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Retardation of Myopic Progression and Axial Growth in Children by Atropine

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Abstract

Purpose: To determine the effect of atropine on axial length elongation by prospectively examining axial lengths and parameters of refraction in atropine treated and untreated eyes of myopic children.

Design: Randomized prospective clinical trial.

Methods: Four hundred and ninety-two myopic children participated in this study. (Mean age 10.1 years, ranging 5 and 16 years) Initial examination for both treated and control groups included cycloplegic refraction (initial refraction between -0.50 and -3.50D), tonometry, keratometry and axial length measurement by A-scan ultrasonography. Atropine treated eyes received one drop of atropine sulfate 1% daily in both eyes at bedtime. Measurements were repeated every six months for two years.

Results: The control eyes showed steady myopic progression, with mean refractive error changes of -0.25D after six months, -0.56D after one year, and -0.93D after two years. The atropine group demonstrated statistically significant mean refractive error changes of +0.30D after six months, +0.09D after one year and -0.50D after two years. The control eyes demonstrated steadily increasing axial lengths (+0.13mm in 0.5 year, +0.35 in 1 year and +o.45mm in 2 years). The atropine treated eyes showed virtually no axial length elongation after six months, significantly reduced axial length elongation (0.18mm vs. 0.35mm) after one year, and no significant difference compared with control eyes after two years.

Conclusion: Daily atropine by myopic children retards myopic progression and axial length elongation. A non-selective anti-muscarinic blocker atropine seems to retard myopic progression by a combination of deeper cycloplegia and reduction of fibroblast proliferation in sclera.

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Introduction

The development and progression of myopia in children has been demonstrated to be due to axial length elongation of the eye in most cases [1,2]. While many studies of atropine treatment in school children report partial inhibition of myopic progression [3-7], no study before 1986 has studied the effects of atropine on axial length in humans. Previous animal studies of form-deprivation myopia showed that atropine inhibited axial elongation in treated eyes [8,9].

Accommodation has been postulated to be one of the factors involved in myopic progression, whereby extended periods of accommodative effort render the individual unable to fully relax accommodation, and hence increasingly myopic. Numerous studies have associated environmental factors which required increased accommodative work with a higher incidence of myopia [10,11,12]. Wiesel and Raviola observed axial length enlargement of the eyes of lid-sutured newborn monkeys [13] and this has since been observed in newborn animals of other species, such as chicks [14] and rabbits [15]. Wiesel and Raviola postulated that degradation of the retinal image caused elongation of the globe via neuronal influence on trophic forces in the growing eye tissue. They further observed that application of atropine ointment in lid-sutured macaca arctoides monkeys prevented such elongation of the globes, concluding that the elimination of accommodation by atropine may prevent elongation of newborn monkey eyes [16]. However, several recent studies suggest that atropine inhibits myopic progression by mechanisms other than by inhibition of accommodation [8,9,17-19] Previous studies on animals certainly have limitations as the phenomena observed have variations by species and the form deprivation and neuronal control theories still lack support. This study was performed to see if the effects of atropine seen in other animals occur in human children.

The purpose of our study is to determine the effect of atropine on axial length in children by prospectively examining atropine treated and untreated children. Axial length and other parameters of refraction were measured serially and were compared between the two groups. This study re-examines the postulated role of atropine or muscarinic inhibitors in myopic eyes.

Design: A randomized prospective clinical trial.

Methods

Four hundred and ninety-two consecutive myopic children who presented to a private ophthalmology office in New York City and who met the inclusion criteria for this study were asked to participate in a clinical trial of atropine treatment for myopia. The inclusion criteria were: (1) refractive error at the initial visit between -0.50D and -3.50D in spherical equivalent errors as measured by cycloplegic refraction 40 minutes after cyclopentolate 1% instillation; (2) total astigmatism less than 1D; (3) age at the initial visit between 5 and 16 years old; (4) initial axial length between 22.0mm and 26.0mm as measured by A-scan ultrasonography; and (5) the absence of tropia, amblyopia, media opacity or other ocular structural abnormality. Spherical equivalent refractive errors, keratometric measurements and Intraocular Pressure (IOP) were compared between the control eyes and atropine treated eyes. The ethnic background of children was mostly of Asian; majority was Japanese, and a minority of Chinese and Koreans.

Prior to entering the study, patients and their parents were advised that the role of atropine in the treatment of myopia was still under investigation. As the study was conducted in the private office in New York City prior to 1986, there was no requirement of approval by Ethics Committee of any institutions, but the patients and parents were well informed of the investigational nature of the trial, and they consented to the trial.-Children were randomly assigned to treatment or control groups. Children in both groups were instructed to instill one drop of solution in each eye once a day from the bottle with label covered with a special label with identification numbers. The bottles of atropine treatment group contained atropine sulfate 1% with buffered preservatives. The bottles of control group contained artificial tears with preservatives. Children, parents, and personnel who gave bottles to children were unaware of the contents of the bottles.

