Myopia control: monotherapy or combination of treatments?

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Abstract

Introduction: Discovering the best approach in the management of myopia control is the main objective of several studies. Nowadays, different strategies are carried out to prevent myopia's development and reduce its progression, such as low-dose atropine eye drops, optical devices including multifocal spectacles and multifocal contact lenses, and orthokeratology (Ortho-K). This paper aims to compare the efficacy of the combination of different treatments for myopia control to the prescription of a single treatment.

Methods: Studies related to the purpose of this review have been researched mainly on PubMed. Literature research using the database yielded 419 papers, 9 of which were analyzed and compared in this review.

Results: A large number of studies is present in the literature concerning the effectiveness of combined therapy compared to monotherapy for the control of myopia progression. In this revision, four studies on the efficacy of low-dose atropine combined with optical devices were selected and also five studies on the combination of atropine with Ortho-K.

Conclusion: Most results indicate that combination treatments offer better myopia control efficiency than some monotherapy strategies, but further research on etiology and management of myopia is needed to prevent its development.

Keywords: combination of treatments; myopia control; current therapies; monotherapy myopia; atropine; multifocal contact lenses; spectacles; glasses; orthokeratology.

1. Introduction

Myopia, also known as near-sightedness, is a widespread refractive error whose prevalence is increasing profoundly. Parallel to the process of urbanization, in combination with a pronounced intensification of education and a marked reduction in time spent outdoors, the prevalence of axial myopia has

increased over the last three decades globally in the younger generations, in particular in East and Southeast Asia (Jonas et al., 2021). The elongation of the axial length of the eye leads to blinding complications and visual impairment and consequently different pathological conditions may occur such as retinal detachment, chorioretinal atrophy, myopic maculopathy, cataract and glaucoma.

The multifactorial etiology of nearsightedness mainly includes a combination of hereditary factors, children who have myopic parents are more predisposed to develop myopia compared to non-myopic children, and environmental factors such as indoor activities (mobile phone usage, time spent near the TV, playing games and reading books at a close distance), and long periods of reading in low illumination are also factors in the progression of myopia (Singh et al., 2022). Different studies also show that outdoor activities prevent the development and progression of myopia in children and university students because exposure to sunlight is an important protective factor that opposes axial elongation of the eyeball.

There is a growing interest in actively contributing to the progression of myopia rather than simply compensating the refracting error associated with this condition. Myopia is no longer treated only as a refractive defect that can be compensated with optical devices but also as a condition that can be treated and managed by therapeutic intervention.

This dissertation compares the effectiveness of monotherapy, where only one treatment is carried out, to the efficacy of the combination of treatments, where therapies are combined together to ensure that eye growth is regulated effectively.

1.1. Current available methods for controlling myopia

Outdoor activities. Recent epidemiological evidence demonstrates that children who spend more time outdoors are less likely to be, or to become, myopic irrespective of how much near work they do, or whether their parents are myopic (French et al., 2013). Increasing exposure to visible light outside can be a determining factor in slowing myopic progression above all because outdoor activities allow relaxing the accommodation for viewing distance. Another hypothesis, according to Cao et al. (2020), states that light can induce the release of dopamine, which helps inhibit axial elongation.

Multifocal ophthalmic lenses and multifocal contact lenses**.** Myopic eyes corrected with single-vision spectacles or contact lenses (CLs) typically show relative peripheral hyperopia. Multifocal lenses aim to reduce or eliminate hypermetropic defocus, which also occurs because of the accommodative lag during prolonged proximal vision. As has been shown by animal studies, the accommodative lag accelerates eye growth, and the possibility that prolonged contraction of the ciliary muscle may affect negatively the growth

of the eye, probably through interactions with the sclera, was also the object of various hypotheses (Wagner, 2019).

Both multifocal spectacles and multifocal CLs are therefore based on the change in peripheral retinal hyperopic defocus that causes central axial myopia. To this end, several technologies of myopia-controlling lenses have been developed, for example:

- Defocus Incorporated Multiple Segments (DIMS), certified by Hoya, provides simultaneously a myopic defocus and a clear central vision, thanks to the presence of about 400 multiple segments of additional power (+3.50D) in the peripheral portion of the lens that surrounds the central zone dedicated to correcting the distance visual defect.
- Highly Aspherical Lenslet Target (HALT), licensed by Essilor, also provides at the same time a myopic defocus across the retina, through a spherical front surface with 11 concentric rings formed by adjacent aspherical lenslets with a diameter of 1.1mm, and a clear distance correction, thanks to an area of the lens in which there are no lenslets. This design generates a volume of myopic defocus in front of the retina at any eccentricity, useful for myopia control.

