

Lewkowicz Martyna, Nowakowska Katarzyna, Pawlina Mateusz, Raksa Karolina, Ziętara Karolina, Koziół Magdalena. Efficacy and safety of atropine to control childhood myopia progression. *Journal of Education, Health and Sport*. 2022;12(8):146-154. eISSN 2391-8306. DOI <https://dx.doi.org/10.12775/JEHS.2022.12.08.014>  
<https://apcz.umk.pl/JEHS/article/view/JEHS.2022.12.08.014>  
<https://zenodo.org/record/6635985>

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of December 21, 2021. No. 32343. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical Culture Sciences (Field of Medical sciences and health sciences); Health Sciences (Field of Medical Sciences and Health Sciences).

Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 21 grudnia 2021 r. Lp. 32343. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przepisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

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The authors declare that there is no conflict of interests regarding the publication of this paper.

Received: 10.05.2022. Revised: 25.05.2022. Accepted: 12.06.2022.

## Efficacy and safety of atropine to control childhood myopia progression

Skuteczność i bezpieczeństwo atropiny w kontrolowaniu progresji krótkowzroczności u dzieci

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**Introduction:** Nearsightedness is one of the most common eye defects in people all over the world. If left untreated, it leads to a number of serious eye complications that can result in irreversible loss of vision. It is estimated that by 2050, Half of humanity will be burdened with this disadvantage, so it has become a priority to try to find ways to prevent and treat myopia, among which the administration of atropine drops is very effective.

**Aim of the study:** The aim of this study is to evaluate the safety and efficacy of atropine in controlling the progression of myopia and to investigate the relationship between the dose of atropine and the effectiveness of controlling the progression of myopia.

**Material and methods:** The PubMed and Google Scholar databases were used to review the literature.

**Results:** Eye drops with 1% atropine showed the greatest efficacy in the control of myopia. However, their use was limited due to the occurrence of side effects such as impaired accommodation and photophobia. In the ATOM 2 study, which investigated the use of atropine at various concentrations in children with myopia, it was found that 0.01% is the optimal concentration with good efficacy and minimal side effects. An important element of the study was the observation of the rebound effect after cessation of atropination. One of the breakthroughs was the LAMP study using atropine at a concentration of 0.05%, 0.025%, 0.01% in eye drops. This study provided evidence for the first time that low-concentration atropine is effective compared with placebo in myopia. In addition, both efficacy and side effects followed a concentration-dependent response ranging from 0.01% to 0.05% of atropine. Among them, 0.05% of atropine was the optimal concentration to achieve the best efficacy and safety profile.

**Conclusions:** Low concentration of atropine is effective in the control of myopia. Its widespread use can help prevent the progression of myopia in high-risk children. However, further investigation of the rebound phenomenon after discontinuation of drops and a long-term, individualized approach to treatment is warranted.

**Key words:** atropine, childhood, myopia

## **Introduction:**

Nearsightedness, otherwise known as myopia, is one of the most common eye defects in people around the world [1,2] It is a refractive error in which a beam of light is incorrectly focused in front of the retina. The reasons for this may be, among others abnormal length of the eyeball (axial myopia) or the power of the optical centers of the eye (refractive myopia). [3] High myopia is often associated with an increased risk of a number of serious eye complications that can result in irreversible vision loss. These include retinal detachment, degenerative changes in the macular choroid, premature cataract, and glaucoma [4-9].

Myopia is the most common refractive error that is a worldwide problem due to the constantly growing number of patients. The American Academy of Ophthalmology (AAO) and the Brien Holden Vision Institute (BHVI) estimate that half of the world's population will be affected by this visual impairment by 2050 [10], and the World Health Organization has recognized

myopia as the main cause of visual impairment in developed countries and has given it the status of epidemic [11] Currently, about 1.6 billion is affected by myopia people all over the world [12] and the number continues to grow. Myopia is the most common refractive error that is a worldwide problem due to the constantly growing number of patients. The American Academy of Ophthalmology (AAO) and the Brien Holden Vision Institute (BHVI) estimate that half of the world's population will be affected by this visual impairment by 2050 [10], and the World Health Organization has recognized myopia as the main cause of visual impairment in developed countries and has given it the status of epidemic [11] Currently, about 1.6 billion is affected by myopia people all over the world [12] and the number continues to grow. Among young adults in developed countries of East Asia, as much as 80-90% suffer from myopia [13-15], while in developed Western countries the proportion is 20-40%. In Poland - according to the latest research carried out by SW Research on behalf of the Hoya company, as many as 62% of children with a diagnosed sight defect suffer from myopia. [16] Such a large percentage of people suffering from this visual impairment has prompted doctors and scientists to try to find effective ways to prevent and treat myopia. Among the activities discussed in slowing the progression of myopia are optical correction, including bifocal eyeglass lenses, orthocorrective lenses, multifocal contact lenses, extra time outdoors, and pharmacological agents such as topical atropine. [17-19]

