Review Article

Atropine in Myopia

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Abstract

Myopia is emerging as a global public health problem with nearly half of the world's population predicted to become myopic by 2050. Genetic factors along with evolving lifestyle modifications like reduced outdoor activity, increased screen time and near work have contributed to this surge. Of several therapies described for anti-myopia therapy, topical atropine is emerging as the most popular management option owing to the ease of administration and minimal side effects. Based on the effect versus side effect profile, 0.01% atropine appears to be the optimal concentration for reducing myopia progression. In this review, we discuss the effectiveness of atropine therapy, its side effects and indications of use in the light of the best available literature. Some questions like duration of therapy, role of higher dose of atropine in non-responders and role of combination therapy with other interventions like orthokeratology still needs to be explored.

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Introduction

With the rising incidence of myopia worldwide, the disease is becoming a major public health issue. According to the Global Burden of Disease estimates, uncorrected distance refractive error is the second most common cause of blindness and the leading cause of moderate to severe vision impairment.[1] In 2010, approximately 1950 million people (28.3% of the global population) were myopic. The prevalence is expected to rise to a staggering figure of 4758 million that accounts for nearly half of the global population by 2050 [2,3] with 10% of them being high myopes.

The problem is most overwhelming in the East Asian countries like Singapore, Taiwan and Hong Kong, where the condition affects around 80-90% of young adults.[4–7]The disease has come to spotlight with a rising prevalence being reported even from countries like United States,[8] Europe[9] and Australia[10] initially thought have a lower prevalence. In United States the prevalence has reportedly increased from 25% in 1971 to 42% in 1999. In Indian scenario, the population-based estimates of prevalence of myopia in children and adults(>30 years) were 5.3%[11] and 27.7%[12] percent respectively. The North India Myopia Study (NIM Study)[13] in 2015 reported the incidence to be as high as 13.1% in the school going children in Delhi.[14] Considering the enormous population of the country, this would amount to a humongous number making myopia an important public health concern.

The World Health Organization (WHO)[15] proposed the following definitions, especially in context of Rapid Assessment of Avoidable Blindness (RAAB) surveys. Myopia is "a condition in which the spherical equivalent objective refractive error is ≤ −0.50 D in either eye". High Myopia is "a condition in which the spherical equivalent objective refractive error is ≤ −5.00 D in either eye". The ocular morbidity caused by myopia is known to increase with every millimeter of axial length elongation. It includes primary open angle glaucoma, cataract, MMD(myopic macular degeneration), retinal detachment, retinoschisis and macular hole.[16–18] The visual impairment due to uncorrected myopia not only affects the patient's quality of life[19] due to psychological, cosmetic, practical, and financial factors but also, amounts to huge economic and social burden to the society[19,20] It has negative bearing on self-esteem, career choice, peer acceptance and relationships.[21]

Genetic background

Ip et al, reported that the prevalence of myopia was 7.6% in children with no myopic parents, 14.9% with one myopic parent, and 43.6% with both parents myopic.[22] The environmental drivers become important especially in individuals already prone via genetic constitution.[23] The genome wide association studies(GWAS) have identified around 39 loci that are associated with refractive error and myopia in adults.[24] Although the genetic risk variants explain approximately 12% of refractive error variation, they explain around 22% of the high myopia cases.[25]

Environmental Factors

Lifestyle and environmental factors are important predisposing factors in myopia. The North India Myopia study found that increased near work like reading-writing, use of computers/ video games and watching television were significant risk factors for progression of myopia in the urban schools of Delhi, while the duration of outdoor activities (>2 hours/day) were protective. The explanation for this protective effect might be that the radiant intensity of sunlight peaks at a wavelength of about 550 nm, corresponding to the peak sensitivity of human retina, while indoor illumination peaks at longer wavelengths.[26] This means that the indoor light will be preferentially focused behind the retina creating a hyperopic defocus, thus stimulating eye growth.[27] Another possible mechanism is high illuminance (around 10,000 to 20,000 lux) outdoors which has been found to be protective in myopia compared to <500 lux typical of indoors.[28,29] However, according to a meta - analysis, although the outdoor time is protective for the development of myopia, it is not effective in slowing the progression in already myopic eyes.[30] Accommodation associated with near work, especially in down gaze adversely affects the axial length, choroidal thickness, and anterior eye biometrics as a function of time.[31,32] Also, lens in accommodation state causes more hyperopic defocus and reduced light intensity in the periphery. All these factors predispose to myopia and therefore the risk of myopia increases by as high as 80% in patients with prolonged near work.

