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Significance of Atropine in Preventing Myopia Progression in Children

Emil Saeed[*], Joanna Konopinska and Zofia Mariak

Medical University in Bialystok, Bialystok, Poland

[*]**Corresponding author:** Emil Saeed, Medical University in Bialystok, Kilinskiego 115-089, Polska, Bialystok, Poland, Tel: 607556959; E-mail: emilsaeed1986@gmail.com

Abstract

School myopia is the most commonly encountered form of myopia. In its progression, the visual near and far point are drawn toward the eye as a result of the accommodation constriction and increased convergence tension. This leads to accommodation deficiency during near work, to binocularism, and to macropsia. In consequence, visual acuity is reduced, and the range of distinct vision is restricted.

There are reports of the effectiveness of administering 1.0% atropine to the conjunctival sac in order to reduce progression of low and medium myopia. The mechanism of this preventive action is still uncertain and not fully understood. It is probably based on removing chronic ciliary muscle tension. Although results of research on this subject are promising, the approach of ophthalmologists and patients to such treatment remains cautious. Is such an approach justified?

Keywords Myopia, Atropine, Children

Significance of Atropine

Atropine belongs to the group of medications that are antagonists of muscarinic receptors, called parasympatholytics. The main effect of their action is limitation or blocking of the effects of stimulation of the parasympathetic nervous system. In therapeutic doses, atropine has practically no influence on the central nervous system. In toxic doses, it induces anxiety, hyperexcitability, disorientation, hallucinations, delirium, and psychotic states, while scopolamine has euphoric, amnestic, and anesthetic effects even at low doses. For this reason, atropine has found applications in preventing nausea, vomiting, and increasing saliva secretion in motion sickness, among other things [1].

Antimuscarinics, administered systematically and conjunctivally, block M receptors of the pupillary sphincter, leading to pupil dilation and photophobia. The impact of atropine on ciliary muscle receptors manifests as cycloplegia and disruption of near sight. After conjunctival administration, this effect may persist up to 8-12 days. The main area of atropine's application in ophthalmology is diagnostics (as a mydriatic and cycloplegic), but it also prevents adhesions in inflammations of the iris and cornea when it is used in alternation with miotics. In healthy persons, atropine does not have an impact on intraocular pressure; however it raises IOP in persons with closed-angle glaucoma by causing pupillary block.

Myopia is the most common eye pathology in humans [2]. As early as in the 3rd century BC, Aristotle observed that myopic persons blink frequently and read and write from very near [3] in 1761, Morgagni proved that the eyeball's axis is lengthened in myopia, and 8 years later, Guerin indicated the relationship between myopia and increased accommodation tension. In 1864, Donders posed the hypothesis that myopia is hereditary. Three years later, Cohn proved that the number of nearsighted persons and the degree of nearsightedness increase along with school attendance based on studies of a massive population. Currently, approx. 1.3 billion people suffer from myopia around the world [4] Moreover, according to the latest reports, the incidence of this lifestyle illness is still growing [5]. This impairment is characteristic of specific human races and societies with a greater level of civilizational development, which is linked to genetic predispositions and environmental impact

The mechanism of the development of nearsightedness is unclear. The process of chronic excessive accommodation is indicated as a possible mechanism, as well as the response to uncontrolled release of retinal mediators stimulating growth of eyeball length during prolonged near work [6]. There is another hipothesis that convergence not accomodation leads to the eyeball prologation while looking to near objects [7]. In addition, genetic mechanisms may play a role [6,8]. Myopia is not just a progressing condition of improper refraction but also exacerbates the risk of serious complications such as myopic maculopathy, retinal delamination, or glaucoma, proportionally to the degree of impairment. Although the causes of nearsightedness and measures preventing against it are unknown, there have been reports that atropine may slow down or even halt its development [5,9-12].

Until recently, there was a lack of randomized population-based studies that would unequivocally solve the problem. In 2006, Chu et al. published the results of a study on 400 Asian children, ages 6-12, with myopia from –1 to –6 diopters.

