Review Article

Latest Updates on Pharmacological Management of Myopia Control: A Review Study

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ABSTRACT

Introduction: Concerns about the increasing prevalence of myopia are because of its rising ocular complications, which in some cases could lead to blindness. Therefore, all practitioners should know the latest updates on myopia control in routine practice.

Materials and Methods: PubMed, Science Direct, and Google Scholar databases were searched for related scientific articles using search keywords. In this regard, the books and articles published from 2016 to June 2021 were included. The selected articles and valid scientific resources were collected, summarized, classified, evaluated, and finally concluded by the authors.

Results: The results of the latest published papers for the prevention of myopia progression can be summarized as follows: choroidal blood supply as a potential "rapid predictor indicator" for the axial elongation, periocular injection of salidroside and formononetin, hyperopic defocus reduction using MiSight contact lenses, the chemical effect of 7-methylxanthine, and the suppressive effect of crocetin dietary supplement.

Conclusion: Using the latest methods of myopia control alongside conventional strategies has a synergistic effect.

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1. Introduction

Myopia is rapidly moving towards an epidemic worldwide. Although much research has been conducted on myopia [1-6], there are still uncertainties about the cellular and molecular mechanisms of the development and progression of myopia. Therefore, finding an appropriate solution to stop the progression of myopia is challenging. Concerns about the increasing prevalence of myopia are because of its rising ocular complications. A systemic review and meta-analysis of 45 studies in 2000 found that 23% and 2.7% of the world's population have myopia and high myopia, respectively, and it is predicted that by 2050, almost 50% of the world's population will be myopic [7].

There is currently no definite way to prevent myopia progression or reduce its prevalence. Clinically, administration of low-dose atropine has been the most effective strategy in preventing myopia progression, with reported efficacy from 60% to 77% [8-10]. The best effective strategies are orthokeratology, multifocal contact lenses, and bifocal and progressive lenses, with reported effectiveness of between 37%-56%, 25%-79%, and 19%, respectively [11, 12]. Today, enormous efforts are made to control and prevent the epidemic nature of myopia and to manage it by delaying the onset of myopia as well as slowing the progression of myopia using the following conventional methods: 1) increasing outdoor activities, 2) reducing the duration of near work, 3) pharmacological interventions, 4) optical strategies (such as bifocal and multifocal lenses, progressive lenses, bifocal soft contact lenses, and orthokeratology lenses), and 5) full-correction of myopia. Many studies have been performed investigating the effectiveness of these methods; it was observed that the effect of drug interventions to prevent myopia progression was greater than the others [7, 13-16].

2. Materials and Methods

In this review article, PubMed, ScienceDirect, Scopus, and Google Scholar databases were reviewed for related scientific articles and books using the search terms: "myopia control," "axial length elongation," "pharmacological interventions," and "optical strategies." We included the books and articles that were published from 2016 to June 2021, had at least one of the keywords, and were relevant to the subject of this review study. More emphasis was placed on recent articles. The selected articles and valid scientific evidence were collected, summarized, classified, evaluated, and finally concluded by the authors.

3. Results and Discussion

Anticholinergic drugs

It was initially assumed that anticholinergic drugs would prevent myopia development by paralyzing accommodation, but in a series of animal studies, it was observed that myopia also developed in cases where there was no accommodation. Since then, studies have focused on the non-accommodative mechanisms that cause myopia [17, 18]. Knowing that acetylcholine plays an essential role in retinal development and regulating eye growth, the studies evaluated the function of acetylcholine and muscarinic receptors (acetylcholine receptors) using anticholinergic drugs. Among the drugs used, atropine sulfate and pirenzepine were more effective. However, pirenzepine was not used because of its higher cost and lower functional level than atropine. So atropine was further studied as the drug of choice to control myopia progression [17, 18].

Atropine

There were two significant problems with using atropine: first, experiencing ocular side-effects such as mydriasis, photophobia, glare, local allergic reactions, accommodation, and near work problems by the users [3]; and second, the likelihood of returning and progression of myopia (rebound phenomenon) after stopping atropine (washout phase).

The remarkable effect of atropine on reducing the progression of myopia was noticeable, but studies were looking for the most appropriate dose and method of taking atropine that has the least side effects with the minimum rate of myopia recurrence [19]. It has been suggested that long-term use of atropine can lead to increased intraocular pressure and glaucoma, but studies have shown that at low doses of atropine, the probability of this occurrence is about 0.005%. However, the mechanism of action of atropine is still under heated dispute [18].

Cellular receptors

Muscarinic receptors (types 1 to 5) are widely distributed in different ocular tissues (iris, cornea, ciliary bodies, ciliary muscles, epithelium of crystalline lens, retina [in amacrine cells], retinal pigment epithelium [RPE], choroid, and scleral [in scleral fibroblasts]). Atropine also affects many other receptors in the eye, including a2A-adrenergic receptors, ɣ-aminobutyric acid receptors, and tyrosine receptor kinases.

