Original Research Paper

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Ophthalmology

ROLE OF ATROPINE 0.01% DROPS FOR CONTROLLING PROGRESSION OF MYOPIA IN CHILDREN

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ABSTRACT **Background:** Myopia is a significant public health problem, affecting 20% to 50% of the population, especially in children older than 12 years of age. **Aim:** This study aimed to assess role of 0.01% atropine in 5-16 years of age group children in preventing myopic progression by comparing changes in cycloplegic refraction and axial length of two groups: 0.01% atropine treated and other given placebo eye drops, over 1-year period. **Design:** Double-blinded randomized control interventional study. **Methods:** 60 patients with progressive myopia were recruited for study and randomised into 2 groups after obtaining parental consent. One group was prescribed atropine 0.01% concentration (b.d)and second group was given placebo eye drops (0.5% CMC). Each group was followed up, on 3 monthly visits, for a total duration of one year. Subjects included had to undergo baseline evaluation followed by visual acuity assessment on the Snellen's, cycloplegic refraction, axial length and pupil size. **Results:** Sixty participants with a mean age of 9.87±3.06 years and 10.33±2.94 years in placebo group and atropine group respectively completed the study.Statistically significant changes were noted in Spherical equivalent of 1.02±0.17 D and 0.32±0.43 D,(p value<0.001) and Axial length of 0.56±0.45 mm and 0.41±0.18 mm ((p value-0.017) in the placebo and 0.01% atropine groups respectively over 1 year. Change in axial length was significantly correlated with change in spherical equivalent (Spearman's rho: 0.651, P<0.001). **Conclusion:** 0.01% atropine drops instilled twice daily, was efficacious in controlling Spherical equivalent progression and retarded increase in Axial length over one year.

KEYWORDS :

INTRODUCTION

In 2010, it was estimated that uncorrected refractive error was the most common cause of distance vision impairment, affecting 108 million people, and the second most common cause of blindness globally. (1) The economic burden of uncorrected distance refractive error, largely caused by myopia, was estimated to be US$202 billion per annum. (2) According to the World Health Organization (WHO)-NPCB survey in 1989, 1.49% population in India is blind of which 7.35% is due to refractive errors. (3) The proportion of blindness due to refractive error has been found to be 19.7% in the NPCB-National Blindness Survey, however though the overall prevalence of blindness has been reduced to 1.1%. (4)

Several strategies have been shown to be effective for myopia control, including under correction of myopic refractive error, alignment fit gas-permeable contact lenses, outdoor time, and bifocal or multifocal spectacles. (5) The most investigated antimuscarinic agents include pirenzepine and atropine. (6,7) Atropine provides the best myopia control, but the cycloplegic and mydriatic side effects make it a rarely prescribed myopia control agent. (7) Low-concentration atropine (0.01%) has become the major treatment of myopic progression in children.

Studies conducted till now were on a predominantly ethnic Chinese population, (8-12) however, only few such studies have been carried out in the Indian population. We aim to study the role of low dose atropine in halting myopia progression specifically in children of 5-16 years of age by measuring axial length and cycloplegic refraction changes.

METHODS

The present study was conducted between January 2018- January 2020 in the Department of Ophthalmology, Government Medical College and Hospital, Sector 32 Chandigarh. It was a randomized control interventional study where a written, informed consent was taken prior to enrolment. It was a Double-blinded study. The trial medications were pre-packaged identically with the number of study subjects and the expiration date. They consisted of the appropriate concentration of atropine sulfate 0.01% (preservative free) and the placebo was 0.5% Carboxymethylcellulose (preservative free). Randomization was done using computer-based software called Research randomizer (Version 4.0) available online at https://www.randomizer.org.

60 patients were randomized into two groups, study group was given 0.01% atropine eye drops and control group will be given placebo eye drops. Both groups were given eye drops twice a day.

The study was registered with Clinical Trials Registry of India (CTRI) available online at https://www.ctri.nic.in.registration number CTRI/2018/03/012348. Patients diagnosed with progressive myopia Aged between 5 to 16 years, either gender were included in the study.

