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Evaluation of myopia management with atropine 0.01% in children in Poland

Maria Szwajkowska[1], Alina Bakunowicz-Łazarczyk[2]

[1]Department of Head and Neck Surgery in the field of ophthalmology of the Provincial Specialist Children's Hospital in Olsztyn, Poland
[2]Clinical Ophthalmology Department with a sub-department of treatment of strabismus of the University Children's Clinical Hospital in Bialystok, Poland

ABSTRACT

Aim of the study: Research on myopia is ongoing all over the world. The best therapeutic outcomes have been observed for pharmacological treatment with eye drops containing atropine, especially at low concentrations. The aim of the study was to determine whether the administration of atropine 0.01% drops might slow down the progression of myopia in children in Poland. In addition, an attempt was made to establish whether age, sex and severity of the visual defect had an impact on the efficacy of treatment with atropine 0.01%.

Material and methods: The study involved a total of 74 children aged 8 to 16 years, with myopia ranging from –1.0 to –6.0 diopters. The group treated with atropine 0.01% eye drops consisted of 50 patients (98 eyes), while the reference group comprised 24 patients (48 eyes). The study spanned a period of nine months. Patients in the study group used atropine 0.01% drops for a total of six months, after which the treatment was interrupted for three months. Patients in the reference group were not given any ophthalmic drugs during this period. The groups were also differentiated by age, sex, and baseline severity of the visual defect.

Results: The analysis revealed a statistically significant effect of atropine 0.01% drops on inhibiting the progression of myopia in children. The drops were found to be more effective in younger children (8-12 years old) and in children with a minor visual defect (–1.0 to –3.0 D) at baseline. The study found no statistically significant difference in the change in mean eye length between the two groups. Also, patient sex did not affect the progression of the defect or the change in eye length in both groups.

Conslusions: Atropine 0.01% eye drops are effective at inhibiting the progression of myopia. They cause no side effects, and are well tolerated by patients. The study shows that starting treatment in younger children, and children with a less severe visual defect, is recommended for the most effective inhibitory effect on the progression of myopia.

KEY WORDS: myopia, atropine, eye drops.

INTRODUCTION

Myopia is an important public health problem in all countries of the world. The defect is associated with numerous complications occurring already in young adults and causing significant impairment in visual acuity. Since the early 21st century, there has been an alarming growth trend in the number of myopia cases worldwide, with over 5 billion – or half of the human population – expected to be affected by the condition by 2050 [1-5]. Myopia has come to be classified as a lifestyle disease, as it affects an increasing number of people, especially children [6, 7].

While the role of genes in the development of congenital myopia is indisputable, the development of acquired myopia is a multifactorial process, and its pathogenesis has not yet been fully elucidated. Environmental factors are believed to account for approximately 80% of human characteristics, including myopia. Research is ongoing to identify the risk factors, especially modifiable environmental factors such as the place of living (especially urban environment), proportion of time spent indoors and outdoors, time spent by the child doing visual tasks at a close distance, amount of sleep, or diet [8, 9]. Studies show that the rate of progression of the defect is faster and the increase in axial length of the eye is greater during the autumn and winter months compared to the spring and summer. This tendency is most likely related to longer school time and more visual tasks done at home, as well as less sunshine and time spent outdoors [10-12]. In 2018, the World Society of Paediatric Ophthalmology and Strabismus (WSPOS) announced a position statement on the prevention of myopia and the efficacy of different treatment

CORRESPONDING AUTHOR
Maria Szwajkowska, MD, PhD, Department of Head and Neck Surgery in the field of ophthalmology of the Provincial Specialist Children's Hospital in Olsztyn, 18 A Żołnierska St., 10-561 Olsztyn, Poland, e-mail: marbia@poczta.fm

modalities. Based on the results of the largest randomized clinical trials from around the world, both genetic factors (especially in defects greater than –5.0 D) and environmental factors are recognized as playing a role in the development of myopia. The most important modifiable environmental factors include the amount of time spent outdoors and on near vision tasks, and the distance during visual work [6, 8].