Atropine, a non-selective muscarinic receptor antagonist, has been extensively studied in recent years to prevent worsening of myopia in children. Although the exact mechanism and site of action of atropine are still unknown [20,21], varying concentrations of atropine are commonly used (low dose 0.01%; moderate dose 0.01% -0.5%; high dose 0.5% - 1 0%) topically as eye drops [22-24]. Numerous studies are still conducted in order to determine the most optimal dose while minimizing the risk of side effects. To date, many uncertainties remain with the clinical use of atropine, such as dosing, safety concerns, and the possibility of generalizing the use of atropine to different ethnic groups.

### **Material and method:**

The PubMed database and Google Scholar were used to review the literature. Articles in English were searched using the following keywords: atropine, atropine eye drops, myopia progression, children.

### **Results:**

The first information about the use of atropine as a method of myopia control comes from the end of the 19th century [25]. Its use has been the subject of numerous studies conducted since the 1960s. [26].

In 1989, Yen et al. [27] conducted the first randomized, placebo-controlled study of the use of 1% atropine to control myopia. The study involved a total of 96 children aged 6 to 14 years, who were randomly assigned to each group. Group I received 1% atropine solution, group II received 1% cyclopentolate solution, and group III received placebo for 1 year. Scientists showed that 1% atropine solution provided the best effectiveness in the control of myopia among 3 groups, with myopia progression by  $-0.22 \pm 0.54$  D / year using atropine,  $-0.58 \pm 0.49$  D / year using cyclopentolate and  $-0.91 \pm 0.58$  D / year with placebo. [27]. At the same time, all children in the group receiving 1% atropine complained of photophobia which significantly impeded everyday functioning. Unfortunately, the study had some limitations as the axial length (AL) was not taken into account, so the effect of atropine on axial extension could not be assessed.

The next steps in the use of atropine to delay the development of myopia were taken in 1999 by Shih et al. [28] Researchers conducted a randomized, controlled study on 200 children aged 6 to 13 years, using 0.5%, 0.25%, 0.1% atropine and 0.5% tropicamide (as a control group). After 2 years of follow-up, the mean progression of myopia in each group was  $-0.04 \pm 0.63$  D / year,  $-0.45 \pm 0.55$  D / year and  $-0.47 \pm 0.91$  D / year in groups 0, 5%, 0.25% and 0.1% of the atropine groups and  $-1.06 \pm 0.61$  D / year in the control group with 0.5% tropicamide, respectively. All groups treated with atropine showed significant efficacy compared to the control group ( $p < 0.01$ ) [28]. The side effects of photophobia were only seen in 22% of the children in the 0.5% atropine group during the first 3 months of treatment, confirming that lower atropine levels were associated with fewer side effects. However, this study was limited by the lack of data on AL as well as on the placebo control group.

In 2006, Chua et al. [29] conducted the Atropine for the Treatment of Childhood Myopia (ATOM 1) study, which provides the strongest evidence that a 1% solution of atropine affects the control of myopia. 400 children participated in the study (346 children completed the study). In each of them, one randomly selected eye was treated with atropine at a concentration of 1% or a drop of placebo. The progression of myopia in the placebo group was  $-1.20 \pm 0.69$  D, and in the study group only  $-0.28 \pm 0.92$  D. The axial length of the eyeball increased in the control group by  $0.38 \pm 0.38$  mm, while in the study group remained unchanged. Moreover, only 18% of participants complained of photophobia. The use of

atropine has been found to be an effective method of slowing the progression of myopia and increasing the axial length of the eyeball [29].

