

Combination Therapy with Atropine 0.05% and Myopi-X® Glasses: Is it Effective in Myopia Control?

© Nilay Akagün, © Uğur Emrah Altıparmak

Acıbadem Hospital Ankara, Clinic of Ophthalmology, Ankara, Türkiye

Abstract

Objectives: To investigate whether the combination therapy of Myopi-X® peripheral progressive addition lenses (PAL; Novax®) and atropine 0.05% provides an additive effect compared to monotherapies with either Myopi-X® PAL or atropine 0.05%.

Materials and Methods: This retrospective cross-sectional study reviewed the clinical records of 51 patients, categorized into three groups: 27 in the Myopi-X group, 13 in the atropine 0.05% group, and 11 in the combination therapy group using Myopi-X peripheral PAL with atropine 0.05%. Baseline characteristics, including age, cycloplegic spherical equivalent (SE), and axial length (AL), were compared between the groups. Twelve months after treatment initiation, changes in SE and AL were assessed and compared between the groups.

Results: Among the 51 patients analyzed, the baseline characteristics differed significantly between the groups, with the atropine 0.05% group showing a higher average age, longer AL, and lower SE compared to the other groups. After 12 months, no significant differences were found in SE changes between the treatment groups ($p=0.35$). Similarly, changes in AL did not significantly differ between the groups ($p=0.10$), although age had a significant impact on AL change ($p=0.01$). No significant differences

were observed in pairwise comparisons of SE or AL changes between the groups.

Conclusion: In this study, combining atropine 0.05% with Myopi-X PALs did not provide an additive benefit. The literature suggests that both treatments are effective in slowing myopia progression individually; however, in our study, their combination did not significantly improve SE progression or axial elongation compared to monotherapies. Further randomized studies with larger patient groups are needed to confirm these findings and assess long-term effects.

Keywords: Myopia management, progressive addition lenses (PAL), atropine 0.05% therapy, combination therapies for myopia control

Introduction

Myopia is a common refractive error worldwide, and its increasing frequency is considered a global epidemic.^{1,2} The prevalence of myopia is expected to increase, and it is estimated that by 2050, myopia and high myopia will affect approximately 50% and 10% of the world's population, respectively.³ In addition to the direct economic and social burden of myopia, the associated ocular complications may lead to substantial visual loss.⁴

Both genetic and environmental factors influence the occurrence and progression of myopia, and some seem to be closely linked. A lack of outdoor activity, high education levels, and prolonged near work are important risk factors.⁵ Currently, the main approaches to myopia control include atropine eye drops of varying concentrations, orthokeratology, dual-focus contact lenses, multifocal contact lenses, and myopia control spectacle lenses.⁶

Combination therapy is a common practice in the medical field for optimizing treatment efficacy while minimizing adverse effects. Examples include cancer care, diabetes treatment, and glaucoma management, among many others.^{7,8,9,10} Similarly, combining therapies with different mechanisms of action may be

Cite this article as: Akagün N, Altıparmak UE. Combination Therapy with Atropine 0.05% and Myopi-X® Glasses: Is it Effective in Myopia Control? Turk J Ophthalmol. DOI: 10.4274/tjo.galenos.2024.17971. [Ahead of Print].

The study was presented as an oral presentation at the EVER 2024 Valencia meeting. The abstract of our oral presentation has been published in Acta Ophthalmologica, volume 103, issue S284, under the title "Abstracts from the 2024 European Association for Vision and Eye Research Congress, 3-5 November 2024, Valencia- January 2025."

Address for Correspondence: Nilay Akagün, Acıbadem Hospital Ankara, Clinic of Ophthalmology, Ankara, Türkiye

E-mail: nildnd@yahoo.com ORCID-ID: orcid.org/0000-0002-1522-3034

Received: 28.06.2024 Accepted: 19.12.2024

DOI: 10.4274/tjo.galenos.2024.17971

more beneficial than monotherapy for reducing the progression of myopia. There are studies in the literature investigating the efficacy of combination treatments aimed at slowing the progression of myopia. Combination therapies involving orthokeratology and atropine, myopia control spectacle lenses and atropine, as well as multifocal contact lenses and atropine have been trialed, with varying outcomes. In this study, we aimed to investigate whether combining Myopi-X® peripheral progressive addition lenses (PAL; Novax®) with atropine 0.05% therapy provides an additive effect compared to monotherapy with Myopi-X lenses or atropine 0.05%.

