REVIEW ARTICLE

Role Of Atropine In Progressive Myopia

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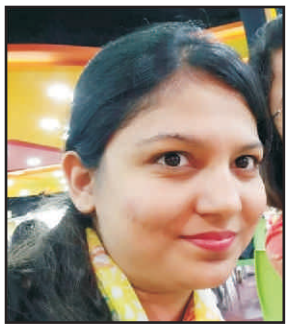
Abstract :

Worldwide, the prevalence of myopia has been rising dramatically, and it is estimated that 2.5 billion people will be affected by myopia by 2020.[1] South-East Asia is now facing a myopia frequency up to 95.5% in young academics,[2,3] but a rising trend has also been observed in recent European studies.[4] The high rise also includes prevalence of high myopia (<-6D; axial length>25mm), which in particular is associated with severe complications, such as myopic macular degeneration and glaucoma.[2] The absolute risk of severe visual impairment is 30% in individuals with axial length of 30mm or more.[5,6]



These dramatic figures create the need for effective counteractions. Current treatment options for progressive myopia can be categorized in conservative and pharmacological interventions.[7] The effects of the conservative regimens, except for orthokeratology are relatively small.[8] Pharmacological intervention has a much higher efficacy, in particular treatment with topically applied atropine eyedrops.[9]

Atropine, a non-selective muscarinic receptor antagonist (M-antagonist), is the most studied pharmacological agent for the intervention of progressive myopia.[10]

By the mid-1800s, atropine was frequently used in ophthalmology for pupillary dilation to examine the posterior segment of the eye and as a temporary treatment to improve vision in cases of cataracts. It was also used to induce mydriasis during cataract surgery and to prevent or break the posterior synechia in cases of uveitis. At that time, it was not used in myopia treatment.[11,12,13]

Donders (1864) was the first to recommend atropine as a treatment for myopia when he suggested it for suspected spasms of accommodation in myopic patients.[14] One hundred years ago, Pollock was the first to employ prolonged use of atropine for the treatment of myopia (for a duration of several months to almost a year); the therapy also required affected children to avoid reading and writing.[15,16,17] However, in the following decades of the 20th century, pharmacological treatment of myopia was not pursued. Few researchers from the 1930s to the 1990s conducted new studies.[18-30] As previously mentioned, several of those studies completely disproved the hypothesis of convergence as the main cause of myopia, as children in those studies continued to read with both eyes, and therefore converge, with no signs of worsening myopia. In spite the evidence of the effectiveness of atropine treatment, it was not popular among ophthalmologists and had notable detractors.[31-34]

Both concentration and frequency of atropine have been modified to minimize the side effects while trying to maintain the benefits. Chou et al. (1997) proposed that application of 0.5% atropine eye drops once per day was effective for slowing the progression of refractive error, even in children with severe myopia.[35] As mentioned earlier, this group of researchers had also compared different concentrations of atropine and concluded that although 0.5% atropine was the most effective, the drop out rate may have reduced its effectiveness. Therefore, in 1999 it was suggested that because daily drops of 0.1% and 0.25% atropine were well-tolerated, those concentrations could be used initially to control the progression of myopia in children with rapid progression or in those who tended to have severe or early-onset myopia.[36]

In 2015, Clark et al concluded through their study that atropine 0.01% significantly reduces the rate of myopia progression over 1 year with minimal side effects. It appears most effective in children with low initial myopia and may not control rapid myopic progression in some patients.[37]

It is uncertain how atropine acts to inhibit myopia progression.[38-43]

Initially, inhibition of accommodation was thought to be important, but subsequent studies have shown that atropine also inhibits myopia in animals (e.g., in chickens) that have no accommodative facility.[39] One theory is that atropine and other muscarinic antagonists may have biochemical effects on the retina or sclera, which in turn affect remodeling of the sclera.[40-41] Another theory suggests that increased ultraviolet exposure (secondary to pupil dilation) may increase collagen cross-linking within the sclera, thereby limiting scleral growth.[43] The sclera as the primary driver of axial elongation does not fit