After visual acuity tests by reading Snellen charts projected on the screen in darkened exam rooms and refractometry by Cannon RK-2 autorefractor, each subject was given cyclopentolate 1% one drop in each eye. After 40 minutes, refractometry was repeated with Cannon RK-2 auto refractor/keratometer, manifest refraction repeated, and axial length measured by Sonometrics' DBR-300 A-scan ultrasonogram with water bath probe by an ophthalmologist.

Initial and subsequent examinations for both the treated and control groups included the following: Snellen visual acuity testing, retinoscopy and manifest refractions 40 minutes following cyclopentolate 1% instillation, Goldmann applanation tonometry, keratometry by Haag-Streit ophthalmometry and axial length measurement by Sonometrics' DBR-300 A-scan ultrasonogram. Measurements were made with the children seated upright and comfortably positioned in a chin and forehead rest. The A-scan probe tip was aligned with the visual axis of the tested eye as the fellow eye was given full refractive correction and fixated on a target at 6 meters. A set of ten acceptable measurements were made per visit, with an acceptable measurement defined as having minimal probe compression, maximal peaks on the ultrasonogram, and a standard deviation of less than 0.1mm for the set of measurements. The axial length was calculated assuming an average sonic velocity of 1550 m/ sec.

Examiners were given daily refraction work sheet per each subject with an identification number of the subject but no other information about the subjects. All refractions were performed 40 minutes after cyclopentolate. Subjects were given distance correction and bifocal add of +2.50 D to +3.00 D were prescribed and they were instructed to use them as needed. Cycloplegic refraction after 1% cyclopentolate and axial length measurements were repeated every 6 months.

Results

Three hundred eyes were treated with atropine and 192 eyes served as controls. We randomized control and treated group consecutively, but those who returned to the first follow up exam after the initial assignment were included in the study and there is a difference in the number between the two

groups. The mean age at entry into the study was 10.1 years for the control eyes and 10.2 years for the atropine treated eyes. The gender distribution was even in both groups. The mean initial refractive power for all age groups was -1.47D for atropine treated eyes, and -0.92D for control eyes. The mean initial axial length for all age group was 24.12mm for the atropine treated eyes, and 23.66mm for the control eyes (Table 1). To evaluate the possibility that age differences may influence results, the data was divided into 3 groups, based on the age at the entry into the study: group I, younger than 9 years; group II, from 9 and under 12 years; and group III, 12 years and older. The numbers of eye examined were in parentheses in Tables. Mean initial refractive power and mean initial axial length (Table 1) in those groups are shown. A-scan axial length measurements were not successful in every patient. Only successful measurements were included in this report. Although the atropine treated eyes had slightly higher mean initial myopic power and had slightly larger axial length than the control eyes, these differences between atropine treated eyes and control eyes were not statistically significant (p>0.1). The error ranges for the data are presented as standard deviations.

Table 1: Mean Initial Group Characteristics.

	Control	Treated
Age	10.1 years (192)	10.2 years (300)
Retractive Error	-0.92 ± 0.69 D (192)	-1.47 ± 0.69 D (300)
Axial Length	23.66 ± 0.58 mm (192)	24.12 ± 0.48 mm (300)
Sex Distribution	Male: 51.0% Female: 49.0%	Male: 47.2% Female: 52.8%

Data for all ages in control eyes showed a steady myopic progression by -0.25D at six months, -0.56D at one year, and -0.93D at two years (Table 2). In contrast, atropine treated eyes lost myopia by +0.30D at six months, and +0.09D at one year. After two years of atropine, a statistically significant mean change of -0.50D was noted; this amounted to roughly one half the amount of myopic progression observed in control eyes after the second year. The number of the observed examinations in this report decreased over the two years due to untimely visits in subsequent examinations, as data of only those within one month of scheduled visits were included in the study and to the relocation of the family.

Table 2: Mean initial axial length and mean initial refractive power in diopters.