Materials and Methods

This retrospective cross-sectional study was approved by the Acibadem Healthcare Institutions Medical Research Ethics Committee (decision no: 2024-8/302, date: 16.05.2024). Informed consent forms were obtained from the parents/guardians of all patients included in the study. The clinical records of patients who used Myopi-X lenses (group 1), received atropine 0.05% eye drop treatment (group 2), or received combined Myopi-X lenses and atropine 0.05% eye drop treatment (group 3) between November 1, 2022 and November 30, 2023 were reviewed. The inclusion criteria were having an age of 5-16 years at the start of therapy, initial myopic spherical equivalent (SE) between -1 and -9 diopters (D), astigmatism less than 2.0 D, anisometropia less than 1.5 D, and a minimum follow-up of 12 months. Patients with other eye diseases (glaucoma, cataract, keratoconus, and any form of strabismus) or any genetic syndromes were excluded from the study. The records included age, date of visit, prescription, and cycloplegic autorefractometry measurements of SE and axial length (AL).

The standard procedure for determining cycloplegic autorefractometry was carried out after the instillation of tropicamide 1% (Tropamid® Forte 1% [10 mg/mL], Bilim İlaç). Two drops were instilled into each eye, 5 minutes apart, and refraction was measured 30 minutes later using a Topcon CRK®-8900 autorefractometer. The device was set to 0.25 D, and the median of the mean from 5 readings per measurement was recorded. AL was measured in each eye using a Zeiss IOL Master 700 instrument. AL measurements were repeated until the standard deviation (SD) was <0.05.

All atropine eye drops were compounded using the same compounding pharmacy to ensure that the eye drops were at the same concentration. Atropine sulfate (1 mg/1 mL ampoule (Türk Tıpsan®, Ankara, Türkiye) was diluted to a concentration

of 0.05% using Eyestil® (sodium hyaluronate 1.5 mg/1 mL; SIFI Pharmaceuticals®, Catania, Italy) in a 10 mL vial.

The primary outcome measures were changes in SE and AL at 12 months.

Statistical Analysis

Continuous variables were summarized as mean with SD. Categorical data were expressed as frequency and percentage. Differences in baseline characteristics across the groups were evaluated by the Kruskal-Wallis test. A generalized linear mixed model (GLMM) was applied to evaluate the treatment effect on SE and AL. The model included treatment and the interaction time by treatment as a fixed effect, age and baseline SE and AL values as fixed covariates, and both eyes and subjects were included as random effects. Two-sided p values less than 0.05 were considered statistically significant. IBM statistics V29.0.1.0 (171) (IBM Corp. Released 2023, Armonk, New York, USA: IBM Corp.) was used for statistical analysis.

Results

The entire dataset comprised 51 patients: 27 in the Myopi-X group, 13 in the atropine 0.05% group, and 11 in the Myopi-X plus atropine 0.05% group. The study sample included 35 (68.6%) girls and 16 (31.4%) boys.

Baseline characteristics are presented in [Table 1](#). Due to the non-random assignment of groups, there were significant differences in some baseline characteristics. Specifically, the atropine 0.05% group was significantly older than both the Myopi-X group and the Myopi-X plus atropine 0.05% group. In terms of baseline SE, the atropine 0.05% group had lower SE values compared to the other two groups. Additionally, the atropine 0.05% group had the highest baseline AL, which was greater than both the Myopi-X group and the Myopi-X plus atropine 0.05% group. Despite these differences, the GLMM analyses were adjusted for baseline age, SE, and AL to account for these variations.

Spherical Equivalent Changes at 12 Months

The treatment groups did not differ significantly in terms of SE change ($p=0.35$). Age, baseline SE, baseline AL, and treatment group were not significantly associated with SE change ($p=0.58$, 0.84, 0.13, and 0.17, respectively). Bonferroni-adjusted post-hoc tests for comparisons between the atropine 0.05% group, the Myopi-X group, and the Myopi-X plus atropine 0.05% group did not reveal any significant treatment effects in any of the pairwise comparisons. Specifically, no significant differences in SE were observed between the atropine 0.05% group and the

Table 1. Baseline characteristics of patients in the treatment groups

	Total (n=51)	Atropine 0.05% group (n=13)	Myopi-X group (n=27)	Myopi-X + atropine 0.05% group (n=11)	p value
Age (years)	9.83±2.29	11.31±1.892	9.25±2.14	9.55±2.40	<0.001
Baseline SE (D)	-3.80±2.17	-5.16±2.74	-3.08±1.68	-3.98±1.73	<0.001
Baseline AL (mm)	24.91±1.10	25.69±1.36	24.53±0.78	24.95±0.96	<0.001

Results are presented as mean ± standard deviation. SE: Spherical equivalent, D: Diopters, AL: Axial length

Myopi-X group ($p=0.27$), between the Myopi-X group and the Myopi-X plus atropine 0.05% group ($p=0.93$), or between the atropine 0.05% group and the Myopi-X plus atropine 0.05% group ($p=0.42$) (Table 2, Figure 1).