All patients included in the study had to undergo visual acuity assessment on the Snellen's visual acuity charts. The observed values were converted to log MAR scale for statistical analysis. Axial length and pupil size was measured on each visit by using Optical Biometer (Ls900 Lenstar, Haag Streit, U.S.A). Spherical equivalent (SE) was calculated as spherical power plus half of the cylinder power. All children were advised to wear their full optical correction. New glasses were prescribed whenever an under correction of > 0.5 D was detected. 0.01% custom-made atropine was provided as ready-made vials without preservatives. Children were given one drop into each eye twice every day. At each visit we checked for any potential side effects . Only those patients whose family verbally confirmed 100% compliance to the treatment and who had 1.year follow.up were included in the study. Children with pathological myopia, other ocular or systemic comorbidity, out of age range, myopia progression of <0.5D/year, limited compliance, and the patients who stopped or missed atropine eye drops during the study were excluded.

RESULTS

Mean age of patients was 9.87±3.06 years and 10.33±2.94 years respectively in placebo group and atropine group, which were significantly comparable.

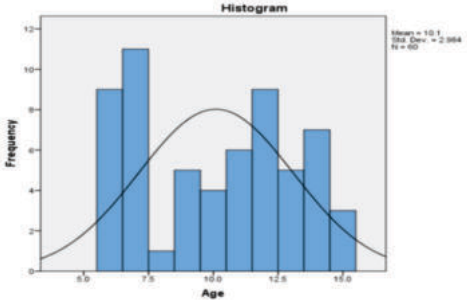

Figure 1: Bar diagram showing number of patients in various age groups.

Table 1: Overall Distribution of myopic eyes as per S.E dioptric power at baseline

Myopia Status	Frequency	Percent
Low Myopia (upto 6.00 D)	87	72.5
High Myopia (>6.00 D)	33	27.5
Total	120	100.0

1.discriptive Values In Both Groups

At the end of 1 year, mean SE change was 1.02±0.17 D and 0.32±0.43 D in the placebo and atropine group respectively. Median values were 1.00D and 0.37D in respective groups.

At the end of 1 year, axial length had a mean change of 0.56±0.45 mm and 0.41±0.18 mm in the placebo and atropine group respectively. Median values were 0.60mm and 0.43mm in respective groups.

At the end of 1 year, pupil had a mean change of 0.12±0.02mm and 0.61±0.29mm in the placebo and atropine group respectively. Median values were 0.12mm and 0.52mm in respective groups.

2. Overall Changes Recorded During Study

Wilcoxon Signed Ranks Test and Mann-Whitney test for comparison of overall change in SE, Axial length and pupil comparison in both groups.

Ranks

	Group	Number	Mean Rank	Sum of Ranks
Change in SE (12m - 0m)	placebo	60	90.42	5425.00
	atropine	60	30.58	1835.00
	Total	120		
Change in Axial length (12m - 0m)	placebo	60	82.15	4929.00
	atropine	60	38.85	2331.00
	Total	120		
Change in pupil (12m - 0m)	placebo	60	30.50	1830.00
	atropine	60	90.50	5430.00
	Total	120		

Test Statistics

	Change in Sp. eq.(12m - 0m)	Change in Axial length(12m - 0m)	Change in pupil (12m - 0m)
Mann-Whitney U	5.000	501.000	.000
Wilcoxon W	1835.000	2331.000	1830.000
Z	-9.578	-6.823	-9.460
Asymp. Sig. (2-tailed)	.000	.000	.000

Table 2: Pairwise comparison using Mann Whitney U test. There was statistically significant total change in SE, pupil size and axial length between the two groups over 1 year.

3. Mean Change In Spherical Equivalent Over Time Within Different Treatment Groups.

Mean spherical equivalent in placebo group was 4.36±1.84, 4.62±1.85, 4.83±1.83, 5.08±1.79 and 5.37±1.80D at baseline, 3 months, 6 months, 9 months and 1 year respectively. Mean spherical equivalent in atropine group was 5.61±2.71, 5.80±2.73, 5.88±2.73, 5.90±2.74 and 5.93±2.75D at baseline, 3 months, 6 months, 9 months and 1 year respectively (Figure 2). There was less progression of mean spherical equivalent in atropine group compared to placebo group as shown in trend analysis of spherical equivalent over time. There was statistically significant change of SE in both groups. (p value < 0.01)

