To assess role of atropine 0.01% eye drops in myopia progression and its effect over ocular surface

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ABSTRACT:

Purpose: Assessment of Eye drop Atropine 0.01 % in controlling myopia progression and its effect on ocular surface. **Methods:** The Prospective study was conducted on 50 participants aged 8-16 years with progressive myopia > 1D/year attending Outpatient department, Department of Ophthalmology, of a Multi-Speciality tertiary health care hospital & research centre. Participants received 0.01 % atropine eye drops once at night in both eyes. Myopic progression (MP), axial length (AL) elongation, ocular surface and any adverse reactions to atropine 0.01 % eye drops are recorded at baseline, 6 months and 1 year. **Results:** Out of 50 participants, 45 (90 eyes) completed study. After 1 year MP was only - 0.52 D (IQR 0.38-0.75), which was statistically significant than baseline MP of more than -1.0 D. Changes in MP, AL was statistically significant in all age groups, baseline MP and gender. No adverse events and no significant changes in ocular surface were noted. Out of 45 participants 6 were non responders (MP> - 0.75 D), other 39 participants were good responders (MP< -0.75 D). There is a moderate negative corelation of age with MP and AL (r= -0.43; r= -0.48 respectively). The children in the non-responder group were younger and having high baseline SE and baseline MP than the responder group, the data was statistically significant ($p<0.001$). **Conclusion:** The results of current study showed the effectiveness of 0.01% atropine in reducing MP and axial length in Central Indianeyes in 1 year.

Keyword: Myopia, .01% Atropine, Myopia Progression

INTRODUCTION:

Progressive myopia in growing children is one of the most prevalent ocular disorder and has become a major health burden in the modern world.[1] The World Health Organization (WHO) defined“high myopia” as −5 Diopter (D) or greater, which isassociated with

increased risk of blindness [2]. Eyes withhigh myopia that develop degenerative changes in themacula, optic nerve and peripheral retina are considered ashaving pathologic myopia, and are at the highest risk ofdeveloping potentially blinding complications [3,4]. Topical atropine has emerged as the most effective and promisingtreatment modality in myopia control for over several decades [5-7]. Topical atropine at a 1% concentration as shown to slow myopia progression and axial elongation in Asian children [8]. However, despite having satisfactory effect of myopia control, adverse effects, such as photophobia and accommodative paresis, allergic conjunctivitis, dry eyes can beproblematic in children, associated with poor treatment results due to inadequate adherence to the therapy [9,10,11]. Hence, a lower concentration of atropine has been used to meet the balance between treatment efficacy and minimal side effects [12]. Recently, 0.01% atropine has gained increased attention among pediatric ophthalmologists for treating childhoodmyopia [13].

Mechanism of atropine action is through the up- and downregulation of retinal andscleral muscarinic receptors with influence on the scleralmatrix has been postulated [14, 15]. Also, atropine might have function at a relatively lower dose, through M1/M4 receptors in the retina. On the other hand, a non-muscarinic anda direct influence of atropine on the scleral fibroblasts couldalso contribute to the effect [16].

Therefore, considering long term use of Atropine 0.01 % in young children safety, efficacy are important aspects. There are still less studies in Indian population. Therefore, the aim of this study is to evaluate the role of controlling myopia progression by low dose 0.01% Atropine drops along with its effects & safety for ocular surface in young children.

SUBJECTS AND METHODS:

The design was a prospective, single centre, interventional study conducted over one year in the Ophthalmology department of a tertiary care hospital and research centre of central India. The study protocol received Institutional ethical committee approval. Previous records of myopic children who underwent cycloplegic refraction at department of ophthalmology in last one year were screened and 50 children of age 8-16 years were selected for the study with Inclusion criteria of myopia ranging from -2.0 D to -6.0 D Spherical Equivalent (SE) in both eyes, SE progression of equal to or greater than 1.0 D in the preceding year, astigmatism of 1.5 D or less, anisometropia of 1.5 D or less and best corrected visual acuity(BCVA) better than 6/9 were selected.Patients withpaediatric pathology (e.g., amblyopia, strabismus, cataract or systemicdisorders), low vision due to retinal dystrophies, any allergies to Atropine eye drops or under any other treatment for myopia control were excluded. Written informed parentalconsent (parents or legal guardians) was taken and verbal consent from participants was obtained.