The goal of myopia management is to inhibit the progression of this refractive defect and slow down the axial elongation of the eye. Currently recommended therapeutic options include appropriate corrective spectacle lenses and contact lenses (modifying relative peripheral hyperopia, bifocal, progressive), surgery, and pharmacological treatment. The best results are obtained by topical treatment with eye drops blocking muscarinic receptors. The main antagonists of these receptors are pirenzepine and atropine. Optimum outcomes are achieved by using drops containing atropine at a low concentration (0.01%). Low-concentration atropine does not cause side effects such as near vision impairment or glare as a result of pupillary dilation and paralysis of accommodation, and induces the lowest rebound effect after the withdrawal of treatment compared to drops containing atropine at higher concentrations. The mechanism of action of atropine in inhibiting the progression of myopia is not entirely understood. In addition to its relaxing effect on the ciliary muscle and impact on accommodation, atropine is known to be implicated in a non-accommodative mechanism as a transmitter. The mechanism involves the uptake of atropine by the retinal amacrine cells and their secretion of dopamine, which is a mediator inhibiting the growth of the eye. By binding to them, atropine can also contribute to scleral remodeling. According to another theory, atropine has a direct inhibitory effect on the synthesis of glycosaminoglycans by scleral fibroblasts, without any involvement of muscarinic receptors. Atropine at a concentration of 0.01% has a minimal effect on the muscarinic M3 receptors responsible for eye accommodation and pupillary dilation, but exerts a potent effect on the M1 and M4 receptors which have a beneficial impact on the control of myopia [13]. According to yet another theory an increased amount of light falling on the retina as a result of pupillary dilation following the administration of atropine has a direct inhibitory effect on eye elongation [14].

AIM OF THE STUDY

Studies conducted to date have mainly focused on children living in Asia. The aim of the present study was to determine whether the administration of atropine 0.01% eye drops might slow down the progression of myopia in children in Poland. In addition, an attempt was made to establish whether age, sex and severity of the visual defect in the study group had any impact on the efficacy of treatment with atropine 0.01%.

MATERIAL AND METHODS

The study group treated with atropine 0.01% eye drops consisted of 50 patients (98 eyes) aged 8 to 16 years (mean 10.7 years). The group comprised 31 girls and 19 boys. The reference group consisted of 24 patients of both sexes (48 eyes), aged 9 to 16 years (mean 12.3 years), with 14 girls and 10 boys. The patients were divided into two age groups: 8-12 and 13-16 years. Subgroups of patients with low (–1.0 D to –3.0 D) and moderate myopia (–3.25 D to –6.0 D) were also distinguished. Overall, the study spanned a period of nine months. During the initial six months, patients in the treatment group received atropine 0.01% drops which were instilled in both eyes every night before bedtime. After that period, the drops were discontinued for three consecutive months. During the same period, patients in the reference group did not use atropine 0.01% drops or any other ophthalmic drugs. Examinations performed at baseline included best corrected distance and near visual acuity (based on Snellen charts), eye length (biometric evaluation, UD-6000 Consultronix unit), refractive defect 30 minutes after prior application of tropicamide 1% eye drops twice in both eyes (evaluation with Righton Retinomax autorefractometer 3), and biomicroscopy with indirect ophthalmoscopy. The assessments listed above were repeated in the study group after one month, three and six months of treatment, and following withdrawal of the drops. In the reference group, the children were assessed at baseline and then three and nine months after study entry. There were no problems with adherence during the six month's treatment regimen. The drug was available from selected pharmacies throughout the duration of the study.

Children born prematurely, with glaucoma and coexisting eye diseases (especially uveitis) were excluded from the study. Other conditions disqualifying from participation included cataract, congenital retinal diseases, amblyopia, strabismus, prior treatment of myopia with orthocorrection or other methods (except for wearing monofocal corrective spectacle lenses or contact lenses). Children with a history of atropine allergy and systemic cardiovascular and respiratory conditions were also excluded.

The conduct of the study was approved by the Ethics Committee at the Medical University of Białystok (decision No. R-I-002/328/2018).