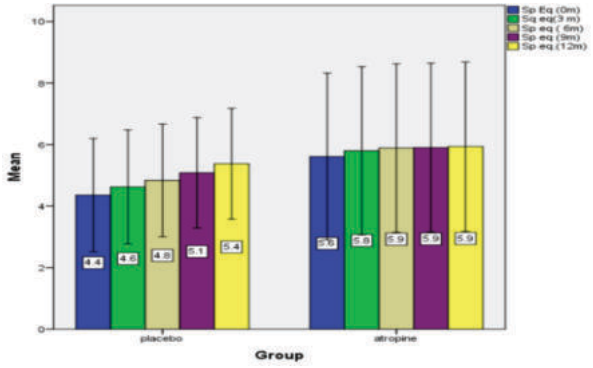

Figure 2: Bar diagram showing mean values of Spherical Equivalent in both groups at different time intervals.

4. Mean Change In Axial Length Over Time Within Different Treatment Groups.

Mean axial length in placebo group was 24.23±1.20, 24.38±1.20, 24.53±1.24, 24.67±1.24 and 24.79±1.25mm at baseline, 3 months, 6 months, 9 months and 1 year respectively. Mean axial length in atropine group was 25.25±1.38, 25.4±1.40, 25.52±1.41, 25.60±1.41 and 25.66±1.45mm at baseline, 3 months, 6 months, 9 months and 1 year respectively. (Figure 3). The changes in both groups were statistically significant.(p value <0.01).

There was less progression of mean Axial length in atropine group compared to placebo group as shown in trend analysis of axial length over time.

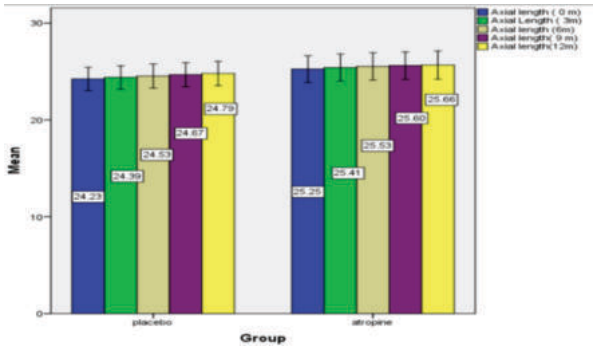

Figure 3: Bar diagram showing mean value of axial length in both groups at different time intervals.

5. Change In Pupil Size Over Time Within Different Treatment Groups.

Mean pupil size in placebo group was 4.97±0.52, 5.00±0.52, 5.04±0.53, 5.08±0.54 and 5.10±0.52mm at baseline, 3 months, 6 months, 9 months and 1 year respectively. Mean pupil size in atropine group was 4.93±0.47, 5.39±0.65, 5.47±0.64, 5.52±0.61 and 5.54±0.58mm at baseline, 3 months, 6 months, 9 months and 1 year respectively. (Figure 4)

Pupil size showed a significant increase at 3 month in atropine group as compared to placebo group. At the end of 1 year, Pupil change was 0.12±0.02mm and 0.61±0.29mm in the placebo and atropine groups respectively, with statistically significant differences between groups (p value <0.001)

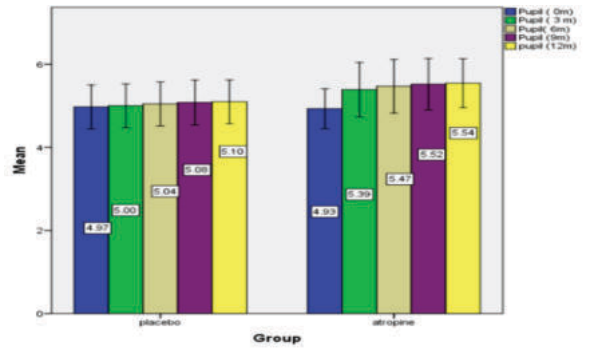

Figure 4: Bar diagram showing mean value of pupil size in both groups at different time

Correlations

As this study was not normally distributed, we calculated the Spearman's correlation coefficient for the atropine, placebo and the whole study population.

1.Whole Study Population:

The change in axial length was significantly correlated with change in spherical equivalent (Spearman's rho: 0.651, p<0.001). The change in pupil size was also moderately correlated with change in spherical equivalent (Spearman's rho: -0.765, p<0.001).

2. Placebo group

The change in axial length was significantly correlated with change in spherical equivalent (Spearman's rho: 0.321, p-0.012) in placebo group.