With DIMS and HALT technology, spectacle lenses have made enormous progress as they behave exactly like contact lenses for myopia control: in addition to soft multifocal contact lenses (SMCLs), there are in fact dual-focus soft contact lenses, called MiSight (Cooper Vision), that thanks to ActivControl™ technology, an optic zone concentric ring design with alternating vision correction and treatment zones with 2 diopters of defocus, is able to slow down the progression of myopia. Moreover, in 2019 in the United States, MiSight contact lenses became the first FDA-approved treatment for myopia control.
By minimizing the hyperopic defocus or introducing peripheral myopic defocus with progressive addition lenses (PALs), peripheral defocus ophthalmic lenses, or different designs of CLs, myopic progression could be prevented.

Orthokeratology**.** Ortho-K (OK) is a non-surgical night technique that aims to reduce myopia by shaping the cornea through a programmed application of rigid gas permeable (RGP) contact lenses of small diameter. The patient is asked to wear the lenses before bedtime and to remove them in the morning: the change generated in the corneal curvature during the night will have neutralized the patient's refractive defect, allowing good vision throughout the day, without the need to wear glasses or contact lenses.

The mechanism by which this effect is obtained is the reversible redistribution of corneal epithelium caused by the application of reverse geometry RGP lenses that flatten the central cornea and steepen the

corneal profile of the mid-periphery.

Subsequent studies, performed mostly on children and adolescents, suggested that OK may slow myopic eye enlargement, potentially by a decrease in relative peripheral hyperopia caused by the steepening of the mid-peripheral corneal surface.

Pharmaceutical approach. There are two pharmaceutical agents for topical use which have been examined for myopia control: atropine and pirenzepine.

Atropine is a non-selective antagonist of the muscarinic receptors that have a high affinity with M1-M5 receptors located in the pupillary sphincter and ciliary muscle leading to mydriasis and cycloplegia. Numerous studies have investigated the effect of this agent on myopic progression and atropine is currently the more widely studied treatment for myopia control.

Pirenzepine is a selective antagonist of the muscarinic M1 receptors. This agent differs from atropine because it is less likely to induce cycloplegia and mydriasis, although one of the main advantages is the minimal effect that it has on pupil size and accommodation. Subjects undergoing treatment with pirenzepine have reported adverse effects of accommodating dysfunction and medication residue (Kang, 2018).

Some clinical studies are currently investigating the effectiveness of a new hypothetical future treatment based on the caffeine metabolite 7-methylxanthine, shortened to 7-MX, a non-selective adenosine antagonist that appears to be an anti-myopic agent.

2. Objectives

Myopia control, as described above, can be handled through behavioral, optical and pharmacological interventions. Despite the numerous possibilities of therapeutic approaches for myopia control, at this time there is no universal treatment to prevent or slow myopic progression and most options fail to achieve 100% effectiveness, at least for a prolonged period.

Not all subjects react in the same way to treatments; in some people, no difference is found between the proposed treatment for myopia control and placebo and in some subjects response to treatment is very slow. To overcome this limit and to control the axial length of the eye, the combined treatment for myopia control should be, as the name suggests, a combination of two different treatment modalities.

These treatments are not mutually exclusive and, for this reason, since they are individually effective in controlling myopia, they are going to be examined in combination.

Currently, numerous publications provide evidence on combination treatments; there are enough studies that propose atropine combined with several optical aids.

We will thus try to understand whether subjecting a patient to a single therapy may produce more advantages than combining two therapies.

3. Material and methods

Research on myopia control has been made mainly on PubMed, one of the major websites of scientific literature, using the following keywords: combination of treatments, myopia control, current therapies, monotherapy myopia, atropine, multifocal contact lenses, spectacles, glasses, orthokeratology.

In the literature, many studies investigate the effectiveness of the combination of atropine with other optical solutions capable of slowing myopic progression. The literature searching through database resulted in a total of 419 papers of which 18 have been assessed in terms of eligibility. Duplicate publications and case reports were excluded from the analysis. Therefore, in this work, only nine papers on this topic were compared and examined. In terms of association of atropine with multifocal lenses and contact lenses, four studies conducted between 2001 and the present were analyzed, since one of the first studies on the combination of multifocal glasses and atropine was carried out in 2001, while in the case of the combination of atropine and Ortho-K, given the large number of studies involved, five systematic reviews and meta-analyses from the year 2020 until today have been mainly considered as they collect all major studies that have been carried out and that have examined the effectiveness and safety of interventions for myopia management.

