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Efficacy And Safety Of Low Dose Atropine Eye Drops In Myopia Control Among Paediatric Patients

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Abstract

Background : Myopia is the most common refractive error in India as well as worldwide. Our study aimed to evaluate the effectiveness of atropine sulphate 0.01% eyedrops in controlling myopia progression among children.
Methods : This retrospective observational study was conducted at Chacha Nehru Bal Chikitsalaya (CNBC), Delhi. Medical records of myopic children aged 5 to 14 years attending Eye clinics from 2021 to 2023, were analysed. Children with spherical equivalent refraction(SER)≤-1.5 D were included, and those with astigmatism > 2D were excluded. Data obtained was divided into two groups: group 1 of 96 children(mean age 9.02 ± 2.16 years) using single vision eye-glasses only, and group 2 of 94 children (mean age 8.71 ± 2.1 years) using both atropine 0.01% eyedrops at bedtime and single vision eye-glasses. Characteristics including age, gender, cycloplegic refraction data were noted. Statistical analyses were done to evaluate changes in SER over 24 months.
Results : The average baseline SER for the control (n = 96) and atropine(n = 94) groups were similar (-5.67± 3.1D and -5.89 ± 2.9 D respectively, p value=0.48). The mean progression in SER from baseline was significantly less for the atropine group than the control group at year 1 (-0.5±0.38D compared with -0.965±0.59D, p<0.001) and at year 2 (-0.86±0.57 D compared with-1.89±1.03 D, p <0.001).
Conclusion : Low-dose atropine significantly slowed the rate of myopia progression in paediatric patients, combined with benefit of favourable safety profile.

Keywords: Myopia, atropine , spherical equivalent refraction (SER), children

Introduction

Refractive error is the leading cause of treatable ocular morbidity among children. Myopia, the most common refractive error, continues to be global health burden worldwide in modern times, and contributes significantly to ocular morbidity among children. Uncorrected myopia can lead to impaired academic performance, difficulty in sports activities and overall compromised quality of life. Decrease in outdoor activities together with long duration of near work owing to educational needs, acted as a major environmental factor leading to early onset and high prevalence of myopia in paediatric population. Interplay of genetic and environmental factors has always been implicated in etiology of myopia. Unprecedented rise in childhood myopia in recent decades emphasises the need to address the role of environmental factors in more comprehensive manner. Overall prevalence of myopia is expected to increase to about 50% by 2050, which equates to nearly 4.8 billion myopics worldwide by that time. Global

prevalence of high myopia was about 4% in 2010, which is projected to reach staggering estimate of around 9.8 % by 2050, amounting to nearly 940 million by that time [**1**].A meta-analysis found increase in global prevalence of myopia from 24.32% to 35.81%, spanning over the years from 1990 to 2023 [**2**]. Several studies concluded myopia as most common refractive error in age group 6-15 years,in urban as well as rural populations in India [**3**]. A cross-sectional population based survey conducted in urban school-going population over the time period December 2000 to March 2001 in a part of New Delhi, India found prevalence of myopia as 7.4% [**4**]. North India Myopia study (NIM study), carried out in January-February 2020,found prevalence of myopia as 13.1% among urban school children in Delhi [**5**].Addressing the overall burden of refractive errors in ocular morbidity, School eye screening program, launched in year 1994 is the second largest program of the National Program for Control of Blindness(NPCB) in India after cataract surgery. It comprises screening of refractive errors including myopia among school-going children.

Unlike many previous studies, our observational study included patients with high myopia also. As high myopia is associated with many vision threatening complications, the need to explore measures for myopia control is imperative in these subjects. Hallmark of pathological myopia is presence of typical fundus findings like posterior staphyloma or myopic maculopathy. Each 1 Diopter(D) progression in myopia aggravates the risk of myopic maculopathy by 58 %, retinal detachment by 30 %, glaucoma by 20 %, posterior subcapsular cataract by 21% [**6**]. Some studies found prevalence of pathologic myopia ranging from 1% to 19% in low myopia(upto -3D) population, while it was noted as high as 50% to 70% among high myopics [**7,8,9**].

Greater time spent outdoors was found to be associated with reduced rate of onset of myopia, but there is no conclusive evidence to support its role in controlling progression among subjects who are already myopic [**10,11,12**].