Age Group	Mean Initial Axial Length (In Millimeters)			Mean Initial Refractive Error (In Diopters)		
	Control	Treated	p-Value	Control	Treated	p-Value
All Ages	23.66 ± 0.58 (68)	24.12 ± 0.48 (146)	< 0.01	-0.92 ± 0.69 (192)	-1.47 ± 0.69 (300)	< 0.01
Under 9 Years	23.44 ± 0.54 (20)	23.83 ± 0.46 (44)	< 0.01	-0.87± 0.36 (52)	-1.33 ± 0.47 (90)	< 0.01
9 To Under 12 Years	23.66 ± 0.48 (36)	24.13 ± 0.43 (74)	< 0.01	-0.99 ± 0.46 (84)	-1.40 ± 0.51 (162)	< 0.01
12 Yrs And Above	23.99 ± 0.73 (12)	24.53 ± 0.48 (28)	>0.1	-0.96 ± 0.60 (56)	-1.60 ± 0.69 (48)	< 0.01

Serial mean axial length measurements for all ages demonstrated a steady and continuous increase in control eyes (Table 3). In atropine treated eyes, there was virtually no elongation at six months on average, some eyes shortened (one third of the eyes in group I), axial length elongated by 0.18mm, one half that observed in control eyes (0.35mm) at one year, both statistically significant changes (p<0.01). After two years, no significant difference in axial length of the 2 groups was seen (p>0.1). A scan axial length measurement was not successful in every patient at every visit. Only successful measurements were included in this report. The numbers shown in the tables represent the numbers of examinations performed and there are less axial length measurements than refractive power measurements.

At six months, atropine treated eyes showed a significant reduction in myopic power by 0.25D, as compared with a -0.29D myopic progression in control eyes (Table 4). The atropine treated eyes shortened by 0.08mm on an average, but one third of the eyes showed significant shortening of up to 0.3mm, while the other one third remained unchanged and the remaining one third showed an elongation, as compared to a mean elongation of control eyes by 0.21mm (Table 4).

Table 3: Changes in axial length in millimeters: All ages, in millimeters and Changes in refractive power in diopters: All ages, in millimeters.

	Changes in Axial Length: All Ages (in millimeters)			Changes In Refractive Power: All Ages (in diopters)		
	Duration of Treatment			Duration of Treatment		
	0.5 Years	1 Year	2 Years	O.5 Years	1 Year	2 Years
Control Eye	+ 0.13 ± 0.16 (68)	+ 0.35 ± 0.35 (48)	+ 0.45 ± 0.29 (24)	- 0.25 ± 0.50 (158)	+ 0.56 ± 0.68 (186)	- 0.93 ± 0.80 (78)
Atropine Treated Eyes	+ 0.01 ± 0.23 (128)	+ 0.18 ± 0.24 (142)	+ 0.41 ± 0.37 (84)	+ 0.30 ± 0.52 (300)	+ 0.09 ± 0.65 (264)	- 0.50 ± 0.70 (136)
p -Value	< 0.01	< 0.01	>0.1	< 0.01	< 0.01	< 0.01

Table 4: Changes in axial length in millimeters: Ages less than 9 years and Changes in refractive power in diopters: Ages less than 9 years.

	Changes in Axial Length: Age < 9 Years (in millimeters)			Changes in Refractive Power: Age < 9 Years (in diopters)		
	Duration of Treatment			Duration of Treatment		
	0.5 Years	1 Year	2 Years	O.5 Years	1 Year	2 Years
Control Eye	+0.21 ± 0.22 (20)	+0.51 ± 0.34 (14)	+0.50 ± 0.32 (6)	-0.29 ± 0.58 (52)	-0.59 ± 0.57 (40)	-0.82 ± 0.89 (18)
Atropine Treated Eyes	-0.08 ± 0.16 (28)	+0.17 ± 0.27 (44)	+0.44 ± 0.40 (20)	+0.25 ± 0.47 (90)	0.00 ± 0.46 (86)	-0.70 ± 0.78 (36)
p- Value	< 0.01	< 0.01	>0.1	< 0.01	< 0.01	>0.1

At one year, atropine treated eyes showed no change in refraction from the baseline, as opposed to a -0.59D myopic increase in control eyes. Atropine treated eyes elongated by 0.17mm, whereas control eyes elongated by 0.51mm.

After two years, the protective effect of atropine in inhibiting both myopic progression and axial length elongation waned, atropine treated eyes progressed by -0.70D, and axial length elongated 0.44mm. Control eyes progressed by -0.82D and elongated by 0.50mm; neither difference were statistically significant (p>0.1).

Group II. Age 9 and over and under 12 years (Table 5), and Group III. Age greater than 12 years (Table 6): Similar changes seen in all age group is observed for axial length and refractive errors.

Table 5: Changes in axial length in millimeters and Changes in refractive power in diopters: Ages between 9 to under 12 years.