Axial Length Changes at 12 Months

The treatment groups did not differ significantly in terms of AL change ($p=0.10$). Age had a significant impact on AL change ($p=0.01$), while baseline SE ($p=0.16$) and baseline AL ($p=0.1$) did not show significant effects. Although age significantly affected AL change, different age groups did not exhibit a significant difference in AL change between the three treatment groups over 12 months. Bonferroni-adjusted post-hoc tests for comparisons between the atropine 0.05% group, the Myopi-X group, and the Myopi-X plus atropine 0.05% group did not reveal any significant treatment effects in any of the pairwise comparisons. Specifically, no significant differences were observed in AL change between the atropine 0.05% group and the Myopi-X group ($p=0.05$), between the Myopi-X group and the Myopi-X plus atropine 0.05% group ($p=0.87$), or between the atropine 0.05% group and the Myopi-X plus atropine 0.05% group ($p=0.21$) (Table 2, Figure 2).

Discussion

The results from this 1-year retrospective study indicated that combining atropine 0.05% treatment with Myopi-X peripheral PAL therapy did not show any additive effect on the individual efficacy of these treatments.

PALs slow myopia progression owing to peripheral myopic defocus, which provides an inhibiting signal that slows axial elongation.¹¹ The design of the Myopi-X lenses is different from that of traditional PALs. The Myopi-X peripheral defocus PALs consist of a central 12-mm optical zone for correcting distance refractive error and a 24-mm transitional circular optical zone with an additive power of 2 or 3 D. It is possible that the peripheral myopic defocus effect of Myopi-X lenses may be higher than that of traditional PALs.

Atropine, a non-specific muscarinic antagonist, has biochemical effects on the sclera that may influence scleral remodeling. Another theory suggests that increased ultraviolet exposure (secondary to pupil dilation) may increase collagen cross-linking within the sclera, thereby limiting scleral growth.¹² A potential mechanism for the combined effect of atropine drops with optical interventions is thought to be the expansion of the peripheral defocus area resulting from pupil dilation,

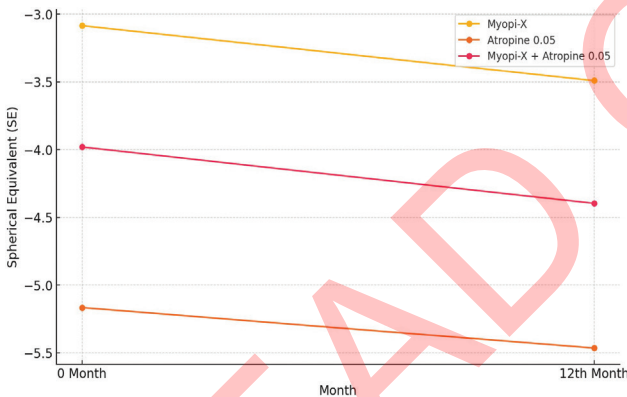


Figure 1. Change in spherical equivalent (in diopters) over 12 months in the different treatment groups

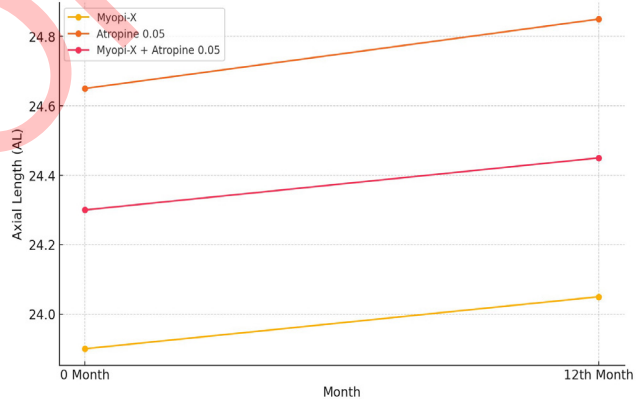


Figure 2. Change in axial length (in mm) over 12 months in the different treatment groups