Digital revolution, more so in past two decades further added to the insufficiency of time spent outdoors by children. Longer duration of indoor stay during Covid-19 pandemic resulted in delayed detection of short sightedness by caretakers of children. Pre-myopia, a refractive status of eye with spherical equivalent (SE) of $\leq$+0.75 D and > -0.5 D in children, with threshold SE defined as per age, predicts high risk of progression to myopia in future [**13**].Early the onset of childhood myopia, higher the spherical equivalent at the time of refractive error stabilisation. After the onset of myopia in children, the rate of myopia progression is around -1 D per year in East Asians and about -0.5 D per year in Caucasians [**14**].Hence it is crucial to intervene early to delay the onset of myopia and control progression of myopia in children during the years of most active eye growth.

Higher the myopia, higher the risk of complications such as retinal neovascularisation, retinal detachment, macular degeneration, foveoschisis, posterior staphyloma, early onset glaucoma, early onset cataracts. Delay in detection of childhood myopia has aggravated the burden of amblyopia. Children spending more hours indoors for near work reported late for refractive error screening. Hence regular screening camps for children are crucial to timely detection of refractive errors. Younger myopic children appears to be more sensitive to environmental influences than older myopics, as younger myopes are in more crucial phase for myopia development and progression[**15**].

Existing strategies for myopia control in children and adolescents include optical correction comprising single vision/bifocal/progressive addition/defocus incorporated multiple segment(DIMS) spectacles and contact lenses, orthokeratology and pharmacological interventions. Effectiveness of topical atropine for myopia control is evident in several clinical studies [**16,17,18,19**]. Though topical Pirenzepine 2% gel proved effective in slowing myopia progression in clinical trials, its therapeutic use in control of myopia is on hold due to regulatory and financial concerns [**20**]. 7-MX (7-methyl xanthine), a non-selective adenosine receptor antagonist, has been found to be effective and non-toxic in controlling axial elongation in animal studies [**21**]. Its widespread usage needs to be further evaluated. Our study aimed to retrospectively analyse the clinical data of myopic children who had been on single vision eye-glasses with/without low dose atropine 0.01% eyedrops daily before bedtime.

Materials and methods

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Inclusion Criteria : Children who visited Eye clinics at Chacha Nehru Bal Chikitsalaya(CNBC), Delhi from 2021 to 2023 were included in our study. Criteria for inclusion were as follows: age 5 to 14 years, children who completed 24 months of follow-up, cycloplegic spherical equivalent ≤ -1.5 D in each eye.

96 patients of group 1(control group)were on single vision eye-glasses, as noted in their clinical records. 94 patients, included in group 2, were using atropine sulphate 0.01% eye drops before bedtime in both eyes, and single vision eye-glasses.

Exclusion Criteria: Patients with keratoconus, corneal opacity, cataract, aphakia, pseudophakia, maculopathy, optic atrophy, history of retinopathy of prematurity, history of previous ocular surgery,strabismus, astigmatism >2 D were not included in this study.

We retrospectively collected data on age, gender, refraction of both eyes of eligible subjects. Cycloplegic refraction had been done by instilling topical homatropine hydrobromide 2%, 3 times every 10 minutes. Retinoscopy and autorefraction(by Nidek ARK autorefractometer)was done 90 minutes after instilling cycloplegic agent.

Definitions : Progression in myopia was defined as any increase in negative spherical equivalent at follow-up visits. Myopia was defined as spherical equivalent(SE) ≤-0.5 D, when ocular accomodation is relaxed.

Low Myopia: Eyes with spherical equivalent(SE) ≤-0.5 D to >-3 D.

Moderate myopia: Eyes with spherical equivalent(SE) ≤-3 D to >-6 D.

High myopia: Eyes with spherical equivalent(SE) ≤ -6 D with relaxed ocular accomodation.

Fast myopic shift : one with SER progression > -0.5 D per year [**22**].

Progression of myopia was evaluated based on refraction data of both eyes in initial visit and 6 monthly follow up examinations in outpatient clinics.

Statistical analysis was done using SPSS software 20. Outcome measure was change in spherical equivalent at 6 months, 1 year, 18 months, 2 years. P-value <0.05 was considered significant. Objective refraction outcomes of all eyes were converted to spherical equivalent, calculated as spherical power plus half of cylinder power.

