Original Article

Role of 0.01% atropine in high myopic children of Moradabad, India (RAMCOM Study)

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Purpose: Low-concentration atropine is an emerging therapy for myopia progression, but its efficacy remains uncertain among high myopic children. This study aimed to evaluate the efficacy and safety of low-concentration atropine eye drop (0.01%) in high myopic children. **Methods:** A non-randomized, parallel-group, longitudinal interventional cohort study. Myopic children were divided into two groups: (1) the intervention arm of children who received one drop of topical 0.01% atropine once a day at bedtime and (2) the control arm, in which enrolled children who were on observation only. Repeated measurements of spherical equivalent refractive errors (SERs) were performed at baseline and 1 and 2 years after treatment. **Results:** A total of 37 eyes were enrolled in the intervention arm (allocated to 0.01% atropine at year 1 follow-up) and 23 eyes in the control arm. After 1 year of 0.01% atropine therapy, the myopia progression was 0.15 ± 0.9 D in the intervention group versus 1.1 ± 1 D in the control group (P = 0.001). Similarly, after 2 years of treatment, the myopia progression was 0.3 ± 1.1 D in the intervention group versus 1.4 ± 1.1 D in the control group ($P \leq 0.001$). **Conclusion:** Compared to no treatment, 0.01% atropine treatment had shown better effect on myopia progression in high myopic children.

Key words: 0.01% atropine, efficacy, high myopia, myopia progression, safety

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Since last few decades, the prevalence of myopia is increasing globally.[1] It was estimated in one study that 49.8% of the world population will be myopic by 2050 and almost 1 billion people will suffer from high myopia (9.8% of the world population).[2] High myopia is defined as "a condition in which the spherical equivalent objective refractive error is ≥−5.00 D in either eye."[3] It is also associated with myopic macular degeneration, cataract, glaucoma, and sight-threatening retinal damage.[1,4] Due to these increased risk of complications, high myopia has a huge economic impact and is a public health concern in India[5] as well as globally.[1] Looking at its adverse social and economic impact, strategies to mitigate myopia progression are warranted in myopic as well as in high myopia patients. Strategies such as orthokeratology, peripheral defocus contact lenses, bifocal or progressive addition spectacles, and increased involvement in outdoor activities have been found effective for controlling myopia progression in children.[3,6]

To date, atropine is the only drug that has been demonstrated to have a dose-dependent inhibitor effect on myopia progression[7,8] Chua *et al*.[9] reported that high-dose atropine (1%) slowed down myopia progression by more than 75% over 2 years. Low-dose atropine (0.05% and 0.01%) has also been reported to be effective in retardation of myopia progression.[1,10,11] The most common side effect of atropine use is photophobia. Less frequent side effects are dry mouth, face flush, headache, increased blood pressure, constipation, difficulty in micturition, and central nervous system disturbances. Recent studies have reported conclusively that over 5 years, low-dose atropine (0.01%) has less side effects than high dose (0.5% and 1%) concentration of atropine.[1,11] Several studies on efficacy of atropine have been conducted on children with moderate myopia.[9-11] However, previous studies have excluded patients with high myopia (≥−5 D). The question of whether atropine has the same ability to prevent the progression of myopia in patients with high myopia remains unanswered. This study attempts to address this important clinical question. In this study, we hypothesized that atropine (0.01%) has a similar mechanism of action, safety, and efficacy in high myopes. The study was designed to assess whether topical low-dose atropine (0.01%) can prevent progression in high myopia and its safety in children. Results of the pilot phase are presented in this manuscript.

Methods

This was a non-randomized, parallel-group, longitudinal interventional cohort study. The study was approved by the institute's ethics committee (Approval No.: IRB/17-18/21) and conducted in compliance with the tenets of the declaration

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of Helsinki. The study was conducted at the pediatric ophthalmology unit of a tertiary eye care institute in North India. Written informed consent was obtained from every enrolled child's parents. Assent to participate in the study was also obtained from children more than 12 years of age. Children with high myopia between 6 and 16 years of age were included. High myopia was defined as "a condition in which the spherical equivalent objective refractive error is ≥−5.00 D in either eye."[3] Exclusion criteria were children with amblyopia, ocular hypertension/glaucoma, prior intraocular surgery, allergy to atropine eye drops, systemic diseases associated with myopia such as Marfan syndrome, Stickler syndrome, and history of cardiac or significant respiratory diseases. Children with prematurity were also excluded.