	Changes in Axial Length: Ages 9 To Under 12 Years (in millimeters)			Changes in Refractive Power: Ages 9 To Under 12 Years (in diopters)		
	Duration of Treatment			Duration of Treatment		
	0.5 Years	1 Year	2 Years	O.5 Years	1 Year	2 Years
Control Eye	+ 0.07 ± 0.12 (36)	+ 0.29 ± 0.33 (22)	+ 0.47 ± 0.25 (10)	- 0.28 ± 0.39 (76)	- 0.63 ± 0.64 (84)	- 1.21 ± 0.84 (36)
Atropine Treated Eyes	+ 0.05 ± 0.17 (72)	+ 0.21 ± 0.26 (74)	+ 0.42 ± 0.36 (52)	+0.32 ± 0.51 (162)	- 0.19 ± 0.70 (138)	- 0.49 ± 0.71 (78)
p- Value	>0.1	>0.1	>0.1	< 0.01	< 0.01	< 0.01

Table 6: Changes in refractive power in diopters and Changes in refractive power in diopters: Ages 12 years and above 12 years.

	Changes In Axial Length: Ages 12 Years and Above (in millimeters)			Changes In Refractive Power: Ages 12 Years and Above (in diopters)		
	Duration of Treatment			Duration of Treatment		
	0.5 Years	1 Year	2 Years	O.5 Years	1 Year	2 Years
Control Eye	+ 0.16 ± 0.28 (12)	+ 0.36 ± 0.44 (10)	+ 0.25 ± 0.32 (6)	-0.09 ± 0.33 (30)	- 0.47 ± 0.60 (56)	- 0.67 ± 0.52 (22)
Atropine Treated Eyes	+ 0.01 ± 0.21 (28)	+ 0.10 ± 0.20 (26)	+ 0.28 ± 0.24 (12)	+0.34 ± 0.48 (48)	- 0.01 ± 0.51 (40)	- 0.35 ± 0.63 (20)
P- Value	>0.1	< 0.01	>0.1	< 0.01	< 0.01	>0.1

Discussion

Myopia may be noticed as early as 4-5 years of age. Early onset myopia later ends up in the category of high myopia. Onset at 6 years old used to be rare, but the onset is becoming earlier, prevalence is increasing. Many ocular professionals suspect near work or predominantly indoor activities to blame. Accommodation is a lenticular function, but progression of myopia is mostly due to elongation of axial length. How can accommodation lead to axial elongation?

Forces for inflation of globe as an expansion force:

A mechanical aspect of forces on sclera is expressed by Laplace's law in which:

$S = pr/2t$

S: Tangential stress (pressure) along the scleral surface

P: Intra-Sphere force, namely pressure, IOP (Intraocular pressure)

R: Radius of the curvature of the sphere, namely eyeball

T: Thickness of the sphere, globe, sclera

The stress on the ocular surface, scleral tissue, is proportionate to IOP and size of the globe and inversely proportionate to the thickness of the globe.

Once the globe gets bigger, it grows more and more. When the sclera becomes thinner by stretching, it becomes more prone to stretch as shown by Laplace's law, thus going into accelerated vicious cycle of inflation of the globe. IOP is regulated by equilibrium controlled by ciliary body.

Scleral collagen as containing factor of expansion.

Unit collagen fiber is 15 Å in diameter and 1500 Å long. It is in triple helical form like DNA. A collagen fibril of a normal sclera has fibrils with 165 Å in diameter by EM. The posterior sclera of pathologically myopic sclera has fibril with diameter of 135 Å as shown by Curtain. Brian Curtin considered this as genetically determined predisposition as a cause of weakness of sclera, but it may be explained by a result of mechanical stretch as explained by Laplace's law. Scleral collagen fibers are arranged like plastic materials. Like plastic materials, applied heat loosen adhesiveness of the fibers and become amenable to stretch. Once cooled the fibers will be reset in new from and shape. The heat in the eye is generated by retinal photoreceptors as light-induced photochemical reaction [20]. This aspect of the event needs to be seriously studied.

Several authors have shown that the empirical use of atropine may prevent or inhibit the progression of juvenile onset physiologic myopia [3-7]. Our study concurs with previously published reports, which show an average myopic progression rate of approximately 0.3 to 1.0D per year in untreated myopes [3,6,21,22].

Axial length elongation is commonly accepted as the basic event in juvenile onset myopia. Our study revealed variable degrees of arrest or deceleration of axial length elongation in atropine treated eyes especially in eyes of children younger than 9 years of age (Group I). The initial reduction in axial length which occurred in one third of the group I atropine treated eyes was an unexpected observation. This phenomenon was observed at six months of atropine treatment, followed by slow and gradual axial elongation, which continued until axial length eventually

caught up with control eyes after two years of atropine treatment. The lack of statistically significant may be due to the drop in number of subjects causing inadequate power to detect the difference. There are many animal studies reporting the retardation of axial growth with atropine. Our study concurs with such observations seen in chicks and newborn monkeys [16].