Table 2. Changes in spherical equivalent and axial length in the Myopi-X, atropine 0.05%, and Myopi-X plus atropine 0.05% groups at 12 months

	Myopi-X® group ¹	Atropine 0.05% group ²	Myopi-X plus atropine 0.05% group ³	p values
Change in SE (D)	-0.44±0.07	-0.13±0.11	-0.55±0.22	0.19 1 vs. 2: 0.08 2 vs. 3: 0.16 1 vs. 3: 0.56
Change in AL (mm)	0.23±0.13	0.17±0.19	0.24±0.22	0.10 1 vs. 2: 0.05 2 vs. 3: 0.21 1 vs. 3: 0.87

Results expressed as mean and standard deviation. SE: Spherical equivalent, D: Diopters, AL: Axial length

which would enhance the effectiveness of combination therapies compared to monotherapies.¹³

Erdinest et al.¹⁴ reported that atropine 0.01% alone or a combination of atropine 0.01% with other therapies (PALs and soft contact lenses with peripheral blur) exhibited better efficacy than bifocal spectacles and single vision lenses (SVLs) for SE progression. However, there was no significant difference between atropine monotherapy and atropine combination treatments. Erdinest et al.¹⁵ also conducted a 3-year retrospective study that compared the efficacy of atropine 0.01%, SVL treatment, and dual-focus contact lens with atropine 0.01% combination treatment. The results indicated that there was no significant benefit of combination treatment compared to atropine treatment alone. An important limitation of these studies was the lack of AL measurements. However, AL is the most significant contributor to refractive error and myopia-related visual impairment.¹⁶

Nucci et al.¹⁷ completed a 1-year unmasked study that compared patients treated with defocus-incorporated multiple segment (DIMS) spectacles, atropine 0.01%, DIMS plus atropine 0.01%, and SVLs. The authors determined that DIMS plus atropine 0.01% demonstrated a significantly better treatment effect than DIMS monotherapy for refractive error but not for AL. Huang et al.¹⁸ conducted a 1-year retrospective study comparing treatment effects among patients treated with DIMS plus atropine 0.01%, DIMS alone, and SVLs. The authors found a greater treatment effect for SE and axial elongation in the combination group. The variations observed between the studies may be linked to the inclusion of Asian patients by Huang et al.¹⁸ and European patients by Nucci et al.¹⁷

The Bifocal and Atropine in Myopia study indicated that there was no significant additive effect of combining atropine 0.01% with a center distance soft multifocal contact lens (SMCL) with +2.50 add. For SE progression and axial elongation over a 3-year treatment period, the difference between the SMCL and SMCL with atropine groups was not statistically significant.¹⁹

Kinoshita et al.²⁰ and Tan et al.²¹ investigated the combination of atropine 0.01% plus orthokeratology. Their results showed that axial elongation was significantly slower among participants randomly assigned to the combination treatment than among those who were assigned to orthokeratology alone. However, Chen et al.²² noted that adding atropine to orthokeratology did not slow the 3-year axial elongation compared to orthokeratology alone after the participants had used orthokeratology monotherapy for a year.

In these studies, atropine 0.01% was employed. Most research indicates that combining 0.01% atropine with optical interventions yields added treatment benefits. However, this extra decrease in ocular growth may be limited to the first 6-month treatment period.

The use of atropine, particularly at lower concentrations, has gained interest because of its efficacy in slowing myopia progression, with minimal side effects.²³ According to the findings from the three-phase LAMP study, 0.05% atropine has emerged as the most effective concentration for controlling

myopia progression in children. This concentration was found to significantly slow the progression of myopia and axial elongation over a three-year period.^{24,25} Based on these results, it can be hypothesized that changing the treatment from atropine 0.01% to 0.05% in combination therapies may alter the outcomes.

Erdinest et al.²⁶ reported the efficacy of combined 0.05% atropine and MF60 contact lens therapy for the first time in the literature. The study compared the efficacy of three treatment groups: the atropine 0.05% plus MF60 contact lens group, the MF60 contact lenses monotherapy group, and the SVL control group. Both the atropine 0.05% plus the MF60 contact lens group and the MF60 contact lens monotherapy group demonstrated superior efficacy compared to the control group. However, there was no significant difference between the atropine 0.05% plus MF60 contact lens group and MF60 contact lens groups. From these results, it can be speculated that atropine 0.05% and MF60 contact lens combination treatment did not have an additive effect on MF60 contact lens therapy alone. These outcomes are similar to those of the present study.

