Original Article

Efficacy of 1% atropine eye drops in retarding progressive axial myopia in Indian eyes

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Purpose: The aim of this study is to assess the efficacy of 1% atropine eye drops for the retardation of progressive axial myopia in Indian eyes. **Methods:** This prospective interventional cohort study included children aged 5–16 years. Both the eyes of myopic children with progressive increase of ≥−0.5D sphere/year with the best-corrected vision of ≥6/6 were treated with once a day application of 1% atropine eye drops and progressive addition photogray lenses. The progression of myopia after 1-year follow-up was analyzed. **Results:** Sixty eyes of thirty myopes were included in the study. The mean age was 10 years and 15 were girls. The mean baseline sphere was −5.2D (−2.5D–−13D). Mean duration of follow-up was 23 months (12–36 months). The baseline rate of progression was reduced from −0.6D/year (range −0.5D/year to −3D/year) to −0.2D/year (range 0D/year to −1.5D/year) after atropine therapy. Seventeen patients (57%) had to use the atropine in the daytime to reach the target progression of <−0.5D/year. There was no difference between the efficacy of atropine drops in the boys and girls ($P = 0.6$). The efficacy of atropine drops did not have a correlation with the age of the patients or the magnitude of baseline myopia (Pearson's $r = 0$). **Conclusion:** 1% atropine eye drops was well tolerated and efficacious for the retardation of progressive myopia in Indian eyes. Effectiveness was better with daytime application. Further studies are necessary to assess the role of 1% atropine in the rapid progressors and patients poorly responding to low-dose atropine.

Key words: Atropine, India, myopia

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Atropine eye drops are used to retard the progression of myopia since 1960. We started using 1% atropine eye drops for progressive simple axial myopic children aged 6–12 years following the publication of ATOM 1 study in 2006.[1] However, that practice never became popular among the fellow ophthalmologists in India. Since the publication of the ATOM 2 study,[2] we are noticing more ophthalmologists resorting to atropine eye drops to reduce the progression of myopia in children because the low-dose atropine (0.01%) is practically free from the important side effects of blurring and photophobia. Moreover, 0.01% atropine drop does not lead to a rebound increase after a sudden cessation of treatment.[3-5]

In the coming years, it is expected that a routine use of topical atropine may become an important preferred practice pattern, not only in slowing the myopic shift in the school-going children but also in the prevention of the onset of myopia in high-risk children.[6,7]

1% concentration of atropine may still be indicated for the myopes with rapid progression, higher myopia at baseline, during the years of active growth, and among the "poor" responders of lower concentrations of atropine. In ATOM 2 study, 1% atropine drop was found to have a higher efficacy (78%) in comparison to 0.01% (50% efficacy) and 20% myopes were diagnosed as "poor" responders to lower concentrations of atropine (i.e., 0.01%, 0.1%, and 0.5%).

There are at least two reasons why atropine may have different efficacy in "Indian" eyes.

1. Atropine is a competitive antagonist of the muscarinic acetylcholine receptor types M1 to M5. The density and the distribution of these receptors vary considerably in differently pigmented eyes.[8] For each muscarinic acetylcholine receptors (mAChRs), for example, mAChR 1 (M1), there is a considerable gene polymorphisms.[9]
2. Previous investigators have found that the cycloplegic effect of atropine varies in different eyes. This observation was attributed to ethnoracial differences, enzymatic differences, and an "atypical muscarinic receptor" of darkly pigmented eyes.[8] One important factor for the variable effect of atropine in different eyes was determined to be due to a difference in the drug distribution using standard radioligand binding methods. Increased nonspecific binding to melanin meant that the higher melanin content of darkly pigmented eyes decreased the bioavailability of

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these drugs to the target receptors.[8] In individuals with light irides, cycloplegic-mydriatic drugs typically perform well with relatively short-time courses of dilation; however, in individuals with dark irides, the results differ between cycloplegic drugs including atropine with some yielding inadequate or slower dilation.[10]

In the era of 0.01% atropine, 1% atropine eye drops continue to have relevance in the management of 25%–30% progressive myopic children who have either (1) rapid progression or (2) who have high baseline myopia or (3) who respond poorly to the lower concentrations of myopia.[2]