The measurement accuracy and instrument sensitivity are also concerns. The range of measurement error for the Sonometrics' DBR-300 ultrasonogram unit is less than 0.02mm per measurement. Larger errors may be caused by variations in surface contact or patient fixation, which potentially account for additional errors. The difference between axial length changes in length between atropine treated and control eyes exceeds the range of these measurement errors. By averaging multiple measurements and by increasing the sample size, the effect of measurement error is insignificant.

To review the pharmacology of atropine and the muscarinic receptor, atropine is a non-selective competitive inhibitor of muscarinic receptors, and it acts by preventing Acetylcholine (Ach) from reaching its receptors. Prolonged use of atropine may decrease the sensitivity of muscarinic receptor and may also down-regulate the number of muscarinic receptors, in either case reducing the long-term pharmacological efficacy of atropine. This is consistent with our data, which demonstrates the initial efficacy of atropine in inhibiting accommodation and axial length elongation in the first year, followed by diminishing efficacy after the first year of treatment. The M1 subunit of muscarinic receptor (M1) is not present in the ciliary body but is found in the retina and sclera [22-24]. M1 activation has been observed to promote the growth of scleral fibroblasts, whereas M2 muscarinic receptor activation has been observed to inhibit the growth of scleral fibroblasts [17,18]. Ach has been theorized to act directly on the scleral fibroblast M1 receptors to promote scleral growth [17]. Pirenzepine, a relative M1 antagonist has weak effect on accommodation and dilation of pupils (M2 effect) [3]. Pirenzepine has been noted to inhibit fibroblast cell cycle progression, in addition to inhibiting scleral extracellular matrix and collagen formation, changes which are normally seen in form deprivation myopia. M2 and M3 antagonists were found to be ineffective in blocking the development of form deprivation myopia in chicks [8].

Muscarinic antagonists may also mediate their action indirectly, by way of growth factors, which then modulate scleral fibroblast activity. Two such growth factors are Epidermal Growth Factor (EGF) and Insulin-Like Growth Factor-1 (IGF-1). Epidermal growth factor acts by tripling the scleral fibroblast proliferation rate in culture [25]. Insulin-like growth factor-1 has been shown to participate in the pathogenesis of myopia [25,26] Neonatal human scleral fibroblasts have been shown to have a high density of EGF receptors [18]. M1 activation increases EGF receptor density and M2 activation decreases EGF receptor density [17,18]. Receptor densities for both IGF-1 and EGF diminish with age [17,27]. This may partially account for the reduced incidence of myopia, as well as the slowed or halted progression of myopia observed with increasing age.

Recent animal studies have suggested a pharmacological role for muscarinic inhibitors as direct modulators of scleral growth, thus possibly elucidating the mechanism by which atropine inhibits myopic progression [8,9,17-19]. Several points can be made which support this hypothesis. Myopia often develops or progresses despite cycloplegia, implying a mechanism other than accommodation by which myopia progresses. Ciliary muscles lack the M1 subunit [22,24], the operative subtype whose inhibition prevents scleral fibroblast growth. Atropine instillation in humans yields pupillary dilatation because atropine inhibits muscarinic receptor subunits other than M1 in the human ciliary body to cause pupillary dilatation. It seems that cycloplegia is not the only mechanism by which atropine inhibits its myopic progression, as it is the inhibition of the scleral M1 receptors which is protective in preventing myopic progression. In addition, chicks lack muscarinic receptor or smooth muscle tissue in their ciliary muscles and receive primarily nicotinic innervation, as evidenced by the chicks' lack of mydriasis with atropine treatment [8,17]. Nevertheless, atropine treatment was noted to reduce both deprivation myopia [8] and spectacle lens compensation in chicks [28,29] This implies that an effect of atropine other than that of muscarinic blockade of accommodation (cycloplegia) is operative in reducing the deprivation myopia and spectacle lens compensation. This is most likely via inhibition of scleral M1 receptors. The eastern gray squirrel is a mammal which lacks the ability to accommodate, yet it too develops form-deprivation myopia [30] A recent study supports the theory that atropine promotes scleral remodeling, whereby effective doses of muscarinic antagonists have been shown to reduce the synthesis of scleral extracellular matrix [19]. These animal models for myopia suggest active scleral growth as the primary event in axial elongation of the globe. One could potentially test the theory of scleral remodeling by noting if atropine inhibits scleral growth in normal eyes.