RESULTS

Statistical analysis was performed with Statistica 13 PL software using appropriate tests. The level of statistical significance was set at $p = 0.05$. The results were considered statistically significant if $p < 0.05$. It was evaluated how the severity of the visual defect in the right eye (RE) and left eye (LE) progressed in the study and reference groups. It was recognized that if the refractive defect increased from –0.25 to –0.5 D, the severity of the defect was the same, and if the increase was over –0.5 D, the defect had progressed.

During the study, the severity of the visual defect in the reference group increased by an average of –0.63 D in the RE ($p = 0.317$) and –0.55 D in the LE ($p = 0.726$). The length of the eye in the reference group with the examined visual impairment decreased by an average of 0.02 mm in the RE (the result was regarded as an error caused by the examination method; it was assumed that no increase in eye length had occurred), and increased by an average of 0.12 mm in the LE. However, the difference was not statistically significant ($p > 0.05$) (Figure 1). In

the study group, the severity of the visual defect in the RE and LE increased on average by –0.22 D and –0.21 D, respectively. The difference was statistically significant ($p < 0.05$) (Table I). The length of the eye in the study group increased on average by 0.19 mm in the RE and by 0.13 mm in the LE. The difference was not statistically significant ($p > 0.05$) (Table II).

Statistical analysis showed a significant difference between the study group and the reference group with regard to the evaluated visual defect in the RE and LE between the baseline and final examinations ($p < 0.05$). In the reference group, the mean increase in the severity of the visual defect in the RE and LE was significantly higher than in the study group.

Analysis of visual defect and eye length by sex

Statistical analysis of the visual defect and eye length between the groups depending on patient sex revealed no significant differences between the baseline and final examinations. The result means that the sex of patients in the study group had no effect on the progression of myopia.

Analysis of visual defect by age

Statistical analysis revealed a statistically significant difference in the visual defect in both eyes between the baseline and final examinations in the study and reference groups in younger children (group 1, children aged 8-12 years). In the reference group, the increase in the severity of the visual defect was found to be significantly higher than in the study group (Table III).

In the group of older children (group 2, 13-16 years), statistical analysis did not find a significant difference between the study and reference groups in terms of the visual defect in both eyes between the baseline and final examinations.

The length of the eye did not change in a statistically significant manner in any of the age groups.

As mentioned above, all the children were also divided into groups depending on the baseline severity of their visual defect. Statistical analysis found a significant difference between the study and reference groups in patients with less severe defect (group 1: from –1.0 D to –3.0 D). The progression of the visual defect in both eyes was found to be significantly less severe in the study group compared to the control group.

In patients with moderate myopia (group 2: from –3.25 D to –6.0 D), statistical analysis revealed no differences between the study and reference groups for both eyes (Table IV).

The length of the eye did not change depending on the visual defect in both groups. Atropine 0.01% drops were well tolerated by the children, and produced no side effects.

DISCUSSION

In spite of multiple publications and growing knowledge of available methods to control myopia, there are still a number of questions that need to be answered: at what age treatment should be started in children, at what severity of the

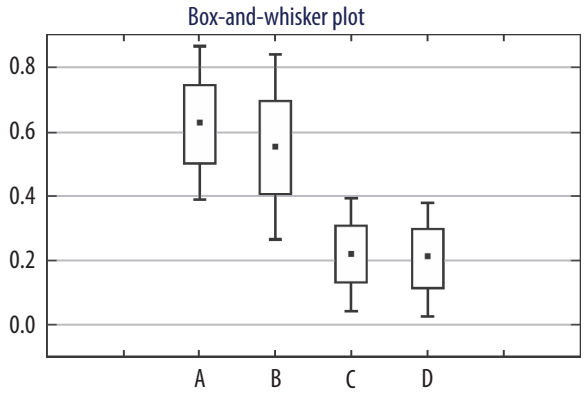

Figure 1. Box-and-whisker plot based on the mean difference in visual defect between the baseline and final examinations of the RE and LE in the study and reference groups

Table I. Progression of myopia in both groups

Study group		Reference group		Statistical significance (*p*)
OP	–0.22	OP	–0.62	$p = 0.010$
OL	–0.21	OL	–0.55	$p = 0.039$