4. Results

There is a large amount of scientific evidence that argues that atropine, associated with another treatment for myopic progression, provides greater effectiveness compared to both treatments used individually. However, most studies in the literature mainly focus on the demonstration of the efficacy of atropine paired with Ortho-K, while the number of studies on combination with soft multifocal contact lenses and spectacles is limited, and some of them are summarized in Table 1.

Table 1. Studies on the efficacy of combined low-concentration atropine and optical devices such as soft multifocal contact lenses (SMCLs) and spectacles on myopia control.

Authors	Participants	Outcomes
Shih et al. (2001)	n = 227 schoolchildren	A (0.5%) + multi-focal lenses slow down the myopic progression rate. The results are mainly due to the contribution of atropine since the difference between multifocal and single vision lenses was not significant.
Erdinest et al. (2021)	n = 4 children	A (0.05%) + MiSight® 1 day (Cooper Vision) showed efficacy at controlling moderate myopia progression during the course of 1 year.
Jones et al. (2022)	n = 138 subjects	A (0.01%) + SMCLs with +2.50-D (center distance) add power has not demonstrated better myopia control that SMCLs alone.
Kaymak et al. (2022)	No data available yet	A (0,01%) + MiyoSmart reduce axial elongation and myopia progression with maximum results.

On the contrary, the combination of low-dose topical atropine and Ortho-K for controlling axial elongation of the eyeball in juvenile myopia has been extensively studied. Table 2 summarizes the main meta-analysis studies on this topic.

Table 2. Recent Meta-Analysis on the efficacy and safety of combined low-concentration atropine and orthokeratology (OK) on myopia control.

Authors	Participants	Outcomes
Wang et al. (2021)	n = 267 subjects	OK + A (0,01%) has more efficacy in slowing axial elongation that OK monotherapy in a short duration of treatment.
Gao et al. (2021)	n = 341 young people	A + OK results in greater effectiveness than OK alone in slowing axial elongation.
Yang et al. (2022)	n = 461 children	Low A + OK delay axial elongation more effectively than the OK lens alone in low and moderate myopia.
Tsai et al. (2022)	n = 3435patients	A alone (0.01%-1%), OK alone and OK + A (0.01%) could slow down myopia progression. There is a synergistic effect of using OK + A (0.01%) and it showed comparable efficacy to that of high-dose atropine.
Zheng et al. (2022)	No data available yet	Low A + OK had a greater effect in slowing myopia progression during a 6-to-12-month treatment interval and was still effective over a 24-month.