Several retinal neurotransmitters have been studied as to their effects either directly on the sclera, or regarding the release of growth factors from the retina or retinal pigment epithelium, with secondary effects on the sclera. Recent studies in chicks have suggested a role of the retina in directing ocular growth. Experimental myopia has been shown to be regional in location in certain cases [31] and several local retinal factors have been implicated in causing or potentiating myopia. Decreased dopamine levels were noted in myopic chick eyes [32] and the dopaminergic agonist apomorphine was found to partially prevent deprivation myopia in chicks and monkeys [34]. This implies that dopamine plays a protective role in the pathogenesis of myopia. Increased levels of Vasoactive Intestinal Polypeptide (VIP) were found in the retinas of myopic monkeys [34,35] and increased VIP messenger RNA (mRNA) expression was noted in the retinal amacrine cells of myopic monkeys [36]. Ach, released into a synaptic junction and then bound to a muscarinic receptor, yields a classical cholinergic response. Chew theorized that Ach acts on the sclera either by direct action on the sclera or by triggering release of a growth factor from the retina or retinal pigment epithelium which leads to scleral growth [17]. Ach may interact with retinal dopaminergic neurotransmission, synergistically inducing Cyclic Adenosine Monophosphate (cAMP) formation [37] this in turn suggests a role for dopamine agonists in preventing experimental form deprivation myopia.

Arguments can be made against retinal Ach as the controller of scleral growth, however. Although it is conceivable that muscarinic antagonists act at the retina to block Ach-mediated control of scleral growth, acetylcholinesterases are abundant in both the retinal and the choroidal circulation and would likely cleave Ach before it reached the sclera from the retina. Topical or subconjunctival delivery of muscarinic antagonist would thereby be greatly diluted before reaching the retina. An adequate systemic level of muscarinic antagonist would therefore be required in order to elicit the desired local scleral effect.

This may indeed be the case, as a study showed that a single drop of atropine sulfate 1% solution administered to human subjects produced a mean plasma level of 0.86 mg/ml within 8 minutes [38]. Systemic absorption after uniocular topical atropine administration may therefore be potentially significant, and fellow-eye controls of eyes treated with atropine would thereby be inadvertently exposed to significant concentrations of muscarinic inhibitor, thus obviating the validity of the fellow eye controls. We eliminated this potential confounding factor, as separate individuals were used as controls in our study. There have been no studies which have demonstrated that atropine primarily targets the retina after topical application. Rather, most experiments in the literature which show the efficacy of muscarinic antagonist in modulating scleral growth have utilized the subconjunctival route of delivery, which theoretically maximizes the scleral exposure to the drug. We know of no report of measurement of retinal Ach levels in animal myopia models, which is a potential topic for a future study.

The effects of atropine other than on muscarinic receptor inhibition should also be considered. Dosages of both atropine and pirenzepine needed to prevent myopic progression have been shown to be much higher than that needed to block muscarinic receptor [39]. This implies possible non-specific effects of these drugs, including retinal toxicity to these drugs, as suggested by changes in the electroretinogram. Prolonged application of atropine in children is a safety concern and we do not advocate atropine as a treatment modality for myopia today.

The recent report by US Pirenzepine Study Group is an interesting development [40]. A 1-year, multicenter, double-masked, placebo-controlled parallel study at 13 US centers with 2% Pirenzepine ophthalmic gel was tried in myopic children 8 to 12 years of age, 117 Pirenzepine treated, and 57 placebo treated. The numbers of patients enrolled in their study are smaller than that of our study and the therapeutic efficacy in preventing myopic growth is also less than that seen in atropine study. Pirenzepine has been known for decades, but it is hard to penetrate the globe and the M1 muscarinic receptor inhibition is partial, while atropine is a non-selective and strong inhibitor of all muscarinic receptors. Due probably to smaller sample size, Pirenzepine Study group have not reported significant effect on axial length changes in treated eyes.

Our study has limitations. A prospective controlled study for a lengthy period is extremely difficult today due to frequent mobility of the family due to employment situations and keeping scheduled visits depends on the availability of parents. Although a relatively large numbers of children enrolled in the study initially, many follow up visits data were deleted due to untimely visits and loss of visits due to relocation of the family as many children enrolled were temporary residents in New York City. Although changes in keratometric power significantly alter refractive errors, we did not analyze changes in keratometric power or intraocular pressure in detail as our primary attention was focused on the changes in refractive state and axial length. A future prospective study with Pirenzepine analogues should include measurements of keratometric power, intraocular pressure, anterior chamber depth as well as axial length by noncontact IOL Master to further learn the changes in ocular parameters with such medications. Recent trials with low concentration Atropine is an interesting development and we await wide and long term effect.