Mechanism of action of atropine

Atropine is an alkaloid extracted from the plant *Atropa belladonna, Datura innoxia, D. metel, D. stramonium and members of the genera Brugmansia and Hyoscyamus.* It is a non-selective muscarinic antagonist that acts on receptors M1 to M5. Earlier it was thought that atropine exerts its effect through the blocking of accommodation. However, even after abolishing the accommodation reflex by optic nerve sectioning, or bilateral Edinger Westphal nuclei destruction, the experimental myopia induction could not be inhibited.[33,34,35] Stone et al. showed that experimentally induced myopia in chicks can be controlled with atropine. This also points to a non-accommodative mechanism, since in chicks the intraocular muscles are striated, and have nicotinic receptors.[36,37] Lastly, the fact that selective M1 antagonist like pirenzepine is effective against myopia, and not the M2 and M3 selective antagonists, further supports the neural locus of action. In humans, M3 is found in ciliary muscles and M1 in neural tissues.[38]

Now, it is thought that retinal pigment epithelium (RPE) serves as a relay for growth-modulating signals that are generated in the retina and acts on the choroid and sclera.[39–43] Some of the chemical mediators that have been described for these signaling pathways are dopamine[44,45] Tumor necrosis factor beta (TGFβ)[46] FGF-2 or basal fibroblast growth factor[47,48] nitric oxide(NO)[49] melatonin[50] and inflammatory cytokines.[51] Cristaldi et al[52] has shown that atropine and 7-methylxanthine modulates the extracellular matrix production (collagen I and fibronectin) differently in scleral and choroidal fibroblasts cell culture. The drugs stimulate the former and inhibit the latter in vitro. This might apply that it leads to reinforcement of sclera and increased choroidal perfusion at the same time. Choroid is also thought to play an active role in signaling from retina to sclera.[53]

Clinical Trials Of Atropine

Various interventions have been described for the prevention and control of school myopia that includes optical therapies like orthokeratology, bifocal soft contact lenses, bifocal and progressive or multifocal spectacle glasses, and pharmacological therapy with atropine. Of these, atropine is the most commonly used intervention owing to the ease of administration and minimal side effects. With the growing popularity of this drug in myopia, it has also become commercially available in many countries including India.

The use of atropine for myopia was first proposed by Donders[31] in 1864 and later encouraged by Pollock[54] in 1916. The first randomized placebo controlled trial to report the efficacy of atropine 1% in controlling childhood myopia was conducted in 1989 by Yen et al in Taiwanese children.[55] But drug related photophobia was a major drawback that was seen in almost all cases. A decade later in 1999, Shih et al. in another randomized placebo controlled trial in Taiwanese population evaluated the efficacy of lower concentrations of atropine for 2 years, and found that 61%, 49% and 42% children, in atropine 0.5%, 0.25% and 0.1% groups respectively had not progressed (defined as progression of <-0.25 D/ year in the spherical equivalent) as against 8% in control group.[56] Although, the treatment was most effective with 0.5% atropine, but considering the high dropout rates due to side effects of photophobia and near vision impairment, they suggested the use of 0.25% or 0.1% atropine to control myopia progression. They further confirmed the efficacy of 0.5% atropine in a clinical trial (2002) comparing atropine with multifocal lenses versus regular lenses and multifocal lenses alone where the myopia progression/axial elongation noted was -0.42±0.07 D/0.22±0.03mm in 0.5% atropine with multi-focal lenses group versus -1.19±0.07 D/0.49±0.03mm in the multifocal lens group and -1.40±0.09 D/0.59±0.04mm in the regular lens group ($p<0.0001$).The multifocal lenses were given in the atropine group to allow clear vision at all working distances. Almost half of the children in the combined atropine and multifocal lens group did not progress. Multi-focal lenses alone had no advantage over single vision lenses.[57]