All participants underwent a detailed ophthalmological examination at the time of recruitment. Best-correctedvisual acuity was measured with Snellen distance chart. Cycloplegic autorefraction was performed using an auto refractor (NIDEK Autorefractor-Keratometer). Ultrasound biometry was performed and a mean of 3 readings was taken for axial length. Hirschberg test and cover-uncover test were done to look for any manifest squint. Schirmer’s 1 test and tear film breakup time (TBUT) was done to assess ocular

surface. The annual baseline rate of MP (BMP) in the child was calculated based on the cycloplegic refraction available in the documented previous-year dataof the patient. A full refractive correction was prescribed to each participant during enrolment.

All participants received treatment with 0.01% Atropine eye drops every night in both eyes for a period of 1 year.

Participantswere followed up at 6 months and at one year. Cycloplegicrefraction in terms of SE and axial length were measured at each follow-up. Any change inthe SE of ≥ 0.5 D on follow-ups was prescribed.Ocular surface disease index(OSDI) for dry eyes[17], Schirmer's 1 test and TBUT recorded at each follow up.

Insufficientresponse was considered present when myopia progressed >- 0.75 D/year, and AL increased >0.2mm/year while good response as SE≤ -0.75D/year and AL ≤ 0.2 mm/year.

STATISTICAL ANALYSIS:

Statistical analysis was done by IBM SPSS software V 22.0. Normally distributed continuous variables were described as mean and standard deviation while SE and AL showed skewed deviation, so median and interquartile range (IQR) was also calculated. Differences in progressionrates in SE and AL were obtained with Wilcoxonsigned-rank test. Correlation between annual progression ofSE and AL was calculated with Pearson's regressionanalysis. Mann- Whitney U test was employed to compare the median difference of MP and AL changes between subgroups. Nonparametric Friedman test was done for statistical comparison of OSDI, TBUT and Schirmer's 1 test at different time points.Throughout the study, $p < 0.05$ was used ascriterion of statistical significance.

RESULTS:

Among the 50 subjects enrolled for study, 5 were lost to follow up within first 4 months, rest 45 subjects (90 eyes) completed the study. Out of 45 subjects, there were 25 males & 20 females. The distribution of children aged 8 to < 12 yearsand≥ 12 years to 16 years were 23 and 22subjects respectively. Age distribution and gender distribution at baseline was statistically insignificant.

Baseline Parameters: All baseline parameters are shown as in [Table 1]

Table 1: Baseline parameters.

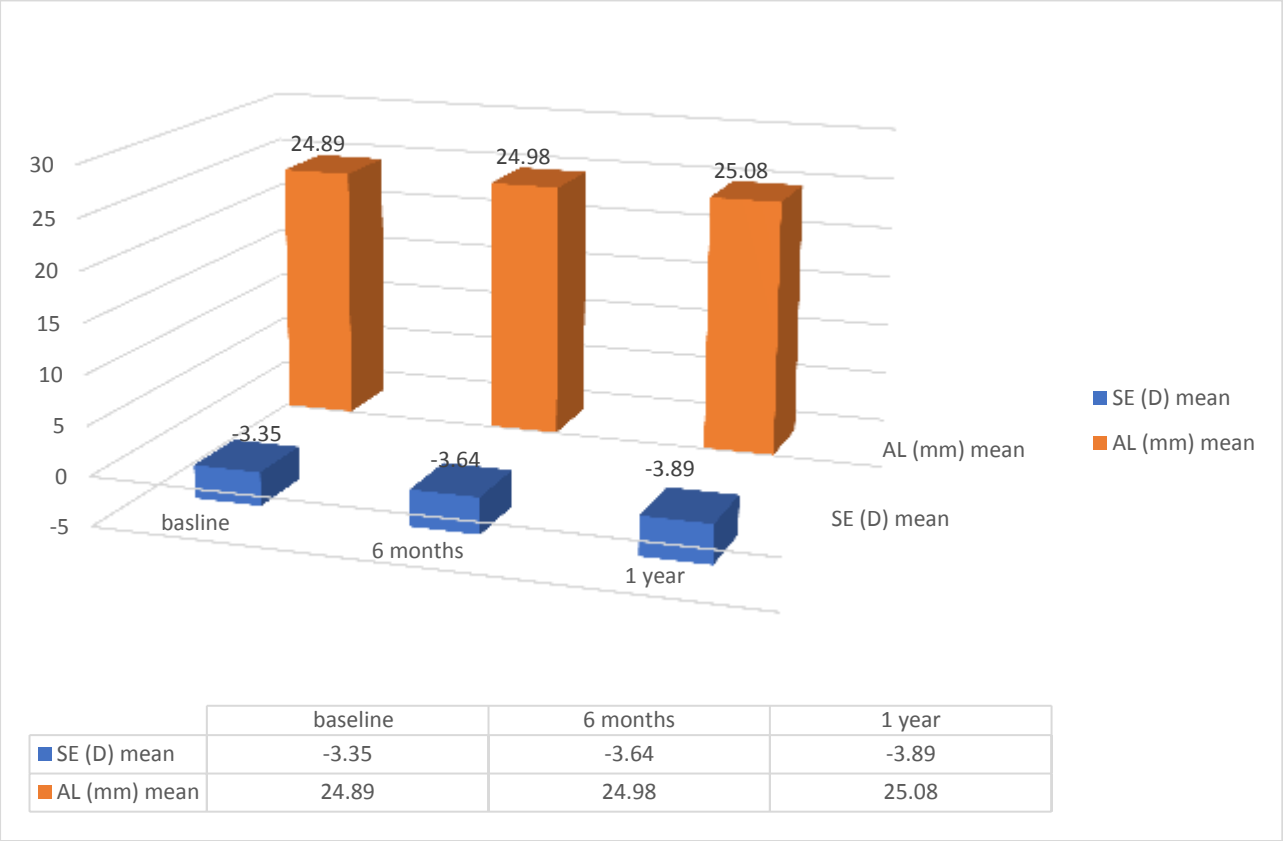
Baseline Parameter	
Mean age	11.76 ± 2.45 years
Mean SE 1 year prior to study	-2.25 ±0.75D
Mean SE at start of study	-3.35 ±0.55 D
Baseline MP	-1.10 ±0.58 D
Mean AL at start of study	24.89± 0.18 mm