Table II. Change in eye length in both groups

Study group		Reference group		Statistical significance (*p*)
OP	–0.19	OP	0.02	$p = 0.054$
OL	–0.12	OL	–0.13	$p = 0.948$

– oznacza wzrost długości gałki ocznej

Table III. Progression of myopia by age

Patients' age	Study group		Reference group		Statistical significance (p)
8-12 years	OP	–0.24	OP	–0.70	$p = 0.009$
	OL	–0.24	OL	–0.78	$p = 0.005$
13-16 years	OP	–0.14	OP	–0.47	$p = 0.275$
	OL	–0.09	OL	–0.09	$p = 0.804$

Table IV. Progression of myopia by severity of the visual defect

Range of visual defect	Study group		Reference group		Statistical significance (p)
From –1.0 to –3.0 D	OP	–0.04	OP	–0.46	$p = 0.021$
	OL	–0.04	OL	–0.59	$p = 0.004$
From –3.5 to –6.0 D	OP	–0.44	OP	–0.82	$p = 0.135$
	OL	–0.45	OL	–0.50	$p = 0.868$

visual defect treatment with eye drops should be initiated, how long patients should be treated and what eye drop concentrations should be used, and what factors should be taken into account before deciding to start treatment. Considering the fact that myopia occurs considerably earlier nowadays than a dozen or so years ago, it is usually recommended to start treatment in school-age children, typically between the ages of 6 and 12.

In the reported studies, treatment was routinely initiated when the defect was at least –1.0 D or –1.5 D, or in children with rapid defect progression [14-16]. Ophthalmologists worldwide are in consensus that treatment with atropine 0.01% drops should last at least two years. Patients in the treatment group of the reported study are now completing a two-year period of using the drops, and the treatment outcomes will be discussed in a separate publication.

It has been highlighted that the younger the age at which myopia develops, the longer the period of treatment that needs to be scheduled. Studies show that atropine at a concentration of 0.01% is both effective and safe, so it can be used for a longer period than the same drug at higher concentrations. Treatment with atropine at higher concentrations (e.g. 0.1% and 0.5%) produces a powerful rebound effect after the initial inhibition of defect progression and increase in eye length. Despite its weaker efficacy at the outset of treatment, atropine at low concentrations (0.01%, 0.02%) retains its beneficial activity over a longer period, and treatment is associated with a smaller rebound effect [15]. Research conducted on a large group of children treated with atropine 0.01% eye drops revealed no side effects accompanying treatment, such as pupillary dilation, accommodation paralysis or reduced visual acuity, especially at near vision [15, 16]. The side effects listed above were not observed in the reported study, either.

The findings of the present study were essentially consistent with those reported in other studies conducted globally. Larkin *et al.* analyzed a total of 100 patients of different ethnic backgrounds aged 6 to 15 years, in the USA. The progression of myopia after one year of treatment was –0.2 ±0.8 D, and after two years –0.3 ±1.1 D [17]. In the ATOM 2 study, the progression was –0.49 ±0.63 D after two years of treatment with atropine 0.01% eye drops [16, 18]. In the LAMP study, the progression was –0.59 ±0.61 D after a year of treatment [14]. A European study published by Sacchi *et al.* in 2019 showed a slowdown in progression to –0.54 ±0.61 D per year in patients treated with eye drops [19].

According to the authors of the publication, myopia corrected only with monofocal lenses progresses on average by 1 D per year in patients aged around 8 years, and decreases linearly to approximately –0.25 D/year at the age of approximately 13 years [15]. In the present study, the progression of the defect in the reference group would be on average approx. –1.0 D/year in the younger group and approx. –0.37 D/year in the older group, so the results correlate with the findings of other studies.