Treatment of Myopia, is currently the largest randomized study on this subject, with a doubleblind trial and the use of a placebo [2]. They administered 1% atropine conjunctivally to children once daily for a period of 24 months. They primarily observed one parameter: progression of myopia in comparison with the preliminary study, conducted 2 weeks after commencement of atropine supplementation. In the group that was given the placebo, mean myopia progression after one year amounted to –0.76 ± 0.44 D, and in the group treated with atropine –0.03 ± 0.5 D. In addition, mean eyeball elongation was also evaluated. It amounted to 0.2 ± 0.3 mm in the placebo group, and in the group treated with atropine: 0.14 ± 0.28 mm. After another year of observation, the differences became even more marked. In the

placebo group, progression of refractive error was –1.20 ± 0.69 D, eyeball length 0.38 ± 0.38 mm, and in the group treated with atropine, respectively: –0.28 ± 0.92 D and 0.02 ± 0.35 mm. The undesired effects most commonly observed during control tests are photophobia and near vision impairment. No case of complicated cataract presented over the course of atropine treatment.

The results of conducted studies were promising. However, it was unknown whether the achieved effect is permanent or whether a so-called rebound effect will take place after treatment is completed. Thus, in 2009, the results of the program's continuation under Tong's management were published, just after atropine administration was concluded. Patients from both groups were tested after another 12 months had passed. The spherical equivalent in the group of children previously treated with atropine amounted to –4.29 ± 1.67 D, and in the placebo group –5.22 ± 1.38 D. Shortsightedness in the group treated with atropine was still lower, but in comparison with the control group, the rate of impairment progression was greater in these children in the third week, amounting to –1.14 ± 0.80 D in comparison to – 0.38 ± 0.39 D. Analysis of the entire 36-month period of study shows that the growth rate of nearsightedness in patients treated with atropine was lower (–0.46 ± 0.26 D/year vs. – 0.53 ± 0.30 D/year). Eyeball elongation was 0.50±0.48 mm on average in the group treated with atropine, and 0.52 ± 0.45 mm in the placebo group [13].

The effect of greater myopia progression after the discontinuation of atropine administration seems to be striking. The intensive progression rate can be explained by the immediate cycloplegic effect of atropine, which was achieved at the visit initiating the research program, and this rate was reduced in the next 6 months of the third year as a result of long-term, cumulated drug administration. However, it is still unknown what the further progression of the impairment was, and whether differences between the groups were equalized or not. To summarize, it can be stated that atropine administration slows down the progression of low and medium myopia and that this effect exhibits certain qualities of permanence because it persists one year after treatment is concluded. Additional studies showed that the amplitude of accommodation returns to normal after treatment is concluded [14].

Czepita et al. obtained similar results in studies on experimentally induced myopia. Its pathomechanism was similar to that of progressive myopia. Under natural conditions, it develops from birth to the 30-35th year of life [15] and is characterized by rapid progression. It leads to reduction of the distance of the near and far point from the eye, restriction of good field of vision to a narrow space, a significant drop in visual acuity, binocularism, and micropsia [16]. The image on the retina is deformed in an eye with progressive myopia, and color vision is impaired, field of vision is narrowed, and scotomas, nyctalopia, and photophobia appear [17,18]. Anatomopathological changes of the eyeball are based on, inter alia, elongation of its axis, growth of equatorial diameter, deepening of the anterior chamber, and thinning of the retina, choroid, and sclera. Degenerations develop around the retina, choroid, optic nerve, and vitreous humor. Dispersion of photoreceptors takes place on the retina, along with narrowing of its vessels and the vessels of the choroid and ciliary body. Moreover, there is loss of the retinal pigment epithelium, which is linked to breaks in Bruch's membrane. The cribriform plate is enlarged and deformed, and the sclera is also deformed, elongated, and narrowed, and the connections between its collagen fibers are weakened [19-21]. These changes are identical to those occurring in eyes with experimentally induced myopia (Table 1). Studies seeking to determine the causes of eyeball elongation and find measures to halt it have been conducted since 1975. These programs are conducted using laboratory animals. It has already been determined that the progression of experimental myopia is decreased as a result of atropine administration (as well as apomorphine, reserpine, and other drugs). The hypothesis of timolol's good effect was rejected [22].

