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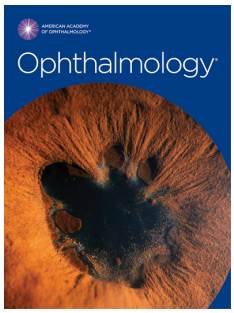

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Atropine for treatment of childhood myopia in India (I-ATOM): multicentric randomized trial

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Abstract

This multicentric, double-blinded, placebo-controlled randomized clinical trial reports 1-year-data proving efficacy of 0.01% atropine drops in reducing myopia progression (spherical equivalent) in Indian children having mild to moderate myopia without any significant effect on axial length elongation.

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Myopia is rapidly emerging as a major public health problem worldwide. A recent meta-analysis documents an increasing trend of myopia in the last four decades in India with a prevalence of around 7.5%.[1] Atropine for the treatment of childhood myopia in India (I-ATOM) was a multicentric, double-masked, placebo-controlled randomized clinical trial conducted at 3 tertiary centers to evaluate the one year efficacy of 0.01% atropine in myopic children with Indian ethnicity. This trial was registered in clinical trial registry, India (CTRI/2016/11/007450) and followed the tenets of declaration of Helsinki. Institutional ethics committee approval was obtained by all participating centers and informed consent was taken from parents/guardians. One hundred children aged 6-14 years having -0.5D to -6D of myopia on cycloplegic refraction, astigmatism ≤1.5D, anisometropia ≤1D, distance best-corrected visual acuity (BCVA) of 20/40 or better and documented myopia progression of >0.5D in the preceding year were enrolled. Our primary outcome measure was change in spherical equivalent (SE) and axial length (AL) at 1 year in cases compared to controls. Secondary measures were change in anterior chamber depth (ACD), lens thickness (LT), vitreous chamber depth (VCD), pupil size, accommodation amplitude (D) and any side effects related to therapy.

The participants were randomized in 1:1 ratio to either atropine or placebo group using computer generated random numbers. Baseline evaluation included assessment of BCVA using ETDRS chart at 4 meters (converted to the logarithm of the minimum angle of resolution, logMAR scale), distance-corrected near vision (DCNVA) using Snellen's near vision chart at 33 cm, near point of accommodation (NPA) using Royal Air Force (RAF) ruler, photopic and mesopic pupil size using PLR-200™ monocular infrared pupillometer (NeurOptics, Irvine, CA) and ocular biometry using IOL master 700 (Carl Zeiss, Meditec AG). The refractive error was noted as spherical equivalent (SE). Accommodation amplitude was calculated as inverse of NPA (in meter).

Commercially available 0.01% atropine sulphate eye drops with stabilized oxychloro complex as preservative (Myopin®, Appasamy Ocular Devices (P) Ltd., Solan, H.P, India) was used. The vehicle, preservative and pH were same in atropine as well as placebo eye drops. Bottles, similarly labeled with the subject identification number and date of expiry, were distributed to all participating centers. The investigators and the participants were masked to the type of intervention. After explaining to the parents about the dose (single drop), time (before bedtime at night), method of administration (in supine position after pulling the lower eyelid) and expected side effects (photophobia, blurring, flu-like symptoms, rashes etc.), bottles were dispensed on every visit. An optometrist who was masked to the group allocation reassessed the parameters on follow-up at 2 weeks, 2 months, 4 months, 8 months and 12 months. Parents were asked to self-report any side effect with topical therapy and subsequently

directly asked about the symptoms. Compliance was monitored by collection of used bottles on every visit. After 1 year, all the participants were started on 0.01% atropine eye drops.

Age (atropine=10.6±2.2years; placebo=10.8±2.2years), mean SE (atropine: -3.5±1.3D; placebo: -3.7±1.3D) and other baseline parameters between the two groups were comparable (Supplemental Table 1). Of 100 recruited children, 8 were lost to follow-up (3 in atropine-treatment group and 5 in placebo-control group).

Mean increase in myopia (SE at 1 year minus baseline values) was -0.16±0.4D (*P*=0.005) in atropine group and -0.35±0.4D (*P*=<0.001) in placebo group (Table 1, Supplemental Figure 1). The difference of mean SE between the two groups was 0.19D (*P*=0.021) with significantly greater myopia progression in placebo compared to atropine group (Table 1). Mean AL elongation in atropine-treatment and placebo-control group was 0.22±0.2mm (*P*=<0.001) and 0.28±0.28mm (*P*=<0.001) respectively at 1 year (Table 1, Supplemental Figure 1). Although, the difference in AL change between the groups (0.06mm *P*=0.19) did not reach statistical significance, there was a greater elongation in the placebo group (Table 1). Similarly, mean change in other ocular biometric parameters like ACD, LT and VCD were not significantly different in the two groups (Table 1, Supplemental Table 2). These findings corroborate with the results of Atropine for the treatment of childhood myopia (ATOM2)[2] and low concentration atropine for myopia progression (LAMP) study[3] where favorable effects of 0.01% atropine in inhibiting myopic SE progression has been observed with minimal effect on AL elongation.