Atropine for the treatment of childhood myopia (ATOM1) was a randomized trial to compare the effectiveness of atropine 1% versus placebo administered once nightly for 2 years in one eye followed by 1 year wash-out period in Singaporean population.[58] All children were given photochromic progressive glasses. Mean myopia progression paralleled with axial length elongation and was significantly less in the atropine group (-0.28±0.92 D/0.02±0.35mm) as compared to placebo group (-1.2±0.69 D/0.38±0.38mm) at 2 years. Overall, there was 77% reduction in the mean myopic progression in the atropine treated eye at the end of 2 years. But a rebound effect was noted after stopping the drug for a year during which the myopia progression in atropine treated eyes (-1.14 D) was far greater than the placebo (-0.38 D). But the mean progression overall at the end of three years (2 years of therapy and 1 year washout) was still less in the atropine treated eyes(-0.46 D) compared to placebo (-0.52 D). The therapy did not seem to have any effect on the astigmatism component of the refractive error and the astigmatism increased equally in both the groups.[59] Based on the three years data, Kumaran et al reported that the effect of atropine was mainly on the posterior part of the eyeball that is, vitreous chamber depth. Blurring of vision, glare and allergy to atropine were main side effects noted with the drug that led to the dropout rate of 17%.[60]

The same group from Singapore then designed ATOM2 to compare the safety and efficacy of lower concentrations of atropine (0.5%, 0.1%, 0.01%) to offset the problems of mydriasis and reduced accommodation noted with higher concentrations.[61] It was a five year study with 2 years of treatment (Phase 1) followed by washout for 1 year (Phase 2). And those who continued to progress were decided to get retreatment with one of the three concentrations, based on study results over the past 3 years (Phase 3). A dose-dependent response was noted at 2 years of treatment with higher concentrations achieving better myopia control. The mean myopic progression and axial length elongation in the 0.5%, 0.1% and 0.01% groups were -0.30±0.60 D/0.27±0.25mm, -0.38±0.06/0.28±0.28mm and -0.49 D±0.63/0.41±0.32mm respectively. Myopia had progressed <0.5D in 63%, 58% and 50% in the 0.5%, 0.1% and 0.01% groups respectively.

Interestingly, after the washout maximum progression was seen with higher concentrations, i.e. -0.87D in 0.5% -0.68D in 0.1% group when compared to -0.28D progression noted in 0.01% group and the change in axial length was not significantly different in the three groups (P=0.787). The effect of rebound phenomena totally reversed the overall results such that the total increase in spherical equivalent noted at the end of Phase 1 and 2 of the study was -1.15 D, -1.04 D and -0.72 D in the 0.5%, 0.1% and 0.01% groups respectively.[62] Higher concentrations of atropine were associated with greater rebound effect, therefore making 0.01% as the optimal concentration for anti-myopia therapy with more modulated and sustained effect. Also atropine 0.01% had minimal effect on pupil dilatation and accommodation amplitude. The lower myopia progression in the 0.01% group continued during phase 3 with a progression of ≥-0.50 D in at least 1 eye to be noted in only 24% in 0.01% group versus 59% and 68% in 0.1% and 0.5% respectively. Also, the axial length increase was minimum in 0.01% group (0.19±0.18mm) than the 0.5% (0.26±0.23mm; P=0.013) and 0.1% (0.24±0.21mm; P=0.042) groups at the end of Phase 3.[63] Thus, 0.01% atropine was recommended over the higher doses to control myopic progression. But an important limitation was a lack of control group. Anticipating minimal or no effect with the super diluted concentration of 0.01% atropine, this group was supposed to serve as control which instead showed favorable results. So, they had to use the historical control from ATOM 1 that had different baseline characteristics. Furthermore, despite the decrease in myopia progression significant axial length elongation continued in 0.01% group.