however with the anatomical finding of a marked thinning of the choroid, most marked at the posterior pole and being in relative terms considerably more pronounced than the thinning of the sclera[44]. If the sclera was the primary tissue governing the axial length of the eye, one would expect a widening of the choroidal space. An alternative model could be to consider BM as the primary structure expanding posteriorly and compressing the choroid, most markedly at the posterior pole, and distending secondarily the sclera. This hypothesis is supported by several anatomical observations: (1) the volume of the sclera (and choroid) is not enlarged in axially elongated eyes, suggesting re-arrangement of available tissue without active formation of new tissue; (2) the thickness of BM is independent of the axial length; and (3) the goal of the process of emmetropization is the adaption of the length of the optical axis that ends at the photoreceptor outer segments. The first firm structure located closest to the photoreceptor outer segments is BM while the sclera is separated from the photoreceptor outer segments by the spongy choroid, the thickness of which additionally shows a diurnal variation. The notion of BM as the primary driver is supported by a recent study in which the biomechanical strength of BM in relationship to its thickness was about 50–100 times stronger as compared to the strength of the sclera (Girard, personal communication). This hypothesis also fits with the observation that the RPE cell density and retinal thickness in the fundus midperiphery decrease with longer axial length, perhaps due to the production of BM in that region leading to a mostly tube-like enlargement of the globe. If BM is the primary driver of axial elongation, the RPE producing BM as its basal membrane would be the target tissue. Interestingly, a recent experimental study on lens-induced myopia in young guinea pigs revealed that amphiregulin antibody if applied intravitreally was associated with a dose-dependent reduction in axial elongation[45]. The RPE has receptors for the epidermal growth factor with amphiregulin being a member of the epidermal growth factor family.

Rationale for treatment

Recently, several publications from Asia have reported efficacy of 0.01% atropine in myopia control while having lower rates of side effects. As a result, there have been renewed interests in the clinical implementation of atropine for myopia control.While most studies have reported active treatment period of 1–2 years, the optimal length of treatment is not known. One strategy is to adopt the ATOM 2 study approach with 2 years of initial treatment, followed by withholding treatment for 1 year, during which time any further progression is monitored. Children who progress after stopping treatment can be offered further treatment. Alternatively, some centers in Taiwan adopt the continuous treatment till late adolescent (around 15–18 years old), as myopia progression is known to slow down in the late adolescent period[46,47]. Some investigators suggest tapering instead of abrupt stop to prevent possible rebound effect; however this has not been studied in detail.

Side effects

Systemic side effects in the ocular use of atropine is uncommon, such as dry mouth, face flush, headache, increased blood pressure, constipation, difficulty in micturition, and central nervous system disturbances. The most frequent ocular side effects with atropine eye drops include photophobia, blurriness of near vision, and local allergic response. Among them, photophobia is the most common and its incidence is positively correlated with the concentration of atropine. All of the patients who received 1% atropine in the study of Yen et al. reported photophobia, and this was described as the major reason that led to over a half of subjects dropping out of the study[48]. In contrast, photophobia was reported in only 22% and 7% of participants who received 0.5% and 0.25% atropine, respectively. None of the participants in the 0.1% atropine group reported significant photophobia[49]. Similarly, photophobia was uncommon in children who received 0.01% atropine in ATOM 2 study, and only 7% of subjects requested photochromatic lenses.

Among the 34 participants (17%) who withdrew from ATOM 1 study, the reasons were hypersensitivity, glare, and poor near-visual acuity. As for ATOM 2, 4.1% children in 0.1% and 0.5% atropine group reported allergic conjunctivitis[50]. Reduction of near visual acuity was reported in the 0.1% and 0.5% groups, but completely recover by 26 months. Rarely, glaucoma may be induced by atropine. The incidence is as low as 1 in 20,000[51]. One study reported 621 children treated with atropine for 3 year and none found ocular hypertension[52].

Conclusion

In conclusion, results from research have demonstrated low concentration of atropine is useful in retarding myopia progression in a certain proportion of myopic schoolchildren. Atropine treatment has now been incorporated into clinical practice in some Asian countries. However, for optimal results, the motivation of parent and children is important, and long-term compliance and adherence with atropine treatment cannot be over-emphasized. Education regarding the consequences of high myopia and sharing the effect of myopia control to children and parents at each visit are helpful strategies to keep them motivated during the course of treatment. Individualized treatment protocol of atropine starting from low concentration seems practical. On top of atropine, good eye-care habits, enhancement of time outdoors and limiting near-work load should also not be overlooked. Though low-dose atropine treatment is promising in myopia control, there are still remaining areas of uncertainty such as treatment strategy and targeting population. Although the current prevalence of myopia in Europe is not as high as in Asia, the prevalence of myopia is steadily rising in Europe and

US as well. The clinical and economic burden will become significant with time, therefore further research on myopia prevention in European populations is important

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