Results

Patients

Our retrospective study included data of 380 eyes from 190 patients: 96 patients were using single vision eye-glasses only, while 94 were on atropine 0.01% eye drops in both eyes before bedtime, plus single vision eye-glasses. In control group, 42 were female children,54 were males. In atropine group, there were 48 girls, and 46 boys. Mean age of children noted in baseline data in control group was 9.02 (±2.16) years, while it was 8.71(±2.1) years in atropine group. Table 1 demonstrates baseline demographic and clinical characteristics of study subjects.

Efficacy

Mean baseline spherical equivalent (SE) of children in control group was -5.67 (±3.1)D, while it was -5.89 (±2.9)D in atropine group. There was no statistically significant difference in baseline SER between both groups(p=0.48). Figure 1 represents mean spherical equivalent(D) at baseline and follow-up visits in both groups of study subjects. Table 2 depicts changes in SE at subsequent intervals in both groups. At each follow-up visit, difference in mean SE change was found to be statistically significant (p value<0.001) between both groups.

The mean SE progression from baseline to year 1 was -0.965(±0.59)D in control group and -0.5(±0.38)D in atropine group. From baseline to 2 year follow up, mean SE progression was found to be -1.89(±1.03)D in control group and -0.86(±0.57)D in atropine group. Difference in mean SE progression between both groups was found to be statistically significant at 1 year and 2 year follow-ups (p value<0.001). Table 3 demonstrates ophthalmic refraction parameters among study subjects in both groups. There was slightly higher prevalence of astigmatism in the control group (82.8 % vs. 78.2%). Prevalence of high myopia was higher in atropine group (42% vs. 38.5%).

Figure 2 and figure 3 represent percentage increase in mean spherical equivalent in younger(5-9 years age) and older(10-14 years age) children over time in control group and atropine group respectively.

Safety

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The use of topical atropine 0.01% was overall very well tolerated. None of our patients had reported photophobia and blurred near vision.

Discussion

The Refractive Error Study in Children (RESC), a joint comparative study of the prevalence rates of refractive errors in countries including China, Chile, Nepal, and India was carried out from 2000 to 2001. In this study, prevalence rates of myopia among children in urban and rural Indian populations were found to be 7.4% and 4.1% respectively [**4,23**].

In our retrospective study, we evaluated the efficacy of topical atropine 0.01% in controlling the progression of myopia in children. Our study found that mean rate of myopia progression was significantly lower among subjects using topical atropine 0.01% and single vision eye-glasses, at 1 year and 2 year follow-ups, compared to that in children using glasses only ($p<0.001$). Figure 4 depicts mean SER progression among study subjects at 1 year and 2 year follow-up visits.

ATOM 1(Atropine for the Treatment of Myopia 1) study had established the role of topical atropine 1% in controlling the progression of myopia, wherein atropine 1% treated patients showed a 77% decrease in the mean progression of myopia compared with placebo [**16**]. At 1% concentration, topical atropine frequently causes glare, photophobia and near reading difficulty [**16, 24**]. ATOM2 study was the first study which reported that atropine 0.01% is optimal concentration with good efficacy and minimal side effects, in myopia control [**17**]. The 5-year report of the ATOM2 study established that 0.01% atropine is similarly effective in slowing down myopia progression as are 0.1% and 0.5% concentrations, over 24 months of treatment (phase 1 of the ATOM2 study). Mean 2-year progression(phase 1) was 0.49±0.63 D, 0.38±0.6 D and 0.30±0.60 D in atropine 0.01%, 0.1% and 0.5% groups respectively. Patients treated with atropine 0.01% experienced significantly fewer incidence of side effects like mydriasis, glare, accomodation loss [**18**]. Moreover, rebound effect in the washout period (phase 2 of the ATOM2 study) was absent, unlike patients treated with atropine 0.1% and 0.5%. Only 24% of patients previously treated with atropine 0.01% needed retreatment(phase 3) compared with 59% and 68% in the 0.1% and in the 0.5% group, respectively. Five-year report of the ATOM2 study concluded that atropine 0.01% was significantly more efficacious in slowing myopia progression with reduced visual side-effects compared with 0.1% and 0.5% doses [**18**]. In our study, patients using atropine 0.01% eye drops daily before bedtime had not reported complaints of photophobia and blurring of near/distance vision.

