5% in children less than 18 months who have light skin or history of sensitivity to cyclopentolate (2, 10).

None of the above mentioned studies and suggestions is based on a randomized clinical trial. The present study was designed to determine whether better cycloplegia may be achieved by increasing the number of cyclopentolate drops. The results of our randomized clinical trial indicate that a single drop of cyclopentolate suffices for achieving adequate cycloplegia in the large majority of patients. Increasing the dose of cyclopentolate did not produce better cycloplegia and increased side effects. The analysis was repeated by separating hyperopic and myopic patients and the results were the same. Some complications such as flashing were only seen after using three drops; nausea and lightheadedness were seen more commonly after two and three drops than after a single drop of cyclopentolate.

All potential confounding variables (such as age, presence and angle of eye deviation, type and amount of refractive error) with a possible effect on measured spherical equivalent were equally distributed in the three groups. One of the interesting findings of this study was that iris color and pigmentation had no effect on cycloplegia while most authors believe that in eyes with dark irides (especially Asian patients) cycloplegics should be instilled more frequently to produce complete cycloplegia (6, 7, 17, 20).

This study demonstrated that a single drop of cyclopentolate produces adequate cycloplegia in children and young patients with any type of strabismus or refractive error. It was also shown that a higher dose of cyclopentolate does not produce better cycloplegia and leads to more complications.

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