In this context, we present a few important differences and similarities in the effectiveness of 1% atropine eye drops among 30 myopic children in comparison to the ATOM studies.[1,2]

Methods

In this prospective interventional cohort study, we included children aged 5–16 years with the best-corrected vision ≥6/6 and a documented myopic progression of ≥−0.5D/year (calculated from sequential cycloplegic refractions of immediate past 1 year). The study was performed between 2013 and 2015 in a standalone tertiary teaching pediatric eye care practice. The parents of the eligible patients were run through a powerpoint presentation regarding the theories and impact of progressive axial myopia in children and the current research regarding the efficacy and safety of different treatment methods by the author MK. The parents were asked to refer to the ATOM 1 study and/or discuss the treatment with their referring ophthalmologist before beginning the treatment. The parents were asked to return with their decision after a week and for any further discussion or clarifications if they chose to start atropine eye drops. After obtaining an oral informed consent, the patients were treated with 1% atropine sulfate eye drops (Bell pharmaceutical, Mumbai) applied at bedtime in both the eyes along with full distance correction of myopia using progressive addition photogray lenses (+3.0D). The patients were followed up at 3 monthly intervals. After two follow-ups, if myopia increased by ≥−0.25D in 6 months, the atropine eye drops were given in the morning (at 7 AM) instead of night application.

Only those patients who did not miss or stop the atropine eye drops during the study period were included for the analysis.

The vision and refraction assessment was done under cycloplegia with a routine use of duochrome test on CP690 Nidek projector chart by a fellowship trained, experienced but unmasked pediatric optometrist. The axial length, accommodation, and pupil diameter of patients were not measured.

Only those patients whose family verbally confirmed 100% compliance to the treatment and who had more than 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.

Paired *t*-test was used as a test of significance to compare pre- and post-treatment progression. Two-tailed Student's *t*-test was used to assess the effect of age, gender, baseline myopia, and the baseline progression on the effectiveness of atropine eye drops. Pearson's *r* was used to assess the correlation coefficient.

Sample size calculation:[11]

The formula used for the calculation of the sample size was appropriate for a continuous variable for the paired data.

We used the formula: $n = (Z_{1-\alpha/2} - Z_{1-\beta/2})^2 S_d^2/d^2$

$Z_{1-\alpha/2}$ = Level of significance = 1% = 2.58

$Z_{1-\beta/2}$ = Power of the study = 90% = −1.28

S_d = Standard deviation = 0.5D

d = Effect size = 0.25D

Sample size was calculated by inserting the values in the above mentioned formula.

$n = (2.58 - [-1.28])^2 (0.5)^2/(0.25)^2$

$= (3.96)^2 \times 0.25/0.625$

$= 14.8996 \times 4$

$= 59.596$

= 60 eyes

The study followed all the principles of the Helsinki Declaration of 1975, as revised in 2000.

Results

We included sixty eyes of thirty myopes in this study with the mean age of 10 years (range 5–16). The gender distribution was equal, 15 girls and 15 boys. The mean baseline sphere (before starting the atropine treatment) was −5.2D (−2.5D–−13.0D). Mean duration of follow-up was 23 months (12–36 months). The baseline rate of progression was −0.6D/year (range −0.5D/year to −3D/year). At the baseline, there was no difference in the progression in boys versus the girls, $P = 0.3$, *t*-test. The rate of progression was reduced to −0.2D/year (range 0D/year to −1.5D/year) after starting the atropine drops. There was no difference in the boys versus the girls, $P = 0.6$, *t*-test. There was no correlation of age or baseline myopia on the effectiveness of atropine therapy ($r = 0$).

In this study, 17 patients (57%) had an increase of ≥−0.25D after 6 months' use of atropine eye drops. They were switched to daytime (morning 7 AM) atropine eye drops following which 13 (of 17, i.e., 76%) patients achieved <−0.5D/year of progression. There was no significant difference in the age, gender distribution, baseline myopia progression or follow-up duration between patients who used night application compared with daytime atropine [Table 1]. Baseline myopia was −1.0D higher in patients who needed daytime atropine. Four patients continued to have a progression ≥−0.5D/year. None of the patients included in the analysis developed atropine allergy during the study period.