Two study arms were created: (1) the intervention arm of children who received one drop of topical 0.01% atropine once a day at bedtime and (2) the control arm, in which enrolled children who were on observation only. No active intervention was given in the control group children except routine clinical examination and monitoring. The children in the control group used single-vision eyeglasses only. The study duration was planned for 3 years. In the first year, all children of both groups did not receive topical 0.01% atropine, and routine refraction and ocular examinations were carried out. After 1 year follow-up, children of the intervention arm were given one drop of 0.01% atropine sulfate eye drop daily for 2 years. Children in the control group were followed up for 2 years and encouraged to wear their correct spectacle power.

Eligible children were screened and selected from the medical database of high myopia children. Parents of eligible children who had completed 1 year of follow-up from their first presentation and had documented high myopic refractive error at baseline and 1 year follow-up were informed about the study and invited to give informed consent for their children. This retrospective cohort was made to reduce the timeline of the study. Hence, randomization was not done. Children whose parents agreed to participate were prescribed one drop of 0.01% atropine at bedtime and were grouped in the intervention arm. Parents who agreed to participate in the study but refused to instill 0.01% atropine in their child's eye were grouped in the control arm. All children were followed up on a half-yearly basis. To minimize observational bias, the investigator responsible to assess outcome parameters was masked for this grouping. Observes were also masked for previous visit refractive error reports. The compliance was monitored by verbally asking parents about drop instillation. Cycloplegic refraction was used to assess refractive error. Refraction was done 30 min after application of a cycloplegic agent (one drop of 0.5% cyclopentolate every 5 min for 15 min). All children were advised to wear glasses constantly during the treatment, and a new lens was prescribed once the change of refraction was more than 0.5 D in either eye. Only those children who had not missed or stopped the atropine eye drops treatment during the study period were included for the analysis. The primary outcome was progression of myopia, defined as the change in spherical equivalent refractive error (SER) relative to baseline.

Statistical analysis

All the analyses were performed using commercial SPSS version 16.0 software (SPSS, Chicago, IL). Data are presented as mean and standard deviation. Tests of significance were two-tailed, and the level of significance was set as 0.05. The change in the refraction for each eye was compared with the paired *t* test. Categorical variables were reported in percentages and compared using the Chi-square test.

Results

Sixty eyes of 34 children were included in the study. In eight children, only one eye met the high myopia criteria, whereas for the rest of the children, both eyes were included. Of all, 11 (32.3%) were female children, whereas 23 (67%) were male. The average age of children was 12.3 ± 2.1 years (range: 8–16 years). A total of 37 eyes were enrolled in the intervention arm (allocated to 0.01% atropine at year 1 follow-up) and 23 eyes in the control arm. Both the groups were age- and gender-matched.

The mean baseline spherical equivalent (SE) of all children was −8.9 ± 2.7 D (range: −5 to − 16.5 D). The mean baseline SE of children enrolled in the intervention group at 1 year (Y1) was −8.9 ± 2.4 D and in the control group was −8.7 ± 3.3 D ($P = 0.81$). The mean SE at Y1 follow-up when no intervention was done was −10.5 ± 2.7 D in the intervention group and −10.3 ± 3.7 D in the control group ($P = 0.82$). [Fig. 1] The myopia progression from baseline to Y1 was 1.5 ± 1.3 D in the intervention group and 1.5 ± 1.3 D in the control group ($P = 0.96$; independent sample Mann–Whitney U Test). Concomitantly, the mean axial elongation in the control group was 0.5 ± 0.7 mm and in the intervention group (observation phase; no atropine-treated eyes till 1 year) was 0.6 ± 0.5 mm ($P = 0.82$). At Y1, there was regression of myopia recorded in one eye, no myopia progression in four (6.6%), up to 1 D progression in 27 (45%), >1 to 3 D in 19 (31.6%), and >3 D in nine (15%) eyes. At Y1 follow-up, 0.01% atropine therapy was started in 37 eyes of 19 children.

At year two (Y2) follow-up, after one year of 0.01% atropine therapy, the myopia progression from Y1 to Y2 was 0.15 ± 0.9 D in the intervention versus 1.1 ± 1 D in the control group ($P = 0.001$) [Fig. 2]. The mean axial elongation from Y1 to Y2 in the control group was 0.33 ± 0.4 mm