	[31]	[23]	[17]	[32]	[33]	[34]
Type of experimental myopia	Negative lenses or light diffusers	Goggled eyes	Monocularly deprived by placement of a translucent occluder over the left eye	Lids were surgically fused at birth and kept closed for one year	Lens-induced myopia and form-deprivation myopia	Translucent goggles
Animals	Chickens	Leghorn cockerels	Chicks	Macaque monkeys	Chicks	Chicks
Methods	Intravitreal injections of atropine daily for 4 days, starting at day 8 post-hatching. Finally, atropine was intraperitoneally injected for 4 days in chicks that wore monocularly -7D lenses.	Various concentrations of different substantions, among them-atropine, were injected into goggled eyes three times at 48-hour intervals. Fellow control eyes received saline. Control animals received saline in both eyes.	A series of intravitreal injections of atropine (n=8) or saline vehicle (n=8)	Arctoides atropine administration	10-microL intravitreal injections in combination of Apomorphine alone or given with atropine.	Atropine solution was injected into the vitreous at two-day intervals.
Results	Intraperitoneal injection inhibited myopia development only at the highest dose. This inhibition was still less when the same dose was	Other than atropine and pirenzepine, only oxyphenonium caused full rescue from myopia.	Significant reduction in experimentally induced myopia in atropine-injected chicks, associated with a marked reduction in the axial elongation of the deprived eye.	In Macaca arctoides, atropine administration prevents abnormal eye elongation, and this suggests that lid-fusion myopia is caused by excessive accommodation.	Cholinergic mechanisms are indicated by the inhibitory effects of atropine on both lens-induced myopia and form-	Atropine suppressed myopia only at doses at which severe nonspecific side effects

provided through the vitreous of the fellow eye.					deprivation myopia.	were observed in the retina.	

UK: Unknown; D: Diopter

Table 1: Main experimental myopia research.

Canadian scientists achieved retardation of deprivation myopia progression in experimental studies conducted on animals after administering atropine to the vitreous chamber [23]. There were high hopes for progressive lenses that were to prevent excessive accommodation effort and thus retard excessive eyeball growth. Another method was to apply contact lenses that were to limit eyeball elongation by flattening the surface of the cornea. The effectiveness of all of these methods was, however, ultimately questioned.

Other reports can be found about several randomized clinical studies on the effect of atropine on myopia development [24-26] and on retrospective non-randomized research programs [27] (Table 2). They confirmed atropine's positive effect in retarding the development of myopia. Scientists from Hong Kong [14] investigated the effect of

1% atropine ointment, administered once daily to the conjunctival sac for children with medium and high myopia over a period of 1 year. The study included 23 children, aged 7.4 ± 1.6, with refractive error ≥ −3.0 D. The control group was comprised of children selected in terms of age, sex, and refractive error, but without the inclusion of atropine in the regimen. Visual acuity and eyeball length were evaluated. After a year, myopia progression in the group treated with atropine was −0.06 ± 0.79 D, and in the control group −1.19 ± 2.48 D. Eyeball elongation in the group treated with atropine was significantly lower than in the placebo group and amounted to 0.09 ± 0.19 mm vs. 0.70 ± 0.63 mm. Only one child from the atropine-treated group developed an allergic reaction to the administered drug. No other side effects were observed.