There have been literature reports of isolated cases of allergic reactions to atropine (ATOM 1, LAMP and others), but they usually occur when the drug is used at higher concentrations. They may develop from several weeks to even several years after starting treatment with atropine drops [20]. Other possible effects include signs of skin irritation around the eyes due to the preservative used in the drops. There is no need to stop therapy, but the management algorithm proposed by Kothari may be useful in the decision-making process to confirm or rule out allergy to atropine eye drops [20]. Meibomian gland dysfunction or treatment with other ophthalmic drugs may be additional risk factors for the development of allergy. Parents should be advised to apply pressure to the lacrimal points after instilling the drops, and to wipe excess drops from the skin around the eyes. This also prevents skin discoloration (hypopigmentation) which resolves gradually after drug withdrawal. The effect of using drops with low atropine concentrations (0.125% and 0.25%) on intraocular pressure was also evaluated. After one year, no significant changes were observed in relation to the control group [21]. Photochemical damage to the retina due to pupillary dilation has not been documented. When drops with higher atropine concentrations are used, sunglasses with UV filter are recommended, together with near vision correction, if needed. Atropine at a concentration of 0.01% does not cause pupillary dilation or perceptible paralysis of accommodation. In the available studies, the maximum concentration of atropine not inducing any clinical side effects (comparable to the use of atropine 0.01%) was 0.02%, though in the LAMP study all concentrations (0.05%, 0.025% and 0.01%) were well tolerated [14, 22]. The optimal concentration of atropine in eye drops should be determined based on the balance between drug efficacy and safety, with a minimal adverse effect on the comfort of life.

Among children treated with atropine eye drops, there is a group of non-responders, though the mechanism underlying poor response to atropine treatment is unknown [6, 23]. In such patients, options to consider include increasing the drug dosing frequency (to twice a day) or the concentration of the drug (e.g. to 0.02%), or combining pharmacological treatment with another therapeutic modality, such as orthocorrection [24, 25]. In the reported study group, there were two patients with progression greater than 0.5 D after nine months of treatment; they

were treated with eye drops administered twice daily, which again slowed down the rate of defect progression.

In addition, atropine 0.01% drops seem to be a cost-efficient pharmacological option, and they are well tolerated even by younger children, though they require regular use. In all cases, both patients and their parents should be instructed about the need to spend more time outdoors and perform less visual work, especially with electronic devices.

CONCLUSIONS

The analysis performed in the study revealed a statistically significant effect of atropine 0.01% eye drops on inhibiting the progression of myopia in children. The drops were effective both in younger (aged 8-12) and older (aged 13-16) children. However, the progression of the visual defect was less pronounced in younger children, and these results were statistically significant. During the nine-month study, there was no statistically significant difference in the change in mean eye length between the treated and untreated groups. Patient sex was found to have no effect on the progression of the defect or the change in eye length in both groups. Statistical analysis of the study group showed a significant difference in the progression of the visual impairment in both eyes depending on the severity of myopia (with greater progression observed in patients with defects higher than –3.25 D).

In our study, atropine 0.01% drops were found to have inhibited the progression of myopia compared to the group of untreated children. The best effects were seen in younger children (aged 8-12 years) and with a less severe visual defect at baseline.

Based on the study findings, atropine 0.01% drops seem to be a safe and effective method of controlling the progression of myopia.

DISCLOSURE

The authors declare no conflict of interest.