In the ATOM2 study, the results obtained on a group of 400 children were analyzed and classified into three groups in the quantitative ratio of 2: 2: 1 depending on the concentration of the atropine used, 0.5%, 0.1%, and 0.01%. Within two years, there was an average increase in myopia in individual groups of the order of  $-0.30 \pm 0.60$  D;  $-0.38 \pm 0.60$  D;  $-0.49 \pm 0.63$  D, while the change in the length of the eyeball was  $0.27 \pm 0.25$  mm, respectively;  $0.8 \pm 0.28$  mm;  $0.41 \pm 0.32$  mm. [30]

An important aspect in the conducted research was the rebound effect, i.e. an increase in myopia after cessation of atropinization. The children in studies ATOM1 and ATOM2 were followed at the end of the first two-year study period. It turned out that after one year, the greatest increase in myopia occurred in eyes that were treated with 0.5% and 1% atropine [29, 30]. Additionally, children from the ATOM2 group underwent further examination. It was found that the higher the concentration of atropine used, the greater the percentage of children experienced the disease progression by  $\geq -0.50$  D within one year from the cessation of atropinization. In the group in which atropine 0.5% was used, such an increase in myopia was observed in 68% of children, after atropinization with a 0.1% solution - 59% of children, and after using atropine 0.01% in only 24% of children. So it was concluded that the use of low concentration atropine eye drops is better tolerated and has less rebound after treatment discontinuation.

Another meta-analysis was conducted by Gong et al. [31] It included 19 studies on the use of atropine at various concentrations in the inhibition of the progression of myopia. Scientists proved that the efficacy of atropine is independent of the concentration from 0.01% to 1% of atropine, however high doses were associated with more side effects such as the occurrence of photophobia (43.1% with 1% atropine, 17.8% with the use of atropine). for 0.5% atropine, 6.3% for 0.01% atropine).

A similar study to determine the optimal dose of atropine in the control of myopia progression was carried out by Hong Kong researchers. In 2018, scientists published the results of the LAMP study in which they assessed the effects of treatment with atropine eye drops at various concentrations. In this study, it was observed that over a 1-year period, the use of atropine drops (0.05%, 0.025%, 0.01%) was associated with a slower progression of myopia, and the effect was greater with the higher the drug concentration [32]. Due to the promising results of the phase 1 trial, LAMP acronym, it was decided to evaluate the efficacy and safety of long-term use of atropine in children with myopia, and a phase 2 trial was conducted,

which was an extended follow-up of patients from the LAMP trial. 350 out of 438 children aged 4–12 completed the two-year follow-up period. The overall progression of myopia from baseline was the lowest among patients treated with 0.05% atropine eye drops and amounted to -0.55 D. In children receiving 0.025% atropine eye drops, the progression of myopia was -0.85 D and at a dose of 0.01% it was -1.12 D. The mean change in the axial length of the eyeball in the corresponding groups at that time was 0.39 mm, 0.50 mm and 0.59 mm, respectively. The authors of the study concluded that over the period of 2 years, the most effective atropine concentrations (0.05%, 0.025% and 0.01%) in terms of delaying the progression of myopia and changes in the axial length of the eyeball, as in the first year of the study, remained drops at a concentration of 0.05%. It was also observed that atropine at a concentration of 0.01% was more effective in the second than in the first year of its use, which was not observed for the other two doses of the drug. Treatment with atropine, regardless of the dose, was well tolerated and did not adversely affect the patients' quality of life. Symptoms of photophobia were similar in all groups (7.8% with 0.05% atropine, 6.6% with 0.025% atropine and 2.1% with 0.01% atropine).

The current randomized controlled trials confirm the efficacy of atropine at a low concentration compared to placebo, and 0.05% provides the best efficacy and safety in controlling the progression of myopia and AL prolongation. However, there are still many important issues that require further research. Firstly, it is important to determine the optimal concentration of eye drops over a longer period of time, the duration of therapy, and to assess long-term efficacy and long-term side effects. Also, the rebound phenomena following atropine discontinuation observed in studies ATOM 1 and ATOM 2, which may have an impact on the treatment regimen and the withdrawal strategy, should not be forgotten.

### **Conclusion:**

In conclusion, the results of the studies showed that low atropine concentration is useful in delaying the progression of myopia in a certain percentage of school-age children with myopia. The widespread use of low-concentration atropine, especially in East Asia, may help prevent the progression of myopia in high-risk children. The results of the LAMP study provide the latest evidence for the use of low concentration of atropine, in particular 0.05% of atropine, due to its higher efficacy and, at the same time, a well-tolerated safety profile. However, a longer period of observation of the effect of atropine is needed. Further investigation of the rebound phenomenon after discontinuation of drops and a long-term, individualized approach to treatment is also warranted.

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