Following this landmark trial, a lot of interest has revived in the use of low concentration atropine in myopia. A meta-analysis by Li et al., suggested that the atropine therapy achieved better results in Asians than in non-Asians by slowing the myopia progression by 0.54D/year and 0.35D/year respectively and the concentration does not seem to affect the outcomes. But these results could be confounded by the absence of RCTs in non-Asian population.[64] Another meta-analysis by Pineles et al. concluded that atropine therapy is effective in reducing the myopia progression in children by as much as 1D/year and recommended the use of 0.01% atropine.[65] Cooper et al. proposed that the highest tolerable dose of atropine with minimal side effects in white population was 0.02%.[66]

Low-Concentration Atropine for Myopia Progression (LAMP) Study was a Hong Kong based randomized masked study started in January 2016 to compare the efficacy of low dose atropine (0.05%, 0.025%, and 0.01%) in myopic children.[67] The study has been divided into four phases: Phase 1(1-year) comparing treatment versus placebo, phase 2(1-year) switching over of placebo to the best determined concentration, phase 3 (1-year) washout period to look for rebound effect and phase 4 (2-years) when atropine will be resumed in children showing progression > 0.5D at concentration to be decided. In phase 1, a concentration dependent response was noted with mean change in spherical equivalent/axial elongation to be -0.27±0.61D/ 0.20±0.25mm, -0.46±0.45D/ 0.29±0.20mm, -0.59±0.61D/ 0.36±0.29mm, and -0.81±0.53D/ 0.41±0.22mm in the 0.05%, 0.025%, and 0.01% atropine groups, and placebo groups, respectively (P<0.001 for both). All concentrations were well tolerated. There was a reduction of 67%, 43%, and 27% in myopia progression and51%, 29%, and 12% in axial length elongation in the 0.05%, 0.025%, and 0.01% atropine groups, respectively, when compared with the placebo group. Importantly, there was no significant difference in axial length change between the 0.01% and placebo group implying that 0.01% does not have appreciable effect on the axial length elongation. Similar trend was seen in ATOM 2 with no significant change in the axial length at 2 years in 0.01% group (0.41±0.32mm) versus the control group of ATOM 1 (0.38±0.38mm). Based on the above findings, 0.05% was found to be most effective in myopia therapy that was also corroborated by the results of Phase 2. But it is too soon to comment on the optimal concentration of atropine as LAMP is an ongoing study with results of phase 3 and 4 awaited. It would be interesting to observe the rebound effect and what impact it will have on the myopia progression eventually after the cessation of treatment.

The effectiveness of atropine for myopia control has been proven beyond doubt by such well powered randomized clinical trials and meta analyses.[68,69] But the study populations in these trials are predominantly of Asian ethnicity, thus there is need to evaluate the efficacy of atropine in different ethnic groups. Atropine 0.01% was found to reduce progression from -1.05 D/Y to -0.04 D/Y at 1 year in 56 German schoolchildren.[70] Diaz-Llopis et al studied 0.01% atropine in 100 Spanish children. Myopia progression was reduced by 25% (-0.14 versus -0.65 D in the no treatment group).[71] Clark et al showed in a multiethnic cohort in California that atropine 0.01% was effective in low initial myopia, while it might fail in cases with rapid progression.[72] A substantial number of children may be resistant, irrespective of ethnicity. Low dose atropine has proved to be effective in different ethnic cohorts from Germany, Italy,[73] Korea.[74] Netherlands,[75] and Spain. In a study by Fang et al, atropine 0.025% has been found to be effective in the prevention of onset of myopia in pre-myopes (defined as spherical equivalent ≤1D).[76,77] But, it needs further elucidation.

There are many other ongoing registered RCTs especially in non-Asian population like the CHAMP-UK(Childhood Atropine for Myopia Progression-United Kingdom)[78] in British, MOSAIC(Myopia Outcome Study of Atropine in Children) study[79] in European and WA-ATOM(Western Australia Atropine for the Treatment of Myopia) study in Australian population.[80]

There are no published well-designed RCTs in Indian population. A cohort study from India reported the effectiveness of 1% atropine that reduced the rate of progression from a mean of -0.6D/year to -0.2D/year at 23 months follow-up.[81] The authors concluded that 1% atropine maybe considered for myopes with rapid progression, higher myopia at baseline, during the years of active growth, and among the "poor" responders to the lower concentrations of atropine. They emphasized the possible preference of