	[2]	[14]	[29]	[35]	[24]	[28]	[25]
Study plan: prospective/retrospective	+/-	+	+/-	+/-	-/+	-/+	-/+
Double masked study	+	UK	+	+	-	-	-
Randomiztion	+	UK	+	+	-	-	-
Quantity of myopia	1-6 D	≥ 3D	1-6 D		-0.5-5.5 D	<+1 (premyopia)	UK
Group size (individuals)	246	46	186	96	114	50	117
Follow up (years)	2	1	2	1	1	1	4.5
Concentration	1%	1%	0.5% 0.25% 0.1%	1%	0.5%		0.025%
Dosage	1 daily	1 daily	1 daily	1 daily	1 daily	1 daily	1 daily
Results: D/year (atropine group vs control group)	-0.28 ± 0.92 vs -1.2 ± 0.69	0.06 vs 1.19	-0.04 ± 0.63 -0.45 ± 0.55 -0.47 ± 0.91	-0.219 vs -0.914	-0.25 ± 0.26 vs -0.75 ± 0.35	-0.14 ± 0.24 vs -0.58±0.34	-0.23 vs -0.86

UK: Unknown; D: Diopter

Table 2: Study outcomes and results of the main clinical trials.

Fang et al. decided to go one step further and put out a hypothesis that administering 0.025% atropine to the conjunctival sac may not only retard the progression of myopia, but also prevent its initiation [28]. They included 50 children, ages 6-12, in their research. At the end of observation, mean spherical error in the atropine group amounted to −0.14 ± 0.24 D vs. −0.58 ± 0.34 D in the control group. Newly diagnosed myopia developed in 21% of children treated with atropine and in 54% of children not treated with atropine.

Lee et al. also attempted to prove the preventive effect of atropine on the development of myopia [24]. They included 114 eyes in 57 school-aged patients, with a refractive error ranging from −0.5 to −5.5

D, in their retrospective, 12-month study, for which they then administered a 0.5% atropine solution to the conjunctival sac. The average annual myopia progression was −0.28 ± 0.26 D in the group treated with atropine vs. −0.75 ± 0.35 D in the control group. A lower percentage of persons with uncontrolled myopia progression (≥ −0.5 D) was observed among children treated with atropine: 6% vs. 77.8%. Many researchers evaluated the effectivness of smaller atropine's concentrations (0.5, 0.25, 0.1 or even 0.05%) in myopia prevention [25,27,29]. The results suggest similar effectiveness of 0.5 and 1% concentration.

A study on a large clinical population is currently being conducted by scientists from Singapore. It is intended to compare the effectiveness of atropine, administered conjunctivally and in various concentrations, in patients with myopia [30].

Despite ongoing studies, the mechanism of atropine's preventive effect on limiting myopia development remains uncertain. Speculations on this subject boil down to its effect on ciliary muscle tension. Studies conducted on animal models indicate the probability that other mechanisms exist, however [23]. The application of atropine rules out experimental induction of myopia with eyeball elongation, and but total cycloplegia by means of surgical damaging of the Edinger-Westphal nucleus or even total destruction of the optic nerve do not. This observation suggests an alternative route of atropine's action, e.g. by affecting the sclera and retina. The potential coexistence of these mechanisms, by simultaneously retarding accommodation and scleral growth, also cannot be ruled out. On the other hand, atropine administration to all myopic children seems to be of dubious safety due to the possibility of the occurrence of late side effects such as complicated cataracts or toxic effect on the retina. It is also unknown whether long-term cycloplegia will not cause early presbyopia in the future. There are few reports on the subject of the effect of cholinolytic substances on the developing eye, particularly in the case of long-term administration. The tendency of recurring myopia progression after discontinuation of atropine remains undetermined. Concerns of an ethical nature in regard to some studies are also not without significance. Administration of atropine to one eye causes some children to be in a condition of anisometropia at the end of the observation period [2]. Furthermore, in one Asian study, intensified photophobia reduced the time children spent outside of their homes and resignation from school sports activities [13]. Before a final decision is made on introducing atropine into standards of myopia treatment in children, there is an absolute need to conduct more broad, randomized clinical studies that will account for the significance of environmental and genetic risk factors of myopia development.

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