Atropine binds to anterior tissues, including the conjunctiva, within the first 5 hours after instillation into the eye and attaches to the posterior tissues of the eye after 24 hours. Previous studies on the effect of atropine on different ocular structures found that the main targets of atropine are the retina and sclera, although it also has significant effects on the choroid and RPE. In the retina, atropine increases dopamine secretion, which plays an essential role in regulating ocular growth and development [18]. Atropine in the sclera reduces the proliferation of scleral fibroblasts (FB) and prevents the weakening of the extracellular matrix and increases the thickness of the sclera, and therefore prevents the elongation of axial length (AL) [18].

RPE plays a key role in maintaining retinal homeostasis, and it regulates the signals that regulate eyeball growth from the retina to the sclera and choroid and modulates scleral growth. The choroid mechanically adjusts its thickness to hold the retina on the focal plane of the eye (choroidal accommodation) and also plays an active role in emmetropization. Transforming growth factors and basal fibroblast growth factor are located inside the choroid and retinal pigment epithelium. Atropine prevents the growth of the eyeball and increases AL by changing the secretion and function of each of these factors and increasing the thickness of the choroid [18].

Several studies were performed to obtain the most appropriate dose of atropine. Initially, 1% atropine was used in the studies, but due to various ocular complications and a higher rate of myopia recurrence after treatment discontinuation, atropine 1% became obsolete, and studies focused on lower doses of atropine [18-20].

Atropine for the treatment of childhood myopia (ATOM) studies

The initial idea of using one of the most widely used concentrations of atropine (atropine 0.01%) came from ATOM study. This study was performed in two phases. In the first phase, ATOM1, the patients were divided into experimental and control groups; one drop of 1% atropine was instilled into one eye in the experimental group every night for 3 years. Finally, although atropine 1% was highly effective in preventing myopia progression, this dosage was not approved because of the ocular complications and significant recurrence of myopia after cessation of treatment. In 2012, the second phase of the study, ATOM2, started with 400 participants in 3 stages. The participants were myopic children aged 6 to 12 years divided into 3 groups, and for each group, atropine with different concentrations of 0.5%, 0.1%, and 0.01% was used. In the first stage of the study, each eye received a drop of atropine at a specific dose every night for two years. In this study, because of the low concentration, 0.01%, it was first assumed that it would not have much effect, but the findings revealed different results. After 2 years (stage 1), it was observed that in the group receiving 0.01% atropine, the rate of myopia progression decreased by about 60% (from 1.20 to 0.49). In the second stage, they stopped using atropine for a year (washout phase), and in the third stage, for people with an increase in the myopia of more than 0.50 diopters in the second stage, they started 0.01% atropine again for 2 years. At the end of the study, 0.01% atropine had a significant effect on reducing myopia progression, the patient's tolerance to this dose was desirable, and the rate of myopia regression (rebound) was low, too. However, in the first 2 years of using 0.01% atropine, no effect was observed to prevent the AL progression. Studies have shown that following the drop administration, if the pupil size increases by more than 3 mm and the amplitude of accommodation reach less than 5 diopters, the patient will probably return to the clinic and report complications. Generally, concentrations higher than 0.02% may be associated with clinical symptoms. In this study, it was observed that the increase in pupil size by using atropine with concentrations of 0.5%, 0.1%, and 0.01% were 3.11, 2.42, and 0.91 mm, and the amplitude of accommodation values were 3.6, 0.6, and 11.7 diopters, respectively [7, 21].

In some countries, 0.01% atropine was marketed under the brand name Myopine. American Academy of Ophthalmology also found 0.01% atropine suitable for controlling myopia, and according to the WHO report in 2015, 0.01% atropine is a reliable strategy for controlling myopia in Asian countries such as Singapore. The ATOM2 study did not have a control group, and it was not clear that finally, which one was the most appropriate concentration [7, 21-23].

Low-concentration atropine for myopia progression (LAMP) study

The LAMP study aimed to provide a globally accepted guideline for myopia control. The strongest evidence to support atropine therapy for myopia control comes from the LAMP study. This study was the first double-blind and randomized placebo controlled-trial study conducted in 2018 in Hong Kong. For this study, 4 operational phases have been planned. So far, the information of the first 2 phases has been published, and phases 3 and 4 still continue. The participants were 438 children aged 4 to 12 years with the myopia of at least