Parameters Studied: Mean SE and Mean AL, OSDI, TBUT, Schirmer's 1 test was done at baseline, 6 months and at 1 year.

Myopic progression (MP): total change in SE from baseline to last follow up at the end of 1 year. After 1-year mean MP in 90 treatment eyes was 0.54± 0.45 D. This reduction in MP from baseline MP was statistically significant (p <0.001).

Axial length (AL) change: total change in axial length in 90 treatment eyes was 0.18± 0.11 mm. it could not be compared with progression with those prior to treatment as AL data prior to treatment was not available in all participants.

Figure 1: Mean changes in SE (D) and AL (mm).



	baseline	6 months	1 year
SE (D) mean	-3.35	-3.64	-3.89
AL (mm) mean	24.89	24.98	25.08

The corelation between SE and AL measured during the study was strong with Pearson's r: 0.72 (p<0.01).

Out of 45 subjects 6 were non responder at the end of 1 year (MP> - 0.75 D), 39 were good responder (MP< - 0.75 D).

The gender distribution between responder and non-responder was insignificant. There is a moderate negative corelation of age with MP and AL (r=-0.43; r=-0.48 respectively). The children in the non-responder group were younger and having high baseline SE and baseline MP than the responder group, the data was statistically significant (p<0.001). [Table 2]

Table 2: Distribution between Responder and non-responder group.

	Entire cohort	**Good Responder**	**Non-Responder**	**P value**
Number (eyes)	45(90)	39(78)	6(12)	

Males	25(50)	22(30)	3(6)	0.957
Females	20(40)	17(28)	3(6)	
Baseline age	11.76 ± 2.45	13.86 ± 1.12	8.42 ± 0.40	<0.001
Baseline SE	-3.35 ± 0.60 D	-3.54 ± 0.75	-5.10 ± 1.1 D	<0.001
Baseline MP	-1.10 ± 0.58	-0.92 ± 0.24 D	-1.35 ± 0.40 D	<0.001
Total SE Change	-0.56 ± 0.45 D	-0.48 ± 0.25 D	-1.19 ± 0.48 D	<0.001
Total AL Change	0.18 ± 0.11 mm	0.14 ± 0.08	0.28 ± 0.11	<0.001

The ocular surface symptoms of the participants which were taken into consideration were evaluated at baseline, 6 months and at 1 year. Dry eye symptoms were evaluated using OSDI score showed insignificant changes in dry eye cases from baseline to at the end of 1 year. Tear film breakup time (TBUT) and Schirmer's 1 test showed insignificant changes from baseline to end of 1 year. Only 4 eyes of 2 participants showed mild discomfort after immediate administration of drops which also subsided within few minutes after administration. No subjects complained of red eye or any blurring of vision during the whole study period.