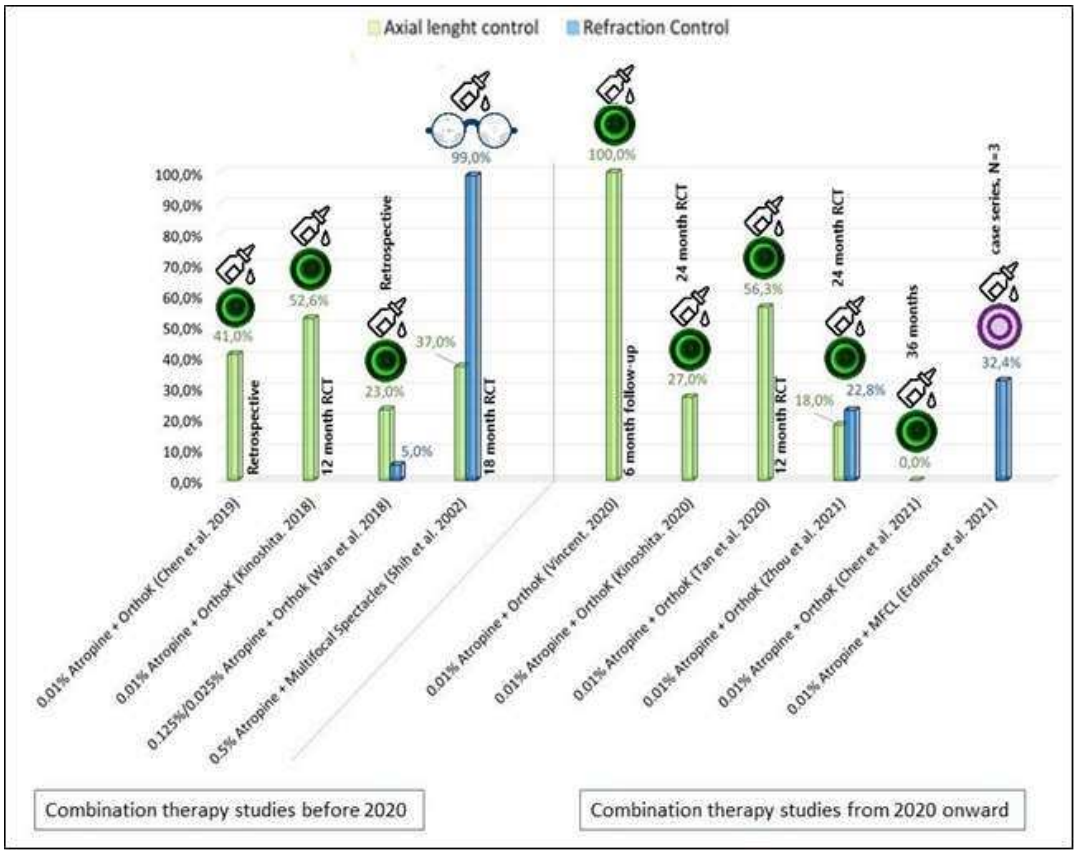
5. Discussion

Each study selected, from 2001 to the present, and each of the meta-analysis mentioned above, published from the year 2020 until today, conveys the importance and need to develop methods to slow down myopic progression.

Shih et al. (2001) examined the effectiveness of the combined treatment of atropine and multifocal lenses and their study showed that the group treated with 0.5% atropine associated with multifocal spectacles achieved less significant progression of the refractive error than the group handled only with multifocal lenses. Nevertheless, no difference was found between the group wearing multifocal spectacles and the control group to which they have been prescribed single vision lenses: considering that atropine may inhibit accommodation and growth factors that influence eye lengthening, it could be that the major effect in regulating the myopic progression was mainly due to atropine administration rather than the type of lens prescribed.

Different results were found with the latest new generation lenses for myopia control: DIMS and HALT technologies have proven to be more effective in controlling myopia progression and axial elongation than single-vision lenses. Since these lenses have shown good efficacy individually, in early 2022 there were no studies on the combination with other control strategies and there was a strong interest in investigating the potential benefits of the combined treatments, as claimed by Verkicharla and Thakur in April 2022, who have carried out a thorough review of the combined treatment studies, which are summarized in detail in Figure 1. However, during the myopia symposium at the International Myopia Conference (IMC), held 4-7 September 2022 in Rotterdam, Hoya Vision Care shared the latest findings of the clinical application of the MiyoSmart spectacle lenses by Hoya, based on DIMS technology, with 0.01% atropine drops. It was reported that elongation and myopia progression were reduced with maximum effect using the combination treatment (Kaymak et al., 2022).

Figure 1. Efficacy of various studies that investigated combination strategies for myopia control. Adaptation of the original figure of Verkicharla et al. (2022). Recent Updates on Combination Treatments for Myopia Control.



In terms of contact lenses, the amount of scientific evidence is also limited: the most significant study which has been conducted on the combination of center distance SMCLs with 0.01% atropine was the Bifocal & Atropine in Myopia (BAM) study (Huang et al., 2019). Unfortunately, after a long wait for important scientific information on the combination of these myopia control treatments, the three-year non-randomized clinical study has proved that adding 0.01% atropine to SMCL with +2.50D add power does not allow to control myopia more effectively than SMCL alone (Jones et al., 2022), probably because of the low concentration of atropine.

However, Erdinest et al. (2022) have demonstrated that optical (peripheral defocus contact lens) and biological (atropine) components complement each other and may be more effective than isolated

administration. It is the first research in which a combination of 0.05% atropine and peripheral defocus daily replacement soft contact lenses exhibited high efficacy in the control of moderate myopia progression.

The strategy that appears to have provided the most effective results in the control of nearsightedness is low-concentration atropine combined with the OK lens: this treatment, compared to OK monotherapy, can significantly slow down the axial elongation of the eyeball in children with low to moderate myopia.