Table 1: Summary of various studies elucidating the role of atropine in myopia

Author	Design	Country	F/U	Sample size	Age (yrs)	Treatment	Parameters assessed	Baseline SE	Baseline AL	Change in SE (D/ year)	Change in AL (mm/ year)	Comment
Yen et al(55)	RCT	Taiwan	12 months	96	6-14		AL,Km, CR,IOP	-0.5 to -4	Not reported		Not reported	Both atropine and cyclopentolate effective, but atropine was the most potent
				32	10.5	Atropine 1%		-1.52(0.96)		-0.22(0.54)		
				32	10	Cyclopentolate 1%		-1.45(0.85)		-0.58(0.49)		
				32	10.4	Placebo		-1.59(0.92)		-0.91(0.58)		
Shih et al(56)	RCT	Taiwan	Upto 24 months	186	6-13		CR, IOP	-0.5 to-6.75	NA		NA	Atropine 0.5% most effective, but drop out due to side effect more
				41	9.8	Atropine 0.5%		-4.89(2.06)		0.04(0.63)		
				47	9.7	Atropine 0.25%		-4.24(1.74)		0.04(0.63)		
				49	8.9	Atropine 0.1%		-4.41(1.47)		0.04(0.63)		
				49	8.3	Tropicamide 0.5%(control)		-4.5(1.86)		0.04(0.63)		
Shih et al(57)	RCT	Taiwan	18 months	227	6-13		CR,IOP, corneal radius, KM,AL, LT,ACD					No difference in progression between mfpl and svlgroups
				76		Atropine 0.5%+mfpl		-3.28(0.13)	24.62(0.10)	-0.42(0.07)	0.22(0.03)	
				75		Placebo+mfpl		-3.34(0.14)	24.80(0.09)	-1.19(0.07)	0.49(0.03)	
				76		Placebo+svl		-3.20(0.14)	24.75(0.10)	-1.40(0.09)	0.59(0.04)	
Chuaet al(ATOM 1) (58)	RCT	Singapore	24 months	400	6-12		CR, ACD, LT,AL, mfERG			At 2 years	At 2 years	Essentially no change in axial length of the atropine treated eyes, at the end of two years
				200	9.2	Atropine1% treated eye		3.36(1.38)	24.80(0.83)	-0.28(0.92)	0.02(0.35)	
						Atropine 1% untreated fellow eye		3.40(1.35)	24.81(0.84)			
				200	9.2	Placebo treated eye		3.58(1.17)	24.80(0.84)	-1.20(0.69)	0.38(0.38)	
						Placebo untreated fellow eye		3.55(1.21)	24.76(0.86)			
Liang 2008(87)	RCT	China	8-12 months				CR, IOP, AL					Combined therapy with acupressur e was comparable to 0.5% atropine results
				22	9.9	Atropine0.25%		-2.09(1.68)	24.11(0.89)	0.38(0.32)	0.16(0.09)	
				23	10.9	Atropine 0.5%		-2.17(1.48)	24.24(0.53)	0.15(0.15)	0.12(0.12)	
				26	10.2	Atropine 0.25%+acupressure		-1.19(1.20)	24.95(0.77)	0.21(0.23)	0.14(0.11)	
Fang et al(76)	Retrospective, cohort	Taiwan	12-36 months	50	6-12		CR		Not assessed		Not assessed	In premyopes (SE<1 D)atropine 0.025% can prevent myopic shift
				24		Atropine 0.025%		-0.31(0.45)		-0.14(0.24)		
				26		No treatment		-0.17(0.5)		-0.58(0.34)		
Wu et al(91)	Retrospective case control	Taiwan	3-8 years (mean 4.5y)	117	6-12 years, mean 8.4y		CR		Not assessed		Not assessed	45% children on atropine 0.05% were shifted onto 0.1% due to progression of >0.5 D in 6 months.
				97		Atropine 0.05%or 0.1%		-2.45 (1.63) D		-0.31(0.26)		
				20		No treatment		-1.87 (0.94) D		-0.90(0.30)		
Chia et al (ATOM2, phase1) (58)	RCT	Singapore	24 months	400	6-12, mean 9.7 years		CR, AL, AA, PD			At 2 years,	At 2 years,	All the concentrations are effective. Clinical difference in progression among the three groups small.
				161		Atropine 0.01%		-4.5(1.5)	25.1(1.0)	-0.49(0.63)	0.41(0.32)	
				155		Atropine 0.1%		-4.8(1.5)	25.2(0.8)	-0.38(0.60)	0.28(0.27)	
				84		Atropine0.01%		-4.7(1.8)	25.2(0.9)	-0.30(0.60)	0.27(0.25)	
Lin et al(86)	Retrospective, cohort	Taiwan	3 years	210	7-17 years	Atropine 0.125% OK lenses	CR,AL, corneal endothelium					The superiority of one modality over another could not be established definitely Combination of atropine and or thokeratology may be potentially effective.
				105	Mean 11.1			-4.0(1.75)	24.23(1.35)	-0.28(0.18)	0.37(0.09)	
				105	Mean 11.8			-4.25(1.5)	24.12(1.25)	-0.34(0.21)	0.28(0.08)	