No myopia progression (<0.25D increase in SE) was noted in 64% (n=30) children in atropine-treatment group compared with only 30% (n= 13) in placebo-control group; myopia progression >0.5D was seen in 13%(n=6) cases in atropine group compared with 38%(n=17) in placebo group. Younger age and higher myopia at baseline have been associated with poor response to atropine therapy.[4] In this study, mean age and SE of patients showing myopia progression >0.5D was 11±2 years (Range: 7 to 13yr) and -3.12±1.07 D (Range: -2 to -5D) respectively in atropine group. A rapid progression (>1D) that has been noted in the atropine-treatment group in 18%-28% children with Chinese ethnicity[2,3] was seen in none of our atropine-treatment cohort and remained low even in the placebo group (n=4; 8.9%). This was also seen in North India Myopia (NIM) study[5] that noted rapid myopic shift of >1D in only 7.4% of 1279 children at 1 year. This is attributed to either less rapid myopia progression or low environmental risk factors in Indian children.

Mesopic and photopic pupil size, accommodation amplitude, distance and near vision remained stable on follow-up and did not change significantly between the groups (Table 1, Supplemental Table 2). None of the patients reported any blurring of vision, photophobia or

required discontinuation of therapy. In patients who were lost to follow-up, the reason for discontinuation was unrelated to the side effects.

The I-ATOM study noted a significant reduction of 54% reduction in mean SE progression with 0.01% atropine at 1 year in myopic children with no side effects. Mean AL elongation although, was 21% less in atropine group than placebo but was not statistically significant. Limitations of this study include a short follow-up, relatively small sample size, lack of comparison of other atropine strengths (0.05% or 0.02%)[3,6-7] and unanswered questions like optimal duration, rebound effect and whether 0.01% atropine definitely reduces AL elongation. Nonetheless, the results show a similar efficacy of 0.01% atropine eye drops in Indian children with mild to moderate myopia as seen in other ethnic groups.

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Table 1: Comparison of mean change in characteristics of two study groups after 1 year

Variables (Mean ± S.D.) [95% CI]	**Atropine group [n = 47]**	**Placebo group [n=45]**	***P* value^**
Spherical Equivalent (D)	-0.16 ± 0.38 [-0.05 to -0.26]	-0.35 ± 0.4 [-0.23 to -0.48]	0.02
Best corrected visual acuity (logMAR)	0.002 ± 0.08 [.025 to -0.02]	0.002 ± 0.03 [-0.006 to 0.01]	0.98
Axial length (mm)	0.22 ± 0.2 [0.16 to 0.27]	0.28 ± 0.28 [0.21 to 0.37]	0.19
Anterior chamber depth (mm)	0.03 ± 0.16 [-0.02 to 0.07]	-0.01 ± 0.15 [-0.06 to 0.03]	0.2
Lens thickness (mm)	0.01 ± 0.14 [-0.03 to 0.05]	0.05 ± 0.21 [-0.01 to 0.11]	0.64
Vitreous chamber depth (mm)	0.17 ± 0.19 [0.11 to 0.22]	0.24 ± 0.21 [0.18 to 0.3]	0.11
Amplitude of accommodation (D)	-0.98 ± 1.86 [-0.44 to -1.52]	-1.25 ± 2.01 [-0.67 to -1.82]	0.53
Mesopic pupil size (mm)	0.05 ± 0.43 [-0.07 to 0.17]	-0.12 ± 0.64 [-0.3 to 0.06]	0.15
Photopic pupil size (mm)	0.02 ± 0.47 [-0.11 to 0.16]	-0.06 ± 0.58 [-0.64 to 0.52]	0.45