Table 3: Ocular Surface analyzing Parameters.

	Base Line	**6 Months**	**1 year**	**P value**
OSDI	10.4 ± 2.1	11.01 ± 2.6	10.8 ± 2.5	0.423
Schirmer's 1	20.85 ± 2.69	20.55 ± 2.5	20.75 ± 2.55	0.729
TBUT	11.49 ± 4.94	11.6 ± 4.36	11.28 ± 4.89	0.339

DISCUSSION:

This 1-year study showed that once nightly dose of 0.01 % atropine eye drops achieved a clinically and statistically improvement in delaying the myopia and axial length progression in 8-16 years participants of central India.

Studies [10, 19, 20] reported the efficiency of low-concentration atropine in controlling myopiaprogression for more than 2 years. Also, studies [23, 24] have reported the efficacy of low dose atropine in slowing axial length elongation.

In ATOM2 study [10] 400 children in Singapore randomized in 2:2:1 ratio to receive 0.5%, 0.1%, and 0.01% atropine per night for 2 years. The mean MP in the first 24 month was −0.30 ± 0.60 D, −0.38± 0.60 D, and −0.49 ± 0.63 D andthe mean change in axial length was 0.27 ± 0.25, 0.28 ± 0.28, and 0.41 ± 0.32mm in the 0.5%, 0.1%, and 0.01%atropine arms respectively. Atropine wasstopped at the end of 2 years, and all participants weremonitored for a year. During this 'wash-outperiod', reboundprogression of myopia was more

prominentin the 0.5% atropine group (−0.87 ± 0.52 D), comparedto the 0.1% (−0.68 ± 0.45 D) and 0.01% group (−0.28 ± 0.33 D, $p < 0.001$). The overall progression ofmyopiain the 0.01% atropine group was significant lowest (−0.72 ± 0.72 D) at the end of the 3rdyear.Also, eyes in the0.01% atropine group experienced the least increase in axiallength (0.19 ± 0.13 mm), compared to eyes in the 0.5% and0.1% atropine group at the end of 3rd year

During phase 2 of the LAMP study [19] in Hong Kong China, the efficacy of 0.01% was slightly better during the second than the first year. Amulticentre case–control retrospective study in a multi-ethnic cohort of children using 0.01% atropine in the USA [20] showed a change in SE of − 0.3 D during the first year and − 0.2 D during the second year. It is postulated that 0.01 % atropine can have good efficacy over longer period due to cumulative effect over longer time.

In the current study, baseline age had a negative correlation with AL increase and MP in myopic childrenusing 0.01% atropine. Younger, the children were at baseline, more the AL elongation was evidentat the end of the study period. This was consistent with three other studies which explored the same relationshipbetween baseline age, MP and AL increase in myopic children using atropine. Wei *et al*. [21], Joachimsen *et al*. [25], and Lee *et al*. [26] found while using 0.01%, 0.01% and 0.05% atropine, respectivelythat in younger childrenmyopic progression and axial length elongation is more. In current study, participants having lower initial myopia showed good response, this is similar to the retrospective study conducted in theUnited States with higher myopia (− 2.0 D) on average, the author concluded that 0.01% atropine was mosteffective in low initial myopia [22].

Atropine's action is related to pharmacological antagonism of the muscarinic receptors in the lacrimal gland, which causes a significant decrease in aqueous production, with an evident modification of tear stability. It has been described that the ocular surface (cornea, conjunctiva, and accessory lacrimal glands), meibomian glands, and the main lacrimal gland are interconnected by neural reflex loops that maintain an integrated "functionalunit." [27] The neural reflex loops are involved in maintaining the normal tear physiology and can be blocked by atropine [28]. Previous studies [8-12] showed ocular discomfort, dry eyes, near blur but in current study after administration of 0.01% atropine for 1 year, there were no significant changes in the indices for aqueous production and tear stability. This might be related to the low concentration of atropine in the eye drops.

CONCLUSIONS:

The results of current study showed the effectiveness of 0.01% atropine in reducing MP and axial length in Indian population in 1 year. Further studies can be done for longer duration to assess effect of 0.01 % atropine over MP, axial lengthand ocular surface. Also, current study showed that participants having younger age and high baseline SE had the alarming possibility of progressing to higher myopia, thus further studies required in such cases to provide adequate treatment regimens with different atropine concentrations according to basic characteristics of patients.

Funding: No funding sources

Conflict of interest: None declared

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