Low concentration atropine for myopia progression (LAMP) study reported that mean spherical equivalent change was -0.27±0.61D, -0.46±0.45D, -0.59±0.61D and -0.81±0.53D, in 0.05%, 0.025% , 0.01% atropine and placebo groups respectively[**25**].Myopia Outcome Study of Atropine in Children(MOSAIC) trial found that myopic children treated with 0.05% atropine eye drops had 0.13 D less myopia progression compared to those on placebo [**26**].Hansen NC et al reported that myopic children in 2-year atropine 0.01% group had better myopia control compared to those on 6-month 0.1% atropine followed by 0.01% atropine for 18 months [**27**].

Table 4 illustrates mean SER at baseline and each follow-up visit among both groups. Patients in atropine group were significantly less myopic compared to control group ($p<0.03$) at 2 years follow-up. Our study included patients with high myopia also, unlike many of the previous myopia control studies. Retrospective design was limitation in our study. Information regarding axial length, accommodative amplitude, parental history of myopia, was not collected.

Visual cues presented to the eyes during childhood apparently play crucial role in emmetropization and its maintenance [**28**]. Emmetropisation is essential phenomenon during course of normal visual development in childhood. When normal course of emmetropisation continues, hyperopia of +2 D in neonatal period and infancy declines rapidly to +1 D during the first two years of life. Hyperopia gradually stabilises to emmetropia during the period of 2 to 14 years of age [**29**]. Onset of myopia occurs mostly between 6 and 9 years of age [**30**].Disproportionate axial length growth can be result of overshooting of emmetropization [**14**]. If axial length is too long for refractive power of lens and cornea, it causes focussing of light rays from distant objects in front of retina, resulting in blurred images. Visual feedback regulates emmetropization via retinoscleral signalling cascade,as evidenced by several animal studies. Role

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of dopamine, adenosine, retinoic acid has been implicated in retina-to-sclera signalling involved in emmetropisation and myopigenesis [**31**].Uncorrected myopia resulting in prolonged retinal blur acts as stimulus for initiating signalling cascade, affecting extracellular matrix synthesis in sclera, leading to axial elongation of eye. Equatorial expansion of eyes is countered by tensile force generated by ciliary body or crystalline lens [**32**]. Axial lengthening of eye is associated with choroidal and scleral thinning which is more marked at posterior pole, and less pronounced at equator [**33**].

Extent of clarity of image on foveal as well as mid-peripheral retina influences the axial dimension of eye [**34, 35**].Peripheral hyperopic retinal blur has been implicated as risk factor for myopia progression. As myopic eyes have more prolate shape due to higher axial elongation compared to equatorial one, refractive state in these eyes is more hyperopic in retinal periphery [**36**]. In myopic eyes, single vision spectacles or contact lenses shift the plane of focus equally at both fovea and peripheral retina. It results in hyperopic blur in peripheral retina, which accelerates axial myopia progression. Higher the power of correcting single vision spectacles/lenses, higher the magnitude of hyperopic defocus in retinal periphery. Considering this factor, utility of multifocal spectacles with progressive addition lenses(PAL), single vision glasses with defocus incorporated multiple segments (DIMS), bifocal glasses, prismatic bifocal glasses, and multifocal glasses/contact lenses has been investigated in several studies. Progressive addition lenses(PAL) and DIMS lenses decelerate myopia progression as they create peripheral myopic defocus, which inhibits axial lengthening [**37, 38**].However many studies found inconsistent and minimal benefit of these optical correction treatments in myopia control [**39, 40, 41, 42**].Orthokeratology also addresses factor of peripheral hyperopic defocus and induces myopic shift in refractive state of peripheral retina. Modern overnight ortho-K lenses cause central corneal flattening and mid-peripheral corneal steepening [**43**].Over the time period spanning 2001 to 2008, more than 100 cases of microbial keratitis associated with ortho-K had been reported [**44**]. Continued vigilance is imperative during the usage of ortho-K lenses. Parents must be well-informed to ensure safety, as target population includes children.