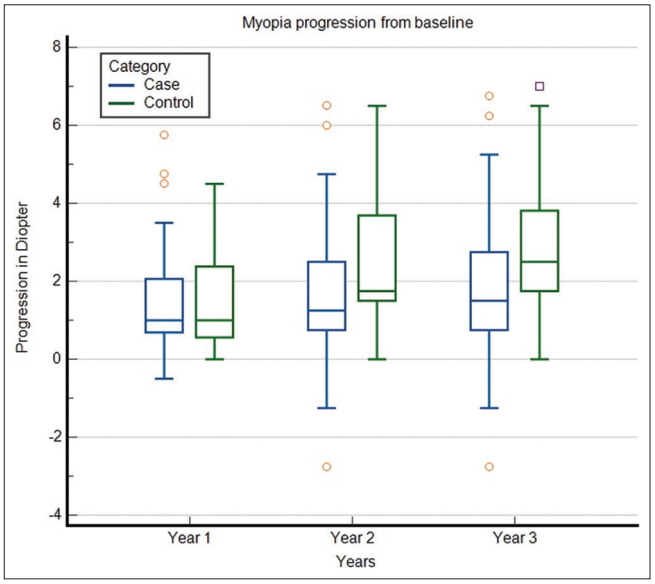

Figure 1: Myopia progression from baseline to Y1, Y2, and Y3

and in the intervention group (atropine-treated eyes) was 0.11 ± 0.29 mm (P = 0.01). The mean SE was −10.6 ± 2.5 D in the intervention group and −11.4 ± 3.6 D in the control group (P = 0.37). The myopia progression from baseline to Y2 was 1.7 ± 1.8 D in the intervention group and 2.6 ± 1.8 D in the control group (P = 0.07) [Fig. 1]. Similarly, the mean axial elongation in the control group was 0.93 ± 0.71 mm and in the intervention group (atropine-treated eyes) was 0.67 ± 0.84 mm (P = 0.21). At Y2 from Y1 in the intervention group; regression of myopia was reported in 10 (27%) eyes, no myopia progression in seven (18.9%), up to 1 D in 13 (35.1%), and >1 to 3 D in seven (18.9%) eyes. However, in the control group, no myopia progression was recorded in nine (39.1%), up to 1 D in seven (30.4%), and >1 to 3 D in seven (30.4%) eyes. This difference in all categories of progression was found to be statistically significant. The myopia progression of >3 D between Y1 and Y2 was not recorded in any eye of intervention as well as in the control group.

At 3-year (Y3) follow-up, the mean SE was −10.8 ± 2.5 D in the intervention group and −11.8 ± 3.6 D in the control group (P = 0.23). The myopia progression from baseline to Y3 was 1.8 ± 1.9 D in the intervention group and 3.0 ± 1.8 D in the control group (P = 0.02) [Fig. 1]. Similarly, the mean axial elongation in the control group was 1.0 ± 0.71 mm and in the intervention group (atropine-treated eyes) was 0.74 ± 0.92 mm (P = 0.19). The myopia progression from Y1 to Y3 was 0.3 ± 1.1 D in the intervention group versus four times, that is, 1.4 ± 1.1 D, in the control group (P =< 0.001) [Fig. 2]. The mean axial elongation from Y1 to Y3 in the control group was 0.44 ± 0.4 mm and in the intervention (atropine-treated eyes) was 0.18 ± 0.45 mm (p = 0.01). Similarly, the myopia progression from Y2 to Y3 was 0.16 ± 0.25 D in the intervention group and 0.4 ± 0.45 D in the control group (P = 0.01) [Fig. 2]. During this period, the mean axial elongation in the control group was 0.11 ± 0.18 mm and in the intervention (atropine-treated eyes) was 0.07 ± 0.19 mm (P = 0.01). At Y3 from Y2 in the intervention group, regression of myopia was recorded in two (5.4%) eyes, no myopia progression in 18 (48.6%), and up to 1 D in 17 (45.9%) eyes. Comparatively, in the control group, no myopia progression was recorded in nine (39.1%), up to 1 D in 12 (52.1%), and >1 to 3 D in two (8.6%) eyes. This difference was also found to be statistically significant. The myopia progression of >3 D between Y2 and Y3 was not recorded in any eye of intervention as well as in the control group. The spherical equivalent at different time points is presented in Table 1. The myopia progression at different time points is presented in Table 2 and Fig. 3.