Conclusion

This prospective controlled study shows that atropine used on daily basis by children has a retarding effect on myopic progression and retardation of axial elongation; like that observed in experimental animals [8, 9, 13-19]. Several plausible hypotheses are presented as to the mechanism by which atropine may be effective. We cannot conclude if there is neurochemical trophic effect on the retina as proposed by Raviola. There is increasing evidence that prohibition of growth factor or fibroblast by M1 receptor blockage to be a possible mechanism. We do not advocate use of 1% atropine for treatment of juvenile myopia today, but the experience with atropine was a necessary steppingstone for trial of pirenzepine and future development of similar pharmaceuticals. There is increasing interest in trials with lower concentration Atropine in children in Asia, and we await result of measurement of ocular parameters including axial length [41]. Pirenzepine and other pharmaceuticals which block M1 muscarinic receptors are of interest for clinicians in learning the mechanism of axial elongation and ultimately in preventing myopic progression in children.

References

1. Sorsby A. Biology of the Eye as an Optical System. In: Duane, TD, editor. Clinical Ophthalmology. Philadelphia: Harper and Row. 1985; 1: 1-17.
2. Duke-Elder S, editor. System of Ophthalmology: Ophthalmic Optics and Refraction. St. Louis: CV Mosby. 1970; 5: 164-167.
3. Bedrossian RH. The effect of atropine on myopia. Ophthalmology. 1979; 86: 713-717.
4. Dyer JA. Role of cycloplegics in progressive myopia. Ophthalmology. 1979; 86: 692-694.
5. Goss DA. Attempts to reduce the rate of increase of myopia in young people - a critical literature review. Am J Optom Physiol Opt. 1982; 59: 828-841.
6. Brodstein RS, Brodstein DE, Olson, RJ, Hunt SC, Williams RR. The treatment of myopia with atropine and bifocals: A long-term prospective study. Ophthalmology. 1984; 91: 1373-1378.
7. Yen MY, Liu JH, Kao SC, Shiao CH. Comparison of the effect of atropine and cyclopentolate on myopia. Ann Ophthalmol. 1989; 21: 180-187.
8. Stone RA, Liu T, Laties AM. Muscarinic antagonist effects on experimental chick myopia. Exp Eye Res 1991; 52: 755-758.
9. McBrien NA, Moghaddam HO, Reeder AP. Atropine reduces axial elongation and myopia in visually deprived chick eyes. ARVO Abstracts. Invest Ophthalmol Vis Sci. 1991; 32: 1202.
10. Donders FC. On the anomalies of accommodation and refraction of the eye. The Sydenham Society, London. 1864: 1-269.
11. Morgan RW, Speakman JS, Grimmshaw SE. Inuit myopia: An environmentally induced epidemic? CMA Journal. 1975; 112: 575-577.
12. Shum, PJ-T, Ko L-S, Ng C-L, Shin S-L. A biometric study of ocular changes during accommodation. Am J Ophthalmol. 1993; 115: 76-81.
13. Wiesel TN and Raviola E. Myopia and eye enlargement after neonatal lid fusion in monkeys. Nature 1977; 266: 66-68.
14. Christensen AM and Wallman J. Evidence that increased scleral growth underlies visual deprivation myopia in chicks. Invest Ophthalmol Vis Sci. 1991; 32: 2143-2150.

15. Vo TD, Coleman DJ, Iwamoto T, Silverman RH, Rondeau MJ. An animal model for myopia: Increase in axial length of the rabbit eye by ultrasonically induced cataract. ARVO Abstracts. Invest Ophthalmol Vis Sci. 1987; 28: 217.

16. Raviola E and Wiesel TN. An animal model of myopia. N Eng J Med. 1985; 312: 1609-1615.

17. Chew SJ, Lind G, Marzani D. A direct effect for muscarinic antagonists on the sclera: implications for the control of myopia. In: Chew SJ and Weintraub J, editors. Proceedings of the Fifth International Conference on Myopia. New York: Myopia International Research Foundation Inc. 1995: 229/1-229/8.

18. Chu E, Chew SJ, Thompson HW, Wilson RB, Beuerman RW. Muscarinic antagonists inhibit normal and epidermal growth factor-induced cell proliferation. ARVO Abstracts. Invest Ophthalmol Vis Sci. 1992; 33: 820.

19. Marzani D, Lind G, Chew SJ, Wallman J. The reduction of myopia by muscarinic antagonists may involve a direct effect on scleral cells. ARVO Abstracts. Invest Ophthalmol Vis Sci. 1994; 35: 2545.