Two patients (excluded from the study) stopped using 1% atropine eye drops due to intolerable light sensitivity despite of progressive addition photogray lenses, one patient (excluded from the study) developed allergy to 1% atropine but could

Table 1: Comparison of the patients continuing nighttime atropine with patients switched to daytime atropine

	Nighttime (*n*=13)	Morning time (*n*=17)	*P* (Student's *t*-test)
Age (years)	10±2.3	10±2.6	1.0
Gender			
Male:female	5:8	6:11	
Baseline myopia (D)	−5.8±3.1	−4.7±1.7	0.02
Baseline progression (D)	−0.6±0.5	−0.7±0.9	1.0
Final progression (D)	−0.2±0.3	−0.2±0.3	0.8
Duration of follow-up (months)	22±14.6	25±13	0.7

be continued on 0.01% atropine, and one patient (included in the study) who continued to use atropine eye drops despite transient burning sensation with the application of 1% atropine eye drop.

Discussion

In this study, topical 1% atropine sulfate eye drops was well tolerated and effective in reducing the myopia progression by 67% in 60 eyes of 30 Indian children when used for more than a year. The retardation of myopia progression was lesser compared to the 78% reduction reported in the ATOM 1 study (progression of 0.14D/year in 1% atropine-treated eyes compared to 0.64D/year in the placebo-treated eyes).[1,2]

There were seven important differences in our study compared to the ATOM 1 study.

1. The population included in our study was entirely Indian. In ATOM 1 study, the population was overwhelmingly (>90%) Chinese. Indians contributed only 3% of the atropine-treated eyes in ATOM 1 study. There are well-recognized differences in the effect of atropine between differently pigmented eyes and in different races.[8-10]
2. The mean age of the patients before starting atropine in this study was 10 years compared to slightly earlier age of 9.2 years in ATOM 1 study.
3. The mean baseline myopia in the present study was −6D compared to −3.4D in ATOM 1 study. The ATOM 1 study had more patients with low and moderate myopia (<−6D). However, the prevalence of high myopia (>−6D in both eyes) in ATOM 2 study was 44%, 49%, and 50% in the atropine 0.01%, 0.1%, and 0.5% groups, respectively. Very high myopia (myopia of 8.0D in both eyes) in ATOM 2 study was present in 7%, 9%, and 17% of children in the 0.01%, 0.1%, and 0.5% groups, respectively. Both the ATOM studies did not report analysis of the correlation between age/baseline myopia and the efficacy of atropine. Although we found no correlation between the age/baseline myopia and effectiveness of atropine eye drops, our study was not adequately powered to give a valid conclusion due to the inclusion of both the eyes of the patients in the study, which would falsely raise the precision of the study for this kind of analysis. Further studies are needed to assess this correlation.
4. ATOM studies included 400 children, a sample size much larger than ours and had a placebo group for the comparison. Hence, the results of their studies are more valid while our study requires further evaluation with larger sample size and a randomized control group
5. The investigators of ATOM 1 study evaluated and reported the effectiveness of atropine based on the change in spherical equivalent as its primary outcome measure. In the present study, we used only myopic sphere for the inclusion or analysis. Atropine eye drops are essentially used to retard the progression of axial myopia and found to have no effect on the changes in the astigmatism that might happen in myopic children.[12] Hence, the change in the sphere would probably reflect the effectiveness of atropine more accurately rather than the spherical equivalent
6. ATOM studies also included masked evaluation of serial axial length measurements as a secondary outcome measure. However, the absence of axial length measurements in this study does not compromise validity of our conclusions because the cause of progressive myopia in children aged >6 years with the best-corrected vision of ≥6/6 is essentially axial. A separate investigation from the authors of ATOM studies did not find any significant change in the anterior chamber depth, lens thickness, and corneal curvature in progressive myopic children aged 7–9 years over a period of 3 years. Only significant biometric change was the axial length elongation and an increase in the vitreous chamber depth.[13]
7. A significant majority (57%) of patients in this study progressed by ≥−0.5D/year with bedtime atropine in contrast to 14% in the ATOM 1 study.[1] When switched to morning application, additional 13 patients out of 17 achieved the target reduction of <−0.5D/year progression. In ATOM 1 study or any other studies published till date, there was no evaluation of the effectiveness of daytime atropine application in comparison to nighttime atropine for progressive myopia (PubMed and Google search for the term "daytime atropine" on September 19, 2017). We believe that daytime atropine application may be more effective than the night application and needs further validation from the future studies on atropine eye drops for myopia.