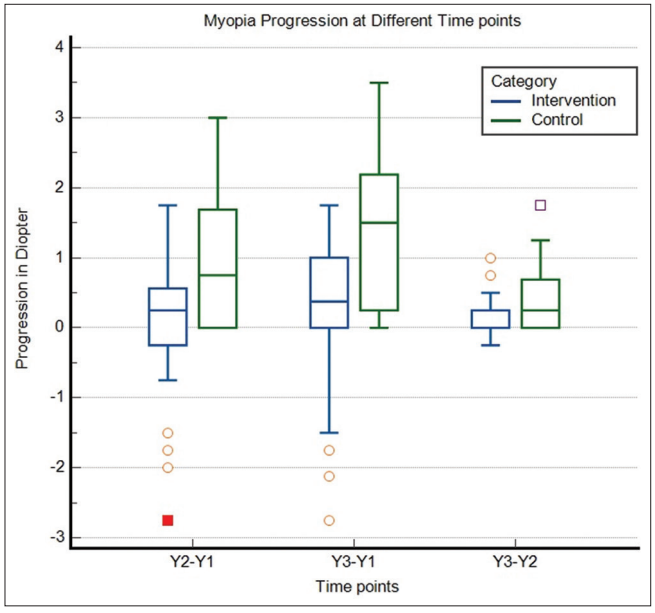

Figure 2: Myopia progression at different time points

Discussion

The results of this study showed that progression of myopia in children with high myopia was significantly less with daily topical dose of 0.01% atropine as compared to children with no active treatment. This finding is strongly corroborated

Table 1: Comparison of spherical equivalent between intervention and control groups at different time points

Variable	Intervention Group	Control Group	*P*
Mean spherical equivalent at Baseline	−8.9±2.4 D	−8.7±3.3 D	0.81
Mean spherical equivalent at Year 1	−10.5±2.7 D	−10.3±3.7 D	0.82
Myopia progression at Year 1 (Y1-Baseline)	1.5±1.3 D	1.5±1.3 D	0.96
Mean spherical equivalent at Year 2	−10.6±2.5 D	−11.4±3.6	0.37
Myopia progression at Year 2 (Y2-Baseline)	1.7±1.8 D	2.6±1.8 D	0.07
Myopia progression at Year 2 (Y2-Y1)	0.15±0.9 D	1.1±1 D	0.001*
Mean spherical equivalent at Year 3	−10.8±2.5 D	−11.8±3.6 D	0.23
Myopia progression at Year 3 (Y3-Baseline)	1.8±1.9 D	3.0±1.8 D	0.02*
Myopia progression at Year 3 (Y3-Y1)	0.3±1.1 D	1.4±1.1 D	<0.001*
Myopia progression at Year 3 (Y3-Y2)	0.16±0.25 D	0.4±0.45 D	0.01*

* Statistically significant

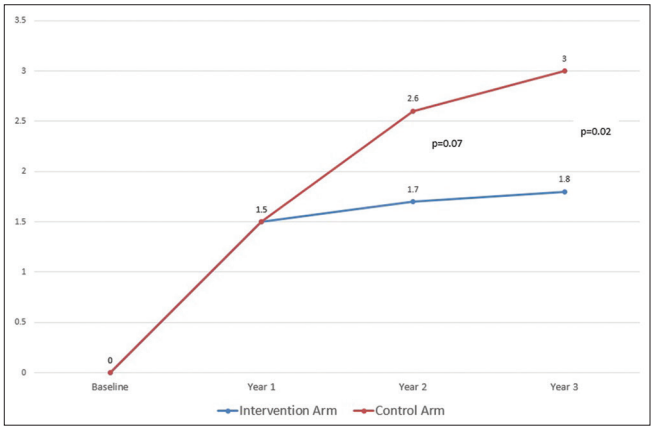

Figure 3: Comparison of myopia progression between the intervention and control groups

Table 2: Myopia progression among intervention and control groups at different time points