References

1. Sanz Diez P, Wahl S, Ohlendorf A. The standardized of high myopia. Graefes Arch Clin Exp Ophthalmol 2019; 257: 1807-1808.
2. Ikuno Y. Overview of the Complications of High Myopia. Retina 2017; 37: 2347-2351.
3. Fricke TR, Jong M, Naidoo KS, et al. Global prevalence of visual impairment associated with myopic macular degeneration and temporal trends from 2000 through 2050: systematic nreview, meta-analysis and modeling. Br J Ophthalmol 2018:102: 855-862.
4. Fujiwara T, Imamura Y, Margolis R i wsp. Enhanced Depth Imaging Optical Coherence Tomography of the Choroid in Highly Myopic Eyes. Am J Ophthalmol 2009; 148: 445-450.
5. Grzybowski A, Armesto A, Irribaren G, et al. The Role of Atropine Eye Drops in Myopia Control. Curr Pharm Des 2015; 21: 4718-4730.
6. Wu PC, Chuang MN, Choi J i wsp. Update in myopia and treatment strategy of atropine use in myopia control. Eye (Lond) 2019; 33: 3-13.
7. Holden BA, Fricke TR, Wilson DA, et al. Global Prevalence of Myopia and High Myopia and Temporal Trends from 2000 through 2050. Ophthalmology 2016 May; 123: 1036-1042.
8. Janowski M, Butle J, Handa J, et al. Concise Review: Using Stem Cells to Prevent the Progression of Myopia - A Concept. Stem Cells 2015; 33: 2104-2113.
9. Oleszczyńska-Prost E. Krótkowzroczność. Część I. Patogeneza w świetle aktualnego stanu wiedzy. Klinika Oczna 2018; 3.
10. Cooper J, Tkachentko AV. A review of Current Concepts of the Etiology and Treatment of Myopia. Eye Contact Lens. 2018; 44: 231-247.
11. Ramamurthy D, Lin Chua SY, Saw SM. A review of environmental risk factors for myopia during early life, childhood and adolescence. Clin Exp Optom 2015; 98: 497-506.
12. Read SA, Collins MJ, Vincent SJ. Light Exposure and Eye Growth in Childhood. Invest Ophthalmol Vis Sci 2015; 56: 6779-678.
13. Loughman J, Flitcroft DI. The acceptability and visual impact of 0,01% atropine in Caucasian population. Br J Ophthalmol 2016; 100: 1525-1529.
14. Yam JC, Jiang Y, Tang SM, et al. Low Concentration Atropine for Myopia Progresion (LAMP) Study: A Randomized, Double-Blinded, Placebo-Controlled Trial of 0.05%, 0.025%, and 0.01% Atropine Eye Drops in Myopia Control. Ophthalmolgy 2019; 126: 113-124.
15. Chia A, Lu QS, Tan D. Five-Year Clinical Trial on Atropine for the Treatment of Myopia 2: Myopia control with Atropine 0,01% Eyedrops. Ophthalmology 2016; 123: 391-399.
16. Chia A, Chua WH, Li W, et al. Atropine for the Treatment of Childhood Myopia: Changes after Stopping Atropine 0,01%, 0,1% and 0,5%. Am J Ophthalmol 2014; 157: 451-457.
17. Larkin GL, Tahir A, Epley KD, et al. Atropine 0,01% Eye Dropsfor Myopia Control in American Children: A Multiethnic Sample Across Three US Sites. Ophthalmol Ther 2019; 8: 589-598.
18. Chia A, Chua WH, Cheung YB, et al. Atropine for the Treatment of Childhood Myopia: Safety and Efficacy of 0,5%, 0,1% and 0,01% Doses (Atropine for the Treatmentof Myopia 2). Ophthalmology 2012; 119: 347-354.
19. Sacchi M, Serafino M, Villani E, et al. Efficacy of atropine 0,01% for the treatment of childhood myopia in European aptients. Acta Optthalmol 2019; 97: e1136-e1140.
20. Kothari M, Jain R, Khadse N. Allergic reactions to atropine eye drops for retardation of progressive myopia in children. Indian J Ophthalmol 2018; 66: 1446-1450.
21. Lee CY, Sun CC, Lin YF, et al. Effects of topical atropine on intraocular pressure and myopia progression: a prospective comparative study. BMC Ophthalmol 2016; 16: 114.
22. Lee JJ, Fang PC, Yang IH, et al. Prevention of Myopia Progression with 0,05% Atropine Solution. J Ocul Pharmacol Ther 2006; 22: 41-46.
23. Diaz-Llopis M, Pinazo-Duran MD. Superdiluted atropine at 0,01% reduces progression in children and adolescents. A 5 year study of safety and effectiveness. Arch Soc Esp Oftalmol 2018; 93: 182-185.
24. Kinoshita N, Konno Y, Hamada N i wsp. Additive effects of orthokeratology and atropine 0,01% ophthalmic solution in slowing axial elongation in children with myopia: first year results. Jpn J Ophthalmol 2018; 62: 544-553.
25. Tan Q, Ng AL, Cheng GP, et al. Combined Atropine with Orthokeratology (AOK) for Myopia Control: Study Design and Preliminary Results. Curr Eye Res 2019; 44: 671-678.