The efficacy of different concentrations of atropine in treating myopia in children and young adults has been widely demonstrated. Nevertheless, topical application of high concentrations (1% - 0.5%) of atropine increases the incidence of adverse reactions such as photophobia, blurred vision, allergic conjunctivitis, and dryness of the face, which make the clinical application of atropine controversial.

It has been found that atropine acts in a dose-dependent manner and that its function is related to the instilled concentration. Many studies have confirmed that high concentrations of atropine are more effective in the treatment of myopia than low concentrations of atropine, but as the dose of atropine increases, side effects also increase. Many recent studies have proven that the application of atropine at low concentrations (0.1% - 0.05% - 0.025% - 0.01%) and with the appropriate frequency of instillation can effectively delay the development of myopia, maintaining a high visual quality, and can also reduce the incidence of side effects such as photophobia, nearsightedness itself and myopic diopter rebound after the suspension of treatment.

The meta-analysis of Wang et al. (2021) and Gao et al. (2021) showed that low-dose atropine combined with the OK lens produces more benefits than the OK lens alone in reducing ocular axial elongation in children with myopia, which is consistent also with the conclusion obtained by Yang et al. (2022).

Tsai et al. (2022) have elaborated a meta-analysis about the effect of combining several dosages of atropine with OK and they found that atropine (0.01% - 1%), Ortho-K, and 0.01% atropine combined with Ortho-K are comparable approaches in terms of efficacy in the slowdown of myopia progression. A synergistic effect has been observed in the combination of 0.01% atropine and Ortho-K, which demonstrated similar effectiveness to that of high-dose atropine for inhibiting axial elongation.

The meta-analysis of Zheng and Tan (2022), as well as confirming that the combination therapy of low-concentration atropine and OK lenses had a larger impact on slowing the progression of myopia for a treatment interval of 6 to 12 months and that always remains effective over a period of 24 months, also affirms that combined therapy does not have a negative impact on the amplitude of accommodation, intraocular pressure, tear film break-up time or corneal endothelial cell density and that the most prevalent side effect of the combination treatment is the increase in pupillary diameter.

The mechanisms underlying the increased effectiveness of dual therapy have not yet been fully clarified and there are various hypotheses in this regard. The enlargement of the pupil caused by atropine, for

instance, allows benefiting more from the effect of myopic defocus induced by Ortho-K lenses and also allows a higher exposure to light which involved a release of dopamine induced by light stimulation. Dopamine is another major research topic. In fact, numerous studies attempt to understand its role in regulating eye growth and in the development of refraction errors in children, so much so that research on drug-releasing contact lenses is expanding.

Safilens, for example, a contact lens manufacturer, has launched a new range of contact lenses, Delivery Tyro, designed to correct vision and regulate eye growth, thanks to the release of tyrosine, an amino acid that can affect the presence of dopamine inside the eye. In another recent study (Hui et al., 2017) several daily disposable and multifocal contact lenses were investigated for their potential to release two anti-myopia drugs, atropine and pirenzepine. Despite the effectiveness of these lenses has not yet been proven, a contact lens-based drug delivery system could be an option for the treatment of myopia that still requires further evaluation and a strong clinical investigation.

6. Conclusion

After analyzing some of the studies in the literature, we can affirm that the research on the combination of treatments for myopia control focuses mainly on the three following categories:

- Atropine with orthokeratology
- Atropine with soft multifocal contact lenses
- Atropine with spectacles.

Most results suggest that combined treatments provide better myopia control effectiveness than some monotherapy strategies, but it is important to take into account that the approach of the combination may not be effective for all individuals. It would in fact be advisable to establish the combined treatments as a second treatment option, maintaining monotherapy as the first treatment intervention and opting for a combination when the progression with monotherapy becomes evident.

Ongoing scientific research could provide significant information on the combination of myopia control treatments and could potentially change the management standard for myopia control in the clinical context. Although further work is needed to optimize treatment methods and to understand the mechanisms underlying myopic progression, the results of studies to date are encouraging for combined treatments.

Myopia is a visual defect that is spreading globally, so much so that timely detection and control of myopia is becoming increasingly part of traditional clinical practice.

Various optical and pharmacological treatments have shown beneficial effects of myopia control, both as monotherapy and in combined therapy. Research on the etiology of myopia and its management

continues, with the aim not only to develop an effective and reliable method to reduce or stop the progression of myopia but above all to discover a means to prevent the development of myopia in children.

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