Variable	Category	Intervention Group	Control Group	*P*
At Year 1 (Y1-Baseline)	Regression of Myopia	1 (2.7%)	0 (0%)	0.17
	No Progression	1 (2.7%)	3 (13%)	
	Progression up to 1D	18 (48.6%)	9 (39.1%)	
	Progression >1 to 3D	12 (32.4%)	7 (30.4%)	
	Progression >3D	5 (13.5%)	4 (17.4%)	
At Year 2 (Y2-Baseline)	Regression of Myopia	3 (8.1%)	0 (0%)	0.27
	No Progression	2 (5.4%)	1 (4.3%)	
	Progression up to 1D	9 (24.3%)	2 (8.7%)	
	Progression >1 to 3D	17 (45.9%)	14 (60.9%)	
	Progression >3D	6 (16.2%)	6 (26.1%)	
At Year 3 (Y3-Baseline)	Regression of Myopia	3 (8.1%)	0 (0%)	0.08*
	No Progression	2 (5.4%)	1 (4.3%)	
	Progression up to 1D	7 (18.9%)	0 (0%)	
	Progression >1 to 3D	19 (51.4%)	15 (65.2%)	
	Progression >3D	6 (16.2%)	7 (30.4%)	
At Year 2 (Y2-Y1)	Regression of Myopia	10 (27%)	0 (0%)	0.02*
	No Progression	7 (18.9%)	9 (39.1%)	
	Progression up to 1D	13 (35.1%)	7 (30.4%)	
	Progression >1 to 3D	7 (18.9%)	7 (30.4%)	
	Progression >3D	0 (0%)	0 (0%)	
At Year 3 (Y3-Y1)	Regression of Myopia	6 (16.2%)	0 (0%)	0.006*
	No Progression	6 (16.2%)	6 (26.1%)	
	Progression up to 1D	16 (43.2%)	2 (8.7%)	
	Progression >1 to 3D	7 (18.9%)	14 (60.9%)	
	Progression >3D	0 (0%)	1 (4.3%)	
At Year 3 (Y3-Y2)	Regression of Myopia	2 (5.4%)	0 (0%)	0.07
	No Progression	18 (48.6%)	9 (39.1%)	
	Progression up to 1D	17 (45.9%)	12 (52.2%)	
	Progression >1 to 3D	0 (0%)	2 (8.7%)	
	Progression >3D	0 (0%)	0 (0%	

*Statistically significant

by the concomitant findings of significantly less axial length elongation in the atropine-treated eyes as compared to untreated eyes. To the best of our knowledge, there has been no study comparing benefits of low-dose atropine in high myopes with a control group. In our study, at baseline, there was no statistical difference between the two arms in terms of refractive characteristics. The myopia progression during the first year was also the same in both arms. Concomitantly, the axial length elongation was also the same in both groups. This reveals that both groups were matched and comparable. After starting treatment with 0.01% topical atropine, the myopia progression at Y2 from Y1 follow-up in the intervention arm was significantly less than that in the control arm. However, the progression from baseline to Y2 was not statistically significant ($P = 0.07$). As these are the results of the pilot study and sample size calculation was not done, this non-significant difference in the progression between the intervention and control arm may have attributed to the less sample size.

Over 2 years in this study, 0.01% atropine achieved a 78% reduction in myopia progression among high myopes as compared to control. Chua *et al*. reported a 77% reduction in myopia progression at 2 years.[9] Kothari *et al*.[12] also reported a 67% reduction by using atropine in myopia in children from India. Both these studies used 1% atropine.[9,12] Wu *et al*.[13] also reported that the adjusted progression of myopia in the 0.05% and 0.1% atropine-treated groups was significantly lower than that of the control group. In previous studies, 3 years of treatment with 0.01% atropine showed the slowest progression of myopia.[11,14,15] In addition, over 5 years, 0.01% atropine eye drops were more effective in slowing myopia progression with less visual side effect compared with a higher dose of atropine.[11,14,15] All these studies included moderate myopes only, whereas our study reported similar results in high myopic children. One-year treatment of 0.01% atropine achieved a 54% reduction, and two-year treatment resulted in a 78% reduction in mean progression. The Atropine in the Treatment Of Myopia (ATOM 2) study reported that cessation of treatment often resulted in a myopic rebound effect, which was more pronounced in eyes that received 1.0%, 0.5%, and 0.1% atropine than in eyes that received 0.01% atropine.[15] Loh *et al*.[16] reported that the greater severity of myopia is a risk factor for myopia progression despite receiving atropine treatment. However, in our study, between Y2 and year 3 (Y3), no progression was reported in 48.6% children with

high myopia. These results highlight the potential efficacy of continuous use of 0.01% atropine in high myopic children. This also suggests that atropine delays the onset of action in high myopic children. Between Y2 and Y3, the regression of myopia was reported in two children. However, the exact mechanism of action of atropine causing regression is unknown to us. Future studies are required to explore this effect. Considering these encouraging results of the pilot phase, we have started a randomized clinical trial to assess the safety and efficacy of 0.01% atropine in high myopic children of 6–16 years of age.

There were a few limitations of this study. Being non-randomized, families chose whether they wanted their child to receive treatment. This may have introduced bias due to parents who were more concerned about myopic progression deciding to be in the intervention group. The compliance was monitored by asking parents about instillation of drops; as per parents, all children were 100% compliant with the treatment, although there may be a recall bias.

Conclusion

In conclusion, among high myopia children, myopia progression can be slowed by 0.01% atropine treatment. The 0.01% atropine treatment was well tolerated and no serious adverse effects were observed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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