3. Atropine group

The change in axial length was significantly correlated with change in spherical equivalent (Spearman's rho: 0.387, p-0.002) in atropine group.

However, No statistically significant correlation was observed in progression of sphericalequivalent when compared between

low(≤6.00D) and high myopic (>6.00D) eyes.

Statistical Analysis

Descriptive analysis

The statistical analysis were carried out using Statistical Package for Social Sciences (SPSS Version 22.0 for Windows). Normality of the quantitative data were checked by Kolmogorov Smirnov test and the Shapiro Wilk test. Descriptive Statistics like mean or median were calculated for all quantitative variables for their central tendencies and standard deviation or inter-quartile range for their measures of dispersion depending upon their normality or otherwise.

Data was then represented by an appropriate graphical visualization method.

Categorical outcomes

Measurable values like age, sex, LogMAR, BCVA change, SE, Axial length and pupil size change was considered. Qualitative or categorical variables were described as frequencies and proportions. Chi square test was used to test statistical significance for categorical variables between the two groups.

The pair-wise comparison of data were made using Mann Whitney U test and within group comparison for change was done using the Wilcoxon Signed Rank as the data was not normally distributed.

The non-parametric Spearman correlation test was performed to analyse the correlation between changes in SE and axial length as well as changes in SE and pupil size. All statistical tests were two-sided and were performed at a significance level of $p<0.05$.

Sample Size

We assumed a mean of 0.28±0.92D progression of myopia in the atropine treated group over 1 year and 1.20 D in the placebo group using ATOM 1 results. (13) Alpha was assumed 0.05. Power was assumed 90%. Drop out rate of 19%. Sample size calculated using statistical calculations came out to be 25. However, we took a sample of 30 patients in each group.

DISCUSSION

As compared with placebo treatment, twice a day, application of 0.01% atropine eye drops in this study was efficacious in retarding the progressive myopia in Indian eyes. It not only controls SE progression but also retards increase in axial length.

More studies are necessary to decide the earliest age for using atropine eye drops for myopia and effectiveness of 0.01% atropine eye drops in the Indian eyes.

Any subject who is progressing by more than 0.5D per year or more may be offered myopia control. Lower cut offs may be justified in children with strong family history of myopia progression especially with early onset. While higher cut offs may be used for children in whom myopia had a late onset.

It is also necessary to do periodic follow ups during the course of therapy. The first follow up after starting therapy is recommended at 8–12 weeks. This is primarily to judge tolerance and look for any side effects.

A child on atropine 0.01% eye drops may rarely complain of allergy, blurry vision for near, photophobia and headaches. This may require use of tinted lenses, bifocal glasses or discontinuation of therapy. Thus, a close monitoring of such cases is recommended.We feel that currently the use be limited to simple myopia (exclude other forms of myopia like pathological myopia and index myopia).

CONCLUSION

The key findings observed in our study are as follows:

1. Myopia is usually progressive between ages 5 to 16 years so we included patients of this age group with a mean age of 9.87±3.06 years and 10.33±2.94 years in placebo group and atropine group respectively, which were significantly comparable.

2. SE change noted over one year was 1.02±0.17 D and 0.32±0.43 D in the placebo and atropine group respectively, with statistically significant differences between groups (p value <0.001). 0.01% atropine reduced SE progression by 68% as compared to placebo group in our study.

3. Axial length had a mean change of 0.56±0.45 mm and 0.41±0.18 mm in the placebo and 0.01% atropine groups respectively, which was found to be statistically significant (p value-0.017) at the end of 1 year. Thus, axial length showed 26% less elongation in 0.01% atropine group as compared to placebo.

4. Patients in our study showed statistically significant increase of mean pupil size of 0.61±0.29mm in atropine group as compared to 0.12±0.02mm in placebo group ($p<0.001$).

5. The change in axial length was significantly correlated with change in spherical equivalent (Spearman's rho: 0.651, $p<0.001$). The change in pupil size was also moderately correlated with change in spherical equivalent (Spearman's rho: -0.765, $P<0.001$) in total population. Also, the change in axial length was significantly correlated with change in spherical equivalent (Spearman's rho: 0.321, p-0.012) in placebo group and (Spearman's rho: 0.387, p-0.002) in atropine group respectively.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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