20. Cooper and C.A. Biochemistry 15. 1970: 2970

21. Fledelius HC. The growth of the eye from age 10 to 18 years, a longitudinal study including ultrasound oculometry. Doc Ophthal Proc Series. 1981; 28: 211-215.

22. Mantyjarvi MI. Changes of refraction in school children. Arch Ophthalmol 1985; 103:790-892.

23. Honkanen RE and Abdel-Latif AA. Characterization of cholinergic muscarinic receptors in the rabbit iris. Biochem Pharmacol. 1988; 37: 2575-2583.

24. Honkanen RE, Howard EF, Abdul-Latif AA. M3-muscarinic receptor subtype predominates in the bovine iris sphincter smooth muscle and ciliary processes. Invest Ophthalmol Vis Sci. 1990; 31: 590-593.

25. Konno F and Takayanagi I. Comparison of the muscarinic cholinoreceptors in the rabbit ciliary body and the guinea-pig ileum. Eur J Pharmacol. 1986; 132: 171-178.

26. Watanabe K, Fujioka M, Takeshita T, Kawahara A, Amano M. Scleral fibroblasts of the chick embryo proliferate by an autocrine mechanism in protein-free primary cultures: Differential secretion of growth factors depending on the growth state. Exp Cell Res. 1989; 182: 321-329.

27. Waldbillig R, Arnold DR, Fletcher RT, Chader GJ. Insulin and IGF-1 binding in chick sclera. Invest Ophthalmol Vis Sci. 1990; 31; 1015-1022.

28. Schaeffel F, Glasser A, Howland HC. Accommodation, refractive error, and eye growth in chickens. Vision Res. 1988; 28: 639-657.

29. Irving EL, Sivac JG, Callender MG. Refractive plasticity of the developing chick eye. Ophthalmic Physiol Opt. 1992; 12: 448-456.

30. McBrien NA, Moghaddam HO, New R. Lid-suture myopia in a diurnal mammal with no accommodative ability. ARVO Abstracts. Invest Ophthalmol Vis Sci. 1990; 31: 253.

31. Wallman J, Gottlieb MD, Rajaram V, Fugate-Wentzek LA. Local retinal regions control local eye growth and myopia. Science 1987; 237: 73-77.

32. Stone RA, Lin T, Laties AM, Iuvone PM. Retinal dopamine and form deprivation myopia. Proc Natl Acad Sci USA. 1989; 86: 704-706.

33. Iuvone PM, Tigges M, Stone RA, Lambert S, Laties AM. Effects of apomorphine, a dopamine receptor agonist, on ocular refraction and axial elongation in a primate model of myopia. Invest Ophthalmol Vis Sci. 1991; 32: 1674-1677.

34. Stone RA, Laties AM, Hemmings HC, Jr, Raviola E, Wiesel TN. Increase in retinal vasoactive polypeptide after eyelid fusion in primates. Proc Nat Acad Sci USA. 1988; 85: 257-260.

35. Raviola E, Wiesel TN, Reichlin S, Lam KSL, Chetri A. Increase in retinal Vasoactive Intestinal Polypeptide (VIP) after neonatal lid fusion in the rhesus macaque. ARVO Abstracts. Invest Ophthalmol Vis Sci. 1991; 32: 1202.

36. Young TL, Raviola E, Russell ME, Wiesel TN. Upregulation of Vasoactive Intestinal Polypeptide (VIP) gene expression in the retina of myopic eyes following lid fusion in monkeys. ARVO Abstracts. Invest Ophthalmol Vis Sci. 1994; 35: 3776.

37. Brown JH and Rietow M. Muscarinic-dopaminergic synergism on retinal cyclic AMP formation. Brain Res. 1981; 215: 388-392.

38. Lahdes K, Kaila T, Huupponen R, Salminen L, Iisalo E. Systemic absorption of topically applied ocular atropine. Clin Pharmacol Ther. 1988; 44: 310-314.

39. Rickers A, Schaeffel F, Hagel G, Zrenner E. Dose-dependent effects of intravitreal pirenzepine on deprivation myopia and lens-induced refractive errors in chickens. ARVO Abstracts. Invest Ophthalmol Vis Sci. 1994; 35: 2547.

40. Siatkowski RM, Cotter S, Miller JM, Scher CA, Crockett RS, Novack. Safety and efficacy of 2% pirenzepine gel in children with myopia. Arch Ophthalmol. 2004; 122: 1667-1674.

41. Huy D.M. Tran, et al. Asia Pac J Ophthalmol (Phila). A Meta-Analysis Assessing Change in Pupillary Diameter. Accommodative Amplitude, and Efficacy of Atropine for Myopia Control. 2021; 10: 450-460.