Is it Possible to Slow the Progression of Myopia?

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The rates of myopia, including high myopia [spherical equivalent ≥-6 dioptres (D)], have been reported to be rising to epidemic proportions in Asia and solutions to this huge public health problem are urgently needed.[1] Many researchers agree that myopia is not determined solely by genes and that environment may play a huge role. Reading increases the risk of myopia, but other potentially modifiable environmental risk factors – such as lighting or posture during reading – have not been found to decrease myopia risks.[2] At present, there are no practical and reliable primary preventive measures for myopia and there is a long way to go before we fully understand the aetiological mechanisms for myopia.[3]

As early as the 19th century, Eugene Fick used contact lenses to treat myopia[4] and many other ophthalmologists and optometrists have evaluated different interventions to retard myopia progression for centuries. However, the identification of an effective treatment remains elusive and few valid conclusions may be derived from previous studies. Nonetheless, treatments are often tested on and recommended to the general public despite the lack of evidence-based data and an incomplete understanding of how treatments, such as optical correction and drug options, work.

Before advocating any treatment, there should be an evidence-based approach to ophthalmic care. Important questions that need to be addressed include the following: is there an effective and safe intervention that may slow the progression of myopia?; if such an intervention is found, who do we recommend this treatment to (such as "high-risk" children)?; and which child is at "high risk" of pathological myopia in adulthood?

In reviewing effective treatments for myopia, sound epidemiologic principles need to be adhered to. The efficacy of interventions should ideally be evaluated in well-designed randomised clinical trials (RCTs) with adequate masking techniques. Randomisation is the cornerstone of a well-conducted clinical trial as this method of assignment of the intervention increases the likelihood that treatment differences are real (that is, due to the intervention) and are not biases (such as in patient selection). Masking may prevent any biases in the ascertainment of the degree of myopia progression that may be present if the knowledge of the intervention group is known to the investigator or patient. Other important points to note are the inclusion and exclusion criteria, whether accurate ocular component measures are available, drop-out rate, follow-up time, compliance with treatment and whether intention to treat or treatment received analyses were conducted.

A recent comprehensive and systematic review of the literature has revealed that the majority of trials evaluating interventions for myopia are not randomised.[5] Most commonly, non-randomised controlled clinical trials, non-controlled clinical trials and retrospective case series have been designed to study the impact of treatment of myopia.[5] The best evidence to date is gathered from RCTs of atropine eye drops, bifocals, soft contact lenses and under correction. A range of other treatments, including orthokeratology, biofeedback training, under correction of myopia, over correction of myopia, distance spectacle wear, ocular hypotensives and 4-step eye exercises, have been evaluated primarily in non-randomised non-controlled trials.[6]

With regards to atropine, several trials conducted in Asian countries, such as Taiwan, have shown that atropine eye drops may be effective in decreasing the progression of myopia.[7-9] Although atropine is known to be a muscarinic receptor antagonist, the exact mechanism of action is not clear. Sites of action have been hypothesised to include the sclera and retina. Atropine may inhibit deoxyribonucleic acid (DNA) and glycosaminoglycans synthesis in the sclera.[10] Atropine eye drops also affect dopamine neurotransmitter release and retinal signals that regulate eye growth.[11] The possible short-term side effects of atropine are relatively mild and include photophobia and difficulty in reading. The long-term possible side effects associated with chronic pupillary dilatation, such as ultraviolet light-induced retinal toxicity and cataract, are still largely

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unknown. Care must be taken to ensure that children comply with daily eye drop administration and appropriate ultraviolet light protective gear are advocated. Other issues include the uncertainty of the desired length of time of drug application for optimal efficacy and the possible reversible effects of atropine if the drug is stopped. A large RCT of atropine eye drops in Singapore schoolchildren has just been completed and the preliminary results showed that mean myopia progression was lower in the atropine group compared with the placebo group.[12] More importantly, atropine was generally well-tolerated and there were no major safety concerns.[13] A more selective M1 subtype muscarinic receptor antagonist, pirenzipine, is presently being evaluated in several ongoing RCTs in Singapore and other parts of the world. Potentially, fewer adverse reactions may be associated with pirenzipine, but its efficacy has yet to be proven.