Kumaran et al(97)	RCT	Singapore	3 years (2 years) of ATOM 1+1 yr off treatment	313	6-12 years		CR,ACD, LT, AL, KM,VCD			At 3 years, changes in median values	At 3years, changes in median values	Rebound progression after stopping treatment was seen. But still the overall progression over 3 years was less with atropine.
				147	9.2 y	Atropine 1%		3.36(1.38)	24.80 (0.83)	-1.35 D	0.26 mm	
				166	9.2 y	Placebo treated		3.58(1.17)	24.80 (0.84)	-1.55 D	0.53 mm	
Yi et al(98)	RCT	China	12 months	132	7-12		CR,AL, IOP, fundus OCT	-0.5 to-2.0 D				Atropine is effective for low myopia
				68	9.91	Atropine 1%		-1.23(0.32)	23.75(0.10)	0.32(0.22)	-0.03(0.07)	
				64	9.72	Placebo		-1.15(0.30)	23.72(0.12)	-0.85(0.31)	0.32(0.15)	
Clark et al(72)	Retrospective, case control	US	Mean 1.1 years	60	6-15		Manifest SE	1.1 D	NA		NA	The strongest clinical improvement was seen in the low myopia group (≤ 1 D)
				30	10.2	Atropine 0.01%		-2(1.6)		-0.1(0.6) D/Y		
				28	10.2	Placebo		-2(1.5)		-0.6(0.4) D/Y		
Polling et al(75)	Prospective, interventional	Netherlands	12 months	77	10.3 (3.2)		CR, AL PD					The effect of therapy was the lowest and the highest in less than 9 and more than 12 years, respectively.
				60		Atropine 0.5%		-6.7(3.6)	25.19 (0.97)	-1.0(0.7 D/Y	-0.11 (0.20)	
				17		Ceased drug		-6.5(2.8)	25.46 (1.21)	-0.5(0.6 D/Y	-0.12 (0.14) [P=0.73]	
Diaz-Llopis et al(71)	RCT	Spain	60 months	200	9-12 years		CR	-0.5 D to -2.0 D	Not assessed		Not assessed	Therapy was abandoned in 2% of children due to side-effect (photophobia, reading difficulty, headaches, mydriasis; another 5% had similar complaints.
				100	10.4	Atropine 0.01%		-1.1(0.5)		-0.14(0.35)		
				100	10.1	No treatment		-1.2(0.4)		-0.65(0.54)		
Yam et al(LAMP phase 1+2) (67,92)	RCT	Hong Kong	12+12 months	383	4-12 years		CR, AL, AA, PD					Atropine 0.05% was the best concentration, and its effect was twice that of 0.01%.
				97	8.23	Atropine 0.01%		-3.77(1.85)	24.70(0.99)	-1.12(0.85)	0.59(0.38)	
				91	8.54	Atropine 0.025%		-3.71(1.85)	24.86(0.95)	-0.85(0.73)	0.50(0.33)	
				102	8.45	Atropine 0.05%		-3.98(1.69)	24.85(0.90)	-0.55(0.86)	0.39(0.35)	
				93	8.42	Placebo for 1 year→0.05%		-3.85(1.95)	24.82(0.97)	-1.00(0.77)	0.58(0.33)	
Moon et al(74)	Retrospective	South Korea	12 months of treatment	285	7.0(2.1)	Control: before atropine	CR, AL, NPA, PD	-2.76(2.38)	24.39(1.36)	-1.61(1.92)	0.55(0.24)	All three concentrations were effective. Korean children might require higher concentration.
				89	8.0(2.2)	Atropine 0.01%		-3.84(2.47)	20.86(1.22)	-0.84(0.86)	0.44(0.32)	
				63	8.4(2.1)	Atropine 0.025%		-3.97(1.65)	24.66(0.93)	-0.56(0.86)	0.30(0.24)	
				133	8.1(2.1)	Atropine 0.05%		-3.94(2.76)	24.91(1.43)	-0.23(0.67)	0.23(0.25)	