Atropine is a non-selective anticholinergic drug that blocks parasympathetic acetylcholine muscarinic receptors in ocular tissues. It has high affinity for all five(M1-M5) muscarinic receptors. Its mechanism of action in control of myopia is yet to be thoroughly understood. Initially, topical atropine use was encouraged for myopia control predominantly because of its cycloplegic action, as excessive accomodation by myopic eyes was believed to be the primary and well-understood reason for myopia progression. Several animal studies later demonstrated multitude of non-accomodative mechanisms underlying the progression of myopia [**45,46**]. Muscarinic receptors are present in several ocular tissues in mammals involving anterior as well as posterior segment. Besides, animal studies demonstrated interaction of atropine with non-muscarinic receptors also, such as alpha-adrenergic receptors, gamma-aminobutyric acid receptors, epidermal growth factor receptor [**47, 48**].It acts likely by decreasing scleral fibroblast proliferation, and by countering scleral extracellular matrix weakening and choroidal thinning [**49**]. Lower levels of retinal dopamine and dysfunction of retinal melanopsin-mediated signalling were found to be the key factors in excessive axial length elongation in mutant mouse models[**50**]. Low concentration topical atropine sulphate is less likely to be associated with side effects like mydriasis, photophobia, glare, loss of accomodation, blurred near vision and rebound phenomenon [**51**]. It might be partly attributed to decreased M3 muscarinic receptor antagonist action at lower concentrations. After stopping atropine sulphate eye drops, rebound of myopic progression has been found to be significantly greater in eyes receiving 0.5% and 0.1 % concentrations, while eyes receiving as low as 0.01% atropine had more sustained control of spherical equivalent [**52**].Moreover, possible risk of ocular hypertension with topical atropine usage has not yet been substantiated in clinical studies [**53, 54**].

Recent mammalian studies of experimental myopia demonstrated that highly selective M1 and M4 antagonists inhibited axial elongation using nanomolar concentrations at retina [**55, 56**]. Hence further development of these highly selective therapeutic agents offers promising future approach towards control of myopia progression.

Low sunlight exposure in children has strong correlation with faster axial length growth [**57**].

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Myopia inhibiting effect of outdoor exposure is explained by enhanced release of retinal dopamine, a retinal transmitter often found linked to emmetropisation and refractive development [**58**]. Retinal dopamine has protective role against uncoordinated, excessive axial elongation. Circadian rhythm dysregulation has been linked to altered eye growth and development of myopia in animal models. Dopamine, GABA(gamma amino butyric acid), melanopsin, neuropsin are retinal transmitters mediating circadian rhythm, in response to diurnal changes in light stimuli received by retinal ganglion cells. The mean diurnal variation in axial length is approximately 0.06 to 0.11 D in human eyes [**59**].Diurnal and/or circadian variations in ocular dimensions have been found linked to refractive status development [**60**].Properties of ambient lighting have been shown to play role in refractive development [**61**].Circadian rhythms are controlled directly or indirectly by suprachiasmatic nuclei (SCN) of the hypothalamus. As outdoor light exposure and well-regulated circadian rhythm has proven benefit in myopia inhibition, parents accompanying children for outdoor activities and raising awareness about importance of sleep-wake cycle synchronised with circadian clock, is a promising behavioural modification to combat myopia to some extent. More frequent outdoor classes in schools can go a long way towards inhibiting or delaying myopia onset.

Conclusion

Our retrospective study results indicate that atropine 0.01% is an effective and well-tolerated pharmacological therapy for control of myopia in children. Mean spherical equivalent progression was significantly lesser in children using topical atropine 0.01% alongwith glasses.

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Table 1: Baseline demographic characteristics in control group and atropine group

Characteristic		Control (N = 96)		Atropine (N = 94)	P-value
Baseline age (years)	Mean (SD)	9.02 (±2.16)		8.71 (±2.1)	0.368#
Age groups (N) (years)	N, 5 to < 8	28		31	
	N, 8 to < 10	28		30	
	N, 10 to <12	24		22	
	N, 12 to <15	16		11	
Gender					
Female	N	42		48	
Male	N	54		46	
Baseline SER (D)	N (number of eyes)	192		188	
	Mean (SD)	-5.67 (±3.1)		-5.89 (±2.9)	0.48*

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	Median	-4.5		-5.25	

SER, Spherical equivalent refraction ; D, Diopter; SD, Standard Deviation,*Unpaired t-test, #mann-whitney U-test