1 diopter who were divided into 4 groups. In the first phase, each group received different doses of atropine (0.05%, 0.025%, 0.01%) and a placebo every day for 1 year. In the second phase, they continued to receive atropine for another year, and the changes were examined. In the third phase, the use of atropine is stopped for 3 years (washout phase). For the fourth phase of the program, atropine therapy should be resumed for 5 years for people with a myopic regression in phase 3. When using different doses of atropine (0.05%, 0.025%, 0.01%) and placebo, it was observed that the amplitude of accommodation decreased by 1.98, 1.61, 0.26, and 0.32 diopters, and the pupil size increased by 1.03, 0.76, 0.49, and 0.13 mm, respectively. According to the information published so far from the LAMP study, 0.05% atropine has been given much attention with a significant effect on reducing the progression of myopia and preventing the increase of AL (unlike 0.01% atropine). Besides, when using 0.05% atropine, the near and far visions were not impaired, and the quality of life of people who received doses of 0.05%, 0.025%, and 0.01% was similar to the placebo group. The LAMP study concluded that 0.05% is the most appropriate concentration [20].

In cases that do not respond to atropine treatment and still show an increase in the myopia of more than 0.5 to 1 diopter per year, the strategy should be changed (using higher doses of atropine or combination therapies) [7].

Studies showed that the effect of 0.05% atropine is approximately similar to the effect of orthokeratology, and these two have a greater effect than progressive lenses [7].

Currently, many studies are being performed on doses of 0.005% to 0.05%, and it has been recommended that we use atropine 0.01% to atropine 0.025% to 0.05% [7, 16, 24-26].

Combination therapies

Combination therapies are used when therapies alone are not entirely effective in preventing myopia progression. For example, using multifocal contact lenses or orthokeratology along with atropine therapy can increase the effectiveness of treatment. Recently, combination therapies are being explored as a new line of treatment. The success rate of orthokeratology plus atropine treatments is less than 100%. However, because the mechanism of the two methods is entirely different, the two methods may be more effective together [27].

Four studies have been conducted in this field. In the first study, Kinoshita et al. divided patients into two groups after 3 months of orthokeratology treatment. In the first group, treatment with atropine was combined with orthokeratology, and the second group used only orthokeratology [28].

A few months later, Wan et al. conducted another study in this field and divided their sample into two groups: the first group with a myopic refractive error below 6 diopters and the second group with a myopic refractive error of more than 6 diopters and both groups were treated with 0.125% and 0.025% atropine. These groups were compared with the control group [29].

In another study, Chen et al. conducted their research in two phases. In the first phase, orthokeratology was used for 12 months, and then 0.01% atropine was added [30]. The previous study with this theme was conducted by Tan et al. and had a 1-month follow-up [31].

The results of these studies were collected, and according to them, the increase in myopia in the treatment group was 0.38 diopters, and in the control group, who performed just orthokeratology was about 0.62 diopters: almost two-fold. Also, the increase in axial length of the eye was 0.37 mm on average in the treatment group and 0.41 mm in the control group [27].

The possible mechanism of this combination therapy is based on dilation of the pupil and thereby increasing retinal brightness by atropine, causing shorter myopic changes in the peripheral of the retina and increasing the effectiveness of orthokeratology therapy [29].

Recently, Zhao et al. examined a 1-month change in choroid thickness in the fovea section by 0.01% atropine treatment and orthokeratology. They concluded a greater increase in the combination treatment group in choroid thickness in that area than in the atropine treatment group alone [32].

Choroidal blood supply as a potential "rapid predictor indicator" for the axial elongation and progression of myopia

Ophthalmologists are interested in having a predictor of myopia progression to use and improve the treatment and prevention of myopia. Two of these are the increase in the axial length of the eye and the thinning of the sclera, along with the deformation of its extracellular matrix [33]. Differences in choroid thickness were found among different ethnic groups. Asians, for example, have the thinnest choroid thickness [34]. Myopia is also more prevalent in Asians, so it can be concluded that thinner choroid thickness may be a risk factor for developing myopia [33].

Many studies have found that the thickness of the choroid in adults becomes 14 to 54 µm thinner every 10 years. Conversely, choroid thickness in children without refractive error increases significantly with age, while in children with higher refractive error, changes in choroid thickness are the same as in adults and decrease [33]. Fontaine et al. also found in a 15-month study that choroid thickness in the fovea increased in non-myopic individuals, while in 115 children aged 2 to 16 years with myopia, there was a decrease in thickness [35].

All of this evidence suggests that thinning of the choroid may indicate the development of myopia and that the choroid area where there is an inadequate blood supply to the capillaries increases in myopic patients [33].

A study in Piglets showed that prazosin, a vasodilator, increased choroidal blood flow and prevented myopia progression and axial length elongation by reducing scleral hypoxia [36].

In general, a decrease in choroid blood supply will reduce its thickness and consequently cause hypoxia of the sclera. These conditions can stimulate the signal pathways leading to myopia development [33].