The role of under or over correction of myopia to halt its progression is controversial. A recent 2-year single, masked RCT conducted in 106 myopic schoolchildren aged 6 to 14 years in Malaysia showed that children allocated with under correction of 0.75 D had a *higher* rate of progression of myopia (-1 D in 24 months) compared with children who were fully corrected (-0.77 D in 24 months).[14] The under corrected group showed greater axial length elongation compared with the fully corrected group ($P = 0.04$). The authors speculate that myopic defocus may speed up the progression of myopia. However, until this has been verified in larger studies in other populations, optometrists and ophthalmologists are advised to refrain from either over correction and under correction of myopia, as there is no proven benefit and possible long-term harm may occur.

There is insufficient evidence from RCTs that bifocal spectacles or contact lens wear are possible treatments to retard myopia.[15-20] The Correction of Myopia Evaluation Trial (COMET); [http://www.nei.nih.gov/neitrials/static/study9.htm), a multi-centre study (Alabama, Massachussetts, Pennsylvania and Texas) of 469 children aged 6 to 11 years in the United States, showed that multifocal lenses slowed the progression of myopia by a small statistical amount that does not warrant any changes in clinical practice.[21-23] This issue of the *Annals Academy of Medicine, Singapore* includes an article by the investigators of the COMET study which describes the issues involved in the conduct of a large-scale multi-centre study. A randomised trial of 428 Singapore schoolchildren showed that rigid gas permeable contact lenses do not reduce the progression of myopia, though there were no major safety concerns.[24] We await the results of several ongoing, well-designed RCTs of multifocal lenses in Singapore and trials evaluating rigid contact lenses in the United States (Contact Lens and Myopia Progression; CLAMP).

If a suitable, safe and cost-effective intervention for myopia is identified in the future, who should receive this treatment? In theory, this treatment modality should be targeted at young myopic children who have greater risks of developing high myopia. High myopia may be associated with complications such as retinal tears and myopic macular degeneration and, later on, with age-related macular degeneration, cataract and glaucoma. High myopia is also associated with increased dependence on optical corrections, such as spectacles or contact lenses, and possibly poorer visual function and quality of life. Thus, the overall aim of these treatments is to reduce the final refractive error and to lower the risks of ocular conditions associated with myopia, such as macular degeneration and choroidal neovascularisation.

The risks of high myopia in adulthood are possibly greater in a "fast myopia progressor". A "fast myopia progressor" is more likely to be Asian, female, with an earlier age of onset of myopia, greater severity of myopia at an early age, parental history of myopia and may read more. For example, a Singaporean child aged 8 years with myopia exceeding -8 D, who reads >7 books a week and whose parents have high myopia, and who has a marker for the myopia gene, is a likely candidate of "pathological myopia" in adulthood. The parents may express concern about the development of pathological myopia when the child reaches adulthood. Thus, if proven to be efficacious and safe, an intervention may be given to high-risk children to prevent progression to pathological high myopia.

In Singapore, myopia research receives intense media, political and public scrutiny. Several collaborative research projects involving the Singapore Eye Research Institute, Singapore National Eye Centre, Department of Community, Occupational and Family Medicine and the Department of Ophthalmology in the National University of Singapore, and the Singapore Polytechnic have shed new insights to the risk factors, aetiology and treatment of myopia. This is an exciting time for myopia research and a multi-pronged approach with the collaboration of specialists in the different fields of animal model work, epidemiology, pharmacology, physiology, anatomy and genetics may provide future answers to the "cure" for myopia.

An increasing number of myopia research projects have been initiated in Taiwan, Hong Kong, Australia and the United States. Myopia workshops and "brainstorming sessions" have been conducted prior to major international meetings, such as the XXIXth International Congress of Ophthalmology (Sydney 2002), and a myopia symposium will be held at the next Singapore Eye Research Institute-Association for Research in Vision and Ophthalmology (SERI-ARVO) meeting on Research in Vision and Ophthalmology in Singapore in February 2005. In 2006, Singapore will host the XI International Conference on Myopia, facilitating the exchange of ideas among local and overseas myopia researchers. To address increasing public concerns, there have been concerted, sustainable efforts in Singapore by the Ministries of Health, Education and Defence to develop strategic plans and to implement public health education programmes to combat myopia. Hopefully, the growing interest in myopia will lead to a better understanding of the pathophysiology of myopia development and the introduction of new treatments to halt