Table 2: Changes in SER over time in control group and atropine group

		Control (N = 96)		**Atropine (N = 94)**		**P-value***
	N (number of eyes)	192		188		
Change in SER(D)						
Baseline -6 m						
	Mean (SD)	-0.512 (±0.35)		-0.27 (±0.26)		<0.001
	Median	-0.5		-0.25		
6 m – 12 m						
	Mean (SD)	-0.453 (±0.36)		-0.27 (±0.24)		<0.001
	Median	-0.3125		-0.25		
12 m – 18 m						
	Mean (SD)	-0.495 (±0.31)		-0.205 (±0.22)		<0.001
	Median	-0.5		-0.25		
18 m-24m						
	Mean (SD)	-0.433 (±0.37)		-0.15 (±0.16)		<0.001
	Median	-0.25		-0.125		

SER, Spherical equivalent refraction ; D, Diopter ; SD, standard deviation ; m, months, *Unpaired t-test

Table 3: Ophthalmic parameters in study subjects

Ophthalmic parameter		Number of eyes in Control (N = 192) group		Number of eyes in Atropine (N = 188) group
Astigmatism (N)		159		147
High Myopia(N)		74		79
High Myopia >=10 D (N)		29		22

Table 4 : Mean SER over time in study subjects SER, Spherical equivalent refraction ; D, Diopter ; SD, standard deviation,

	Control (N = 96)		Atropine (N = 94)		
	Mean (D)	SD	Mean (D)	SD	
Baseline SER	-5.67	±3.1	-5.89	±2.9	

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Year 0.5	-6.19	±3.3	-6.16	±3.1	
Year 1	-6.64	±3.6	-6.39	±3.2	
Year 1.5	-7.13	±3.8	-6.60	±3.3	
Year 2	-7.57	±4.0	-6.75	±3.4	

Figure 1: Mean spherical equivalent over time within control group and atropine group. Spherical equivalent refraction (SER).

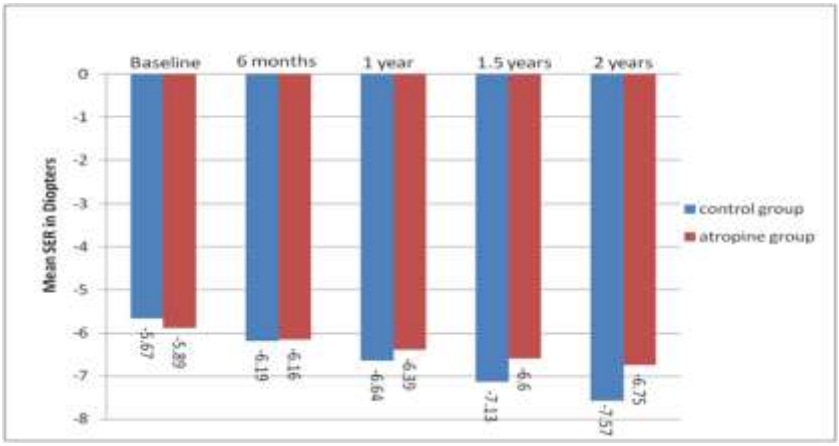

Figure 2: Percent increase in SER over time among younger and older subjects in control group. Spherical equivalent refraction (SER)

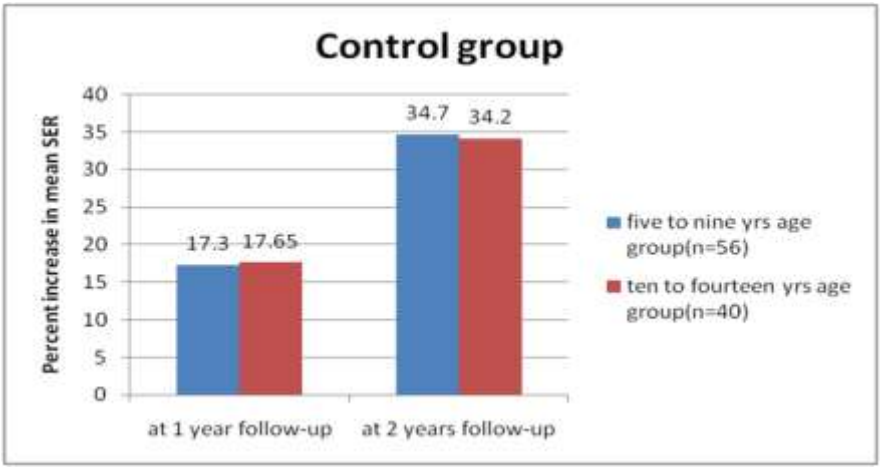

Figure 3: Percent increase in SER over time among younger and older subjects in atropine group. Spherical equivalent refraction (SER)