Combination therapies in medicine involve the use of two or more treatment modalities to synergistically target a disease or a condition. Combining various treatments with complementary mechanisms of action can enhance therapeutic efficacy. However, in some cases, combining therapies with conflicting mechanisms of action may lead to antagonistic effects, ultimately reducing or failing to alter overall therapeutic efficacy. The lack of an additive effect of combined atropine and PAL therapy over monotherapies may be attributed to an unknown antagonistic effect.

In conclusion, there is limited literature available on combination therapies for slowing myopia progression. Based on PubMed results, this study provides new insights by exploring the use of atropine 0.05%, rather than the more commonly used 0.01%, within a combination treatment protocol. Furthermore, this study contributes to understanding the potential additive effects of combining 0.05% atropine with PALs in slowing axial elongation in children with myopia.

Study Limitations

Our study has several important limitations. First, its retrospective design and small sample sizes within each treatment group may limit the generalizability of the findings. Additionally, baseline differences between the groups could influence the results. In this study, cycloplegic autorefractometer measurements were used to assess refractive status. While cycloplegic retinoscopy and subjective refraction are often considered gold standards, autorefractometry is commonly employed in myopia management research due to its repeatability and practicality, particularly in studies with large samples. We acknowledge that autorefractometry may lack the precision of other methods, so these findings should be interpreted in light of this limitation. Finally, our study does not address questions of long-term efficacy. Further randomized clinical trials with larger sample sizes are essential to reduce bias and provide more robust conclusions.

Conclusion

In this study, the combination of atropine 0.05% with Myopi-X PALs did not show any additive effect compared to the individual efficacy of each treatment. Although the literature suggests that both therapies independently slow myopia progression, their combination did not provide significant benefits in terms of SE progression or axial elongation in our study. These findings are consistent with other studies demonstrating limited additive effects when combining atropine with optical interventions. Further randomized trials are needed to confirm these results and explore potential long-term outcomes in larger patient groups.

Ethics

Ethics Committee Approval: Acıbadem Healthcare Institutions Medical Research Ethics Committee (decision no: 2024-8/302, date: 16.05.2024).

Informed Consent: Obtained.

Declarations

Authorship Contributions

Surgical and Medical Practices: N.A., U.E.A., Concept: N.A., Design: N.A., Data Collection or Processing: N.A., Analysis or Interpretation: N.A., U.E.A., Literature Search: N.A., Writing: N.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