ACD	Anterior chamber depth	mfERG	Multifocal electroretinogram	RCT	Randomized control trial
CR	cycloplegics refraction	mfpl	Multifocal progressive lenses	svl	Single vision lenses
D/Y	Diopter per year	IOP	intraocular pressure	VCD	Vitreous chamber depth
AA	accommodation amplitude	LT	Lens thickness		
AL	axial length	NPA	near point of accommodation		
KM	keratometry	OCT	optical coherence tomography		

atropine 1% over the lower concentrations in dark irides population such as in India. Moreover, they also advocated the morning administration of drops, as was done by Brodstein et al.[82] A multicentric randomized blinded trial evaluating the efficacy of 0.01% atropine versus placebo has been registered in Clinical trial registry of India and its results are expected soon.[83]

Combination Therapy With Atropine

Combination therapy for myopia progression using optical, pharmaceutical and environmental interventions may be useful in individuals poorly responsive to a particular modality. Moreover, drugs with differing mechanisms can have additive effect, as in cases of various diseases such as glaucoma, diabetes mellitus etc. In this regard, the effect

of atropine with orthokeratology has been studied, with promising outcomes.[84-86] Some role of acupressure combined with atropine therapy has also been seen.[87]

Implementation In Clinical Practice

Following the surge in the use of atropine in myopia control, 0.01% atropine has become commercially available in several countries including India. According to a survey [88] involving the Mumbai Group of Pediatric Ophthalmologists and Strabismologists in India, every clinician had used atropine 0.01% for myopic progression and two-thirds prescribe it routinely. The cut-off for progression used as an indicator for atropine therapy is 0.5D to 1D per year. A recent global survey including 940 pediatric ophthalmologists worldwide found that atropine 0.01% is the most popular eye drops for preventing myopia progression.[89]

Age, baseline refractive error, evidence of recent progression, and presence of myopia in parents are certain factors that predict the likelihood of myopia progression in a child. Cycloplegic refraction should be done at baseline and again repeated after 2-3 weeks to account for the hyperopic shift due to atropine therapy. The most accepted regimen at present is once nightly administration of atropine 0.01% eye drops. Subsequent follow up can be done at 6 monthly intervals. Parents should be educated about the side effects like photophobia, accommodation problems, dry eye and allergic reactions. They should also be explained about the long duration of therapy, and the possible poor response to therapy. Additionally, role of environmental modulation and lifestyle change should be adequately emphasized upon during counselling.

Though there is no consensus regarding the usage of atropine, the World Health Organization (WHO)(15) has given the guidelines for atropine therapy in myopia. (Table 2)

The period of atropine therapy should be at least for 2 years as the stabilization effect is usually achieved by then. Therapy can be discontinued thereafter if the refractive error remains stable or can be restarted if progression is noted. The age group targeted in most studies related to atropine was 6-13 years, but in Taiwan therapy is given for myopes till 18 years.[90] But in case of sub-optimal responders we have to consider alternate approaches. Alternatives strategies include increasing the concentration of atropine; continuing the same atropine concentration with environmental modifications like increased outdoors activity, change to different treatment modalities like orthokeratology. The role of environmental factors and the benefit of higher concentration is doubtful at this stage. Changing to higher concentration after 6 months of treatment in case of non-responsiveness has been recommended by Wu et al[91] But as reported in ATOM 2 study, the effect of atropine 0.01% is evident only in the second year of therapy, thus, it would be reasonable to wait for the response into the second year. So we are still in the process of figuring out the best approach for myopia prevention. Till then one can follow the above guidelines or treat the patient on a case-to-case basis.