^ *P* value evaluated using Wilcoxon signed-rank test

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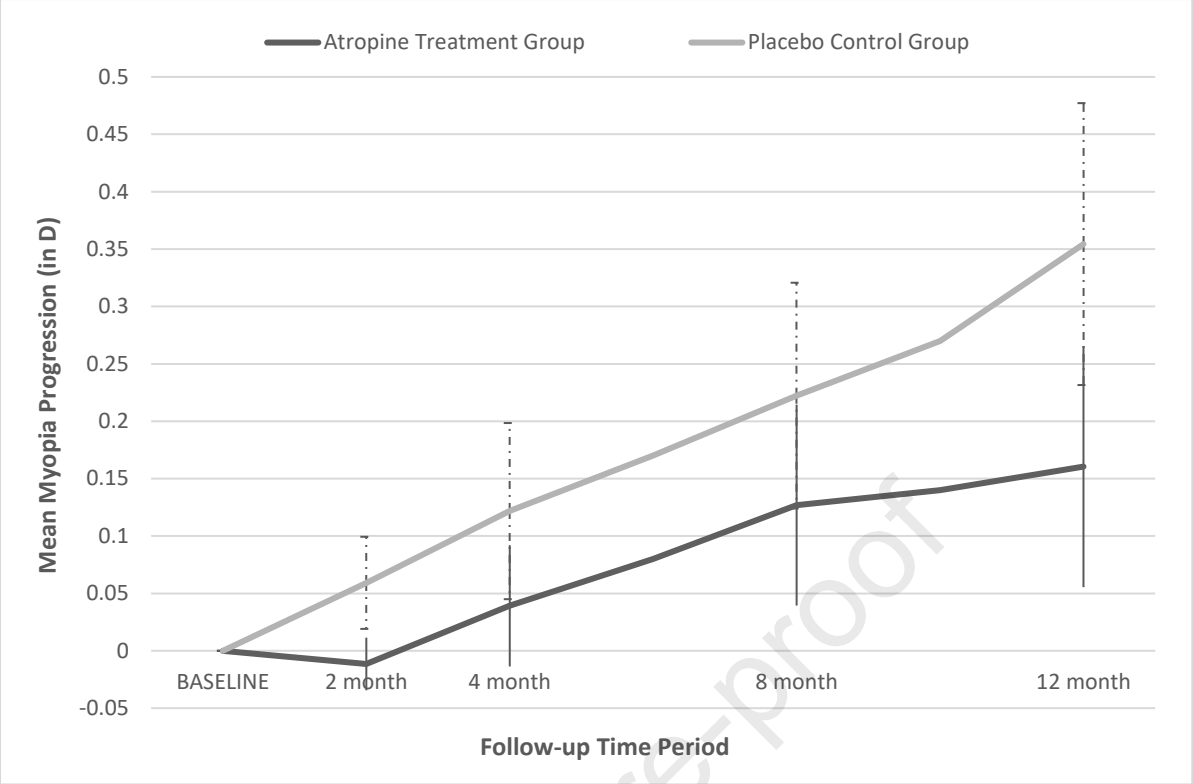

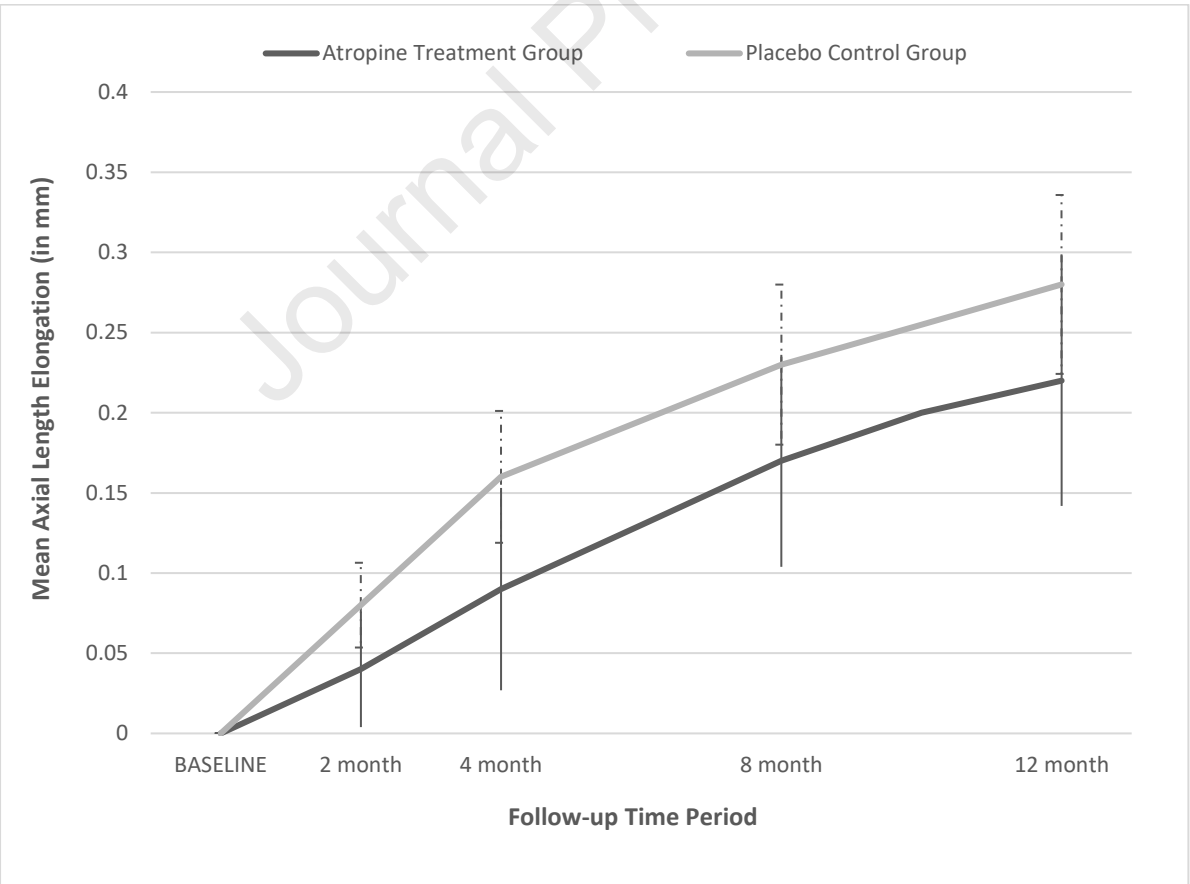

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