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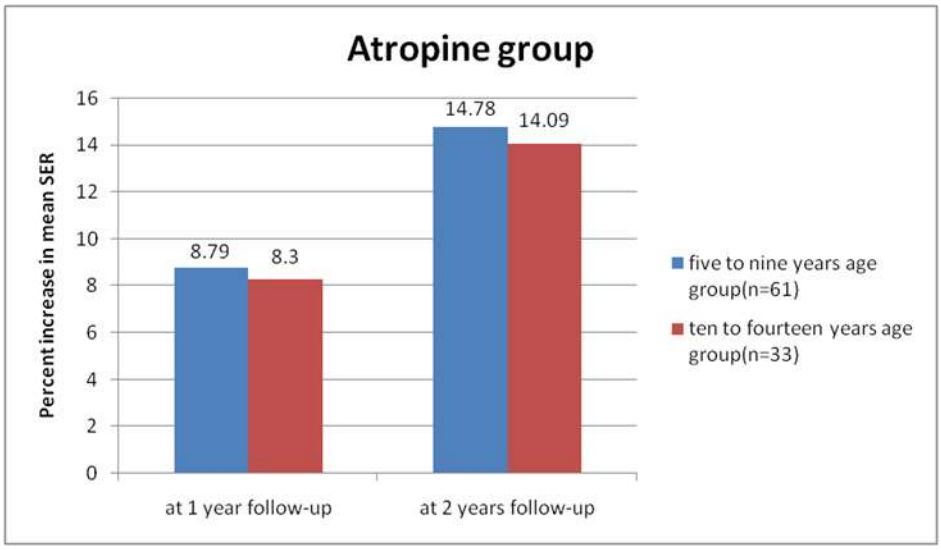
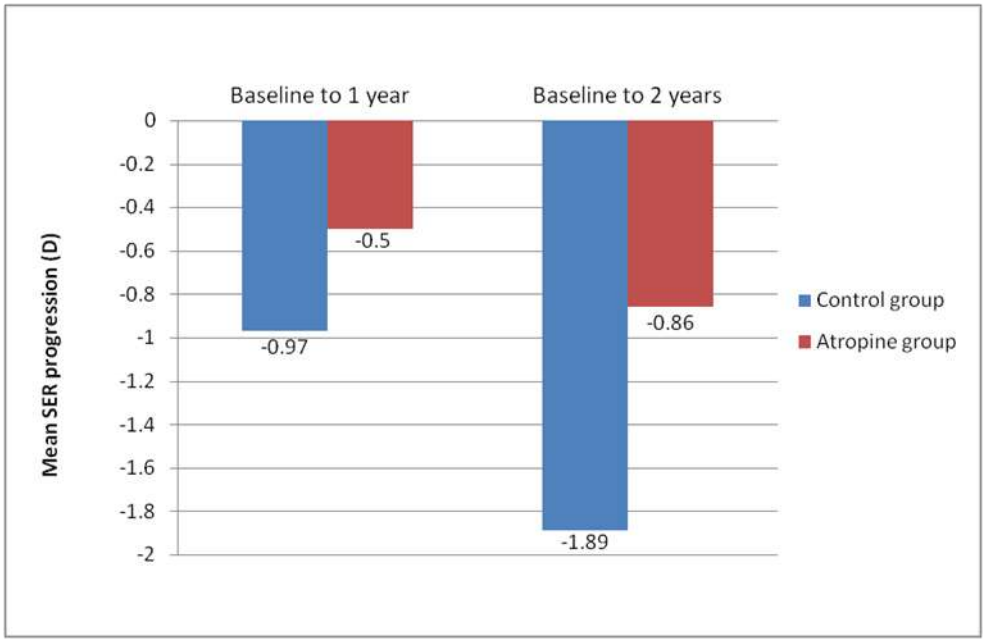


Figure 4: Mean SER progression in control group and atropine group at 1 year and 2 year follow-ups. Spherical equivalent refraction (SER), Diopter (D)



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