Table 2 : Clinical guidelines for children aged 6-10 years with myopia >1.0 D and documented progression >0.5 D per year(15) (Adopted from Myopia Report for Web by the WHO)

Treat children with atropine 0.01% for 2 years		
Good responder:almost no myopic progression(<0.5 D over second year)	Moderate response : myopic progression of 0.5 D to 1.0 D over second year	Poor response: progression > 1.0 D over second year
Taper and stop atropine	Continue atropine 0.01%for a further 1-2 years, then taper and stop atropine	May be a non-responder. Consider taper and stop atropine
Follow subject for a year post stopping atropine Recommence atropine if significant rebound and continue review		

Side Effects

Atropine, especially high doses, should be administered with caution in children with spastic paralysis, Down syndrome, brain disorders and those taking drugs with CNS effects like barbiturates, phenothiazines and anti-emetics. Fever, altered mental status, dry mouth, flushing of skin, tachycardia, urinary retention and constipation, are some systemic side effects that have been reported with higher doses. Parents should be advised to present immediately if signs of adverse reactions are observed.

Common ocular side effects include near blur and photophobia. In ATOM2, accommodation amplitude was reduced to 4.0 D, 6.8 D and 11.8 D in the 0.5%, 0.25% and 0.01% groups respectively. This translates functionally to impaired near visual acuity especially in the former two groups who may need progressive glasses. Pupil size, both mesopic and photopic, was minimally affected (1mm) in the 0.01% group as compared to higher concentrations (change ≥3 mm). But these effects are temporary and complete recovery is noted after cessation of atropine and is quickest in the 0.01% group. In LAMP study, near visual acuity was unaffected at 2 years follow-up in all groups (0.05%, 0.025% or 0.01%) and none required progressive glasses.[92] Accommodation might be symptomatically reduced even with 0.01% atropine, but recovers within 3 months.[93] Sun protection should be advised if prescribing concentrations above 0.02%.[94] Allergic conjunctivitis, allergy associated dermatitis, dry eye[95] and convergence excess esotropia[96] have also been described with atropine use. But overall, low dose atropine has been found to be very acceptable especially in Asians eyes.

Missing Links

Role of atropine therapy for myopia control is an evolving subject with several missing links. Still algorithms have to be developed to address issues like when to start or stop the therapy, duration and concentration of the drug, and the variability in these aspects according to the ethnicity, age of onset, the level of myopia, or progression. Among the three concentrations of atropine(0.5%, 0.025% and 0.01%) used in ATOM2 study,0.01% appears to be the most effective. The two year result of the LAMP trial (atropine 0.05%, 0.025% and 0.01%) has shown 0.05% to be the best with comparable

side effects, while the rebound effect remains to be studied. However, the highest concentration without significant side effects has been shown to be 0.02%. Thus, the best concentration still needs to be determined. The management of non-responders or poor responders (to atropine therapy) is still unknown. Last but not the least, the effectiveness of atropine therapy in late onset myopia has not been studied. The use of atropine among children 13–18 years of age and in pre-myopes needs clinical studies.

Conclusion

To conclude, it can be said that the efficacy of atropine in controlling progression in myopia, is established beyond doubt. Yet, the concentration that is the best compromise between the effectiveness and side-effects remains to be determined. Till date, atropine 0.01% remains the optimal concentration for antimyopia therapy with best effect versus side effect profile. Better elucidation of the pathway of action of atropine, and eye growth in general may help in developing new strategies and agents for myopia control. There is a need of evidence based general guidelines for easier incorporation of atropine in clinical practice. Further, the combination therapy with modalities like bifocal or progressive spectacles lenses, dual focus contact lenses and orthokeratology needs more elucidation.

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