The night application was probably chosen by the clinicians in the previous studies due to (1) an ease of administration and (2) because it offered partial protection against severe mydriasis and cycloplegia during the daytime when the child is most active. The peak mydriatic effect of atropine comes within an hour after instillation and the peak cycloplegic action of atropine comes in a few hours (approximately 3 h) and then phases off over 2–3 weeks.[14,15] Coinciding the peak mydriatic and/or cycloplegic effect of atropine during the daytime when the child had peak activity might be a reason for its increased effectiveness. However, despite a statistically significant difference (P = 0.02) in this study, we cannot recommend morning atropine as our study was not adequately powered.

Four patients in this study continued to have >−0.5D/year progression despite once a day, morning instillation of 1% atropine eye drops. Multiple applications of atropine eye drops, for example, twice a day or increasing the concentration of atropine to 2% or changing the formulation of atropine may not help. Answers to these questions are matter of anybody's guess and further studies are needed.

There is a clear evidence that atropine eye drops has dose-dependent efficacy for retarding the myopia, 1% being most effective (78%) followed by 0.5%, 0.1%, and 0.01% (50% effective),[2] and the rebound effect on cessation is least

with 0.01% followed by 0.1%, 0.5%, and 1%.[2,3,16] Sudden cessation of atropine drops during the years of increasing height can be associated with the rebound increase in myopia progression.[2,3,16] Nevertheless, even after the rebound progression, the absolute myopia progression after 3 years was significantly lower in the atropine group compared with placebo.[16]

In establishing clinical treatment algorithms, sudden stoppage of atropine 1 year or after 2 years of treatment is never necessary, and it was possible that if atropine had been continued longer in the ATOM studies, particularly in children whose myopia increased after atropine was stopped, and then, the overall effect may have been even better.[2]

In ATOM 2 study, 3%–4% of patients developed allergic dermatitis and conjunctivitis.[2] We excluded three patients (two patients due to intolerable photophobia and one due to allergy) due to atropine-related side effects. Previous studies have reported a lack of any significant side effects of atropine on the intraocular pressure and accommodative amplitude, and hence, both these parameters were not evaluated in this study.[1,2]

Even though there was no history of raised body temperature or facial erythema in our study, the instructions to perform punctal occlusion, keeping the lid closed for 5 min after instillation of the eye drops, and wiping the atropine solution from the facial skin if there is any overspill may be given to reduce the risk of systemic side effects.

To maintain the validity of our study, we calculated sample size using higher power (90% instead of conventional 80%) and higher significance level (1% instead of 5%). However, because of the inclusion of two eyes of the same patients, our study cannot provide definite conclusions on the correlation of age/baseline myopia and the effectiveness of atropine or the effectiveness of daytime versus nighttime application of atropine.

At present, questions remain,[2] which children would best benefit from treatment (e.g., in terms of age, level of myopia, rate of progression, and family risk factors), when and how atropine should be started and stopped, and for how long it should be used, whether to use 1% atropine eye drops for the rapid progressors or for those who do not respond adequately to lower concentrations of atropine.

Conclusion

Once a day, application of 1% atropine eye drops in this study was efficacious in retarding the progressive myopia in Indian eyes. More studies are necessary to decide the earliest age for using atropine eye drops for myopia, effectiveness of 0.01% atropine eye drops in the Indian eyes and whether atropine can be used to reduce the myopic shift in children with intraocular lens implants following the pediatric cataract surgery.

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Conflicts of interest

There are no conflicts of interest.

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