Scleral hypoxia as a target for myopia control

We found that a hypoxia-causing factor called HIF-1α exacerbates myopia by altering myofibroblasts. Moreover, antihypoxic therapies will limit the functionality of this factor and stop the progression of myopia [37].

Chinese drugs such as salidroside and formononetin prevent myopia development by the exact mechanism. Furthermore, periocular injection of these two drugs can effectively disrupt the accumulation of myopia-causing factors [37].

Control of myopia in children with misight contact lenses

MiSight contact lenses are used for one day (made by Copper Vision). They are hydrophilic and soft and should be discarded after each use. This contact lens was clinically approved by the FDA to correct and reduce the rate of myopia (in children who are 8 to 12 years old at the beginning of treatment and their refractive error is between -0.75 and -4.00 diopters, and astigmatism should not be above 0.75). These contact lenses have a wide central vision correction zone of 3.36 mm, surrounded by alternating concentric zones near and far. The refractive power of the correction zone corrects the refractive error, but the treatment zones produce +2.00 diopters of myopic retinal defocus simultaneously in near and far vision. The dimensions of the corrective central zone are designed to provide good visual acuity in the distance, and near power is considered a therapeutic zone to prevent myopia from progressing and imposes myopic defocus periphery the retina as a stimulus to reduce eye growth [11].

Recent studies have shown that MiSight contact lenses effectively slow myopia progression in children compared to the control group. The findings of the 2-year study showed that after this period, the progression of myopia in the treatment group was 0.45 diopters and in the control group was 0.74 diopters, and also a smaller increase in axial length in the treatment group of 0.28 mm compared to the group with single vision glasses is reported as 0.44 mm [38]. In another study, Chamberlain et al. concluded that group therapy with these contact lenses showed fewer changes in refractive error compared to the group with single vision contact lenses (0.73 diopters difference) and less change in axial length than the single vision contact lens group was reported over 3 years (0.32 mm difference) [39].

The effect of crocetin dietary supplement on myopia control in children

Crocetin is a substance with a high antioxidant effect that prevents cellular oxidative degradation of substances. It is also one of the carotenoids. The effect of crocetin on myopia control was investigated in one study. The study had 69 cases (6 to 12 years) with cycloplegic refraction as a spherical equivalent between -1.50 and -4.50 diopters. The sample group was divided into two groups of placebo and crocetin use, and their follow-up was 24 weeks. Changes in refractive error were reported in the placebo group as -0.41±0.05 diopters and in the crocetin group as −0.33±0.05 diopters, and the group that used crocetin was less myopic. Changes in axial length were also reported in the placebo group as 0.21±0.02 mm and the treatment group at 0.18±0.02 mm. However, the most significant results were related to changes in choroid thickness, which were -9.2±75.5 µm in the placebo group and 34.1±49.1 µm in the treatment group [40].

These data indicate that the thickness of the choroid is significantly increased using crocetin. As a result, dietary use of crocetin may have a suppressive effect on myopia progression, and no side effects have been reported. Nevertheless, more extensive studies are needed to confirm this effect [40].

Efficacy of 7-methylxanthine (7-MX) and scleral strengthening

7-MX is a metabolite of caffeine and theobromine, and hypothetically it can prevent axial length elongation and myopia progression by thickening and strengthening collagen fibers in the sclera. The drug has been approved in Denmark to prevent myopia. Others have hypothesized that if a metabolite of caffeine in the form of 7-MX and oral use can effectively control myopia, then caffeine in the form of eye drops may effectively prevent myopia [41]. If ocular diseases such as retinal detachment and myopic macular degeneration that occur with the development of myopia are due to thinning and elongation of the sclera, then scleral strengthening can be effective. Attempts were made in this field, such as sclera-strengthening surgeries, cross-linking, and injections, none of which have been successful in humans for a long time [41, 42]. Further studies in this field on human participants seem necessary.

4. Conclusions

A wealth of literature has reported the effect of pharmacological interventions such as ATOM1, ATOM2, and LAMP, as well as the effect of optical strategies, such as orthokeratology lenses, bifocal, and progressive addition lenses on the prevention of myopia progression. However, some new studies have been performed in recent years. The main findings of the latest published papers in this field can be summarized as follows: 1) choroidal blood supply as a potential "rapid predictor indicator" for the axial elongation and progression of myopia, 2) periocular injection of salidroside and formononetin as an effective method on myopia control, 3) myopia control with reducing of hyperopic defocus with MiSight contact lenses, 4) The effect of 7-methylxanthine on prevention of axial length elongation, and 5) suppressive effect of crocetin dietary supplement on myopia progression. These studies have shown that using the latest methods of myopia control along with conventional strategies for myopia prevention would have a synergistic effect.

Ethical Considerations

Compliance with ethical guidelines

The article format is review, dose not require ethics approval.

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Authors' contributions

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Conflict of interest

The authors declared no conflict of interest.

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