- Matsumura S, Matsumura S, Ching-Yu C, Saw SM. Global epidemiology of myopia. In: Ang M, Wong T, eds. *Updates on Myopia*. Singapore: Springer. 2020;3-16.
- Flanagan J, Fricke T, Morjaria P, Yasmin S. Myopia: a growing epidemic. *Community Eye Health*. 2019;32:9.
- Holden BA, Fricke TR, Wilson DA, Jong M, Naidoo KS, Sankaridurg P, Wong TY, Na-duvilath TJ, Resnikoff S. Global prevalence of myopia and high myopia and temporal trends from 2000 through 2050. *Ophthalmology*. 2016;123:1036-1042.
- Haarman AEG, Enthoven CA, Tideman JW, Tedja MS, Verhoeven VJM, Klaver CCW. The complications of myopia: a review and meta-analysis. *Invest Ophthalmol Vis Sci*. 2020;61:49.
- Goldschmidt E, Jacobsen N. Genetic and environmental effects on myopia development and progression. *Eye (Lond)*. 2014;28:126-133.
- Smith MJ, Walline JJ. Controlling myopia progression in children and adolescents. *Adolesc Health Med Ther*. 2015;6:133-140.
- Hong J, Yun CO. Emergence of ad-mediated combination therapy against cancer: what to expect? *Curr Cancer Drug Targets*. 2018;18:139-152.
- Aumeeruddy MZ, Mahomoodally MF. Combating breast cancer using combination therapy with 3 phytochemicals: piperine, sulforaphane, and thymoquinone. *Cancer*. 2019;125:1600-1611.
- Cersosimo E, Johnson EL, Chovanes C, Skolnik N. Initiating therapy in patients newly diagnosed with type 2 diabetes: combination therapy vs a stepwise approach. *Diabetes Obes Metab*. 2018;20:497-507.
- Mehran NA, Sinha S, Razeghinejad R. New glaucoma medications: latanoprostene bunod, netarsudil, and fixed combination netarsudil-latanoprost. *Eye (Lond)*. 2020;34:72-88.
- Erdinest N, London N, Lavy I, Berkow D, Landau D, Morad Y, Levinger N. Peripheral defocus and myopia management: a mini-review. *Korean J Ophthalmol*. 2023;37:70-81.
- Chia A, Chua WH, Cheung YB, Wong WL, Lingham A, Fong A, Tan D. Atropine for the treatment of childhood myopia: safety and efficacy of 0.5%, 0.1%, and 0.01% doses (atro-pine for the treatment of myopia 2). *Ophthalmology*. 2012;119:347-354.
- Wan L, Wei CC, Chen CS, Chang CY, Lin CJ, Chen JJ, Tien PT, Lin HJ. The synergistic effects of orthokeratology and atropine in slowing the progression of myopia. *J Clin Med*. 2018;7:259.
- Erdinest N, London N, Lavy I, Levinger N, Pras E, Morad Y. Myopia control utilizing low-dose atropine as an isolated therapy or in combination with other optical measures: a retrospective cohort study. *Taiwan J Ophthalmol*. 2022;13:231-237.
- Erdinest N, London N, Lavy I, Landau D, Ben Ephraim Noyman D, Levinger N, Morad Y. Low-concentration atropine monotherapy vs. combined with misight 1 day contact lenses for myopia management. *Vision (Basel)*. 2022;6:73.
- Brennan NA, Toubouti YM, Cheng X, Bullimore MA. Efficacy in myopia control. *Prog Retin Eye Res*. 2021;83:100923.
- Nucci P, Lembo A, Schiavetti I, Shah R, Edgar DF, Evans BJW. A comparison of myopia control in European children and adolescents with defocus incorporated multiple segments (DIMS) spectacles, atropine, and combined DIMS/atropine. *PLoS One*. 2023;18:0281816.
- Huang Z, Chen XF, He T, Tang Y, Du CX. Synergistic effects of defocus-incorporated multiple segments and atropine in slowing the progression of myopia. *Sci Rep*. 2022;12:22311.
- Jones JH, Mutti DO, Jones-Jordan LA, Walline JJ. Effect of combining 0.01% atropine with soft multifocal contact lenses on myopia progression in children. *Optom Vis Sci*. 2022;99:434-442.
- Kinoshita N, Konno Y, Hamada N, Kanda Y, Shimmura-Tomita M, Kaburaki T, Kakehashi A. Efficacy of combined orthokeratology and 0.01% atropine solution for slowing axial elongation in children with myopia: a 2-year randomised trial. *Sci Rep*. 2020;10:12750.
- Tan Q, Ng AL, Choy BN, Cheng GP, Woo VC, Cho P. One-year results of 0.01% atropine with orthokeratology (AOK) study: a randomised clinical trial. *Ophthalmic Physiol Opt*. 2020;40:557-566.
- Chen Z, Zhou J, Xue F, Qu X, Zhou X. Two-year add-on effect of using low concentration atropine in poor responders of orthokeratology in myopic children. *Br J Ophthalmol*. 2022;106:1069-1072.
- Yam JC, Jiang Y, Tang SM, Law AKP, Chan JJ, Wong E, Ko ST, Young AL, Tham CC, Chen LJ, Pang CP. Low-concentration atropine for myopia progression (LAMP) Study: a randomized, double-blinded, placebo-controlled trial of 0.05%, 0.025%, and 0.01% atropine eye drops in myopia control. *Ophthalmology*. 2019;126:113-124.
- Yam JC, Li FF, Zhang X, Tang SM, Yip BHK, Kam KW, Ko ST, Young AL, Tham CC, Chen LJ, Pang CP. Two-year clinical trial of the low-concentration atropine for myopia progression (LAMP) study: phase 2 report. *Ophthalmology*. 2020;127:910-919.
- Yam JC, Zhang XJ, Zhang Y, Wang YM, Tang SM, Li FF, Kam KW, Ko ST, Yip BHK, Young AL, Tham CC, Chen LJ, Pang CP. Three-year clinical trial of low-concentration atropine for myopia progression (LAMP) study: continued versus washout: phase 3 report. *Ophthalmology*. 2022;129:308-321.
- Erdinest N, Atar-Vardi M, London N, Landau D, Smadja D, Pras E, Lavy I, Morad Y. Treatment of rapid progression of myopia: topical atropine 0.05% and MF60 contact lenses. *Vision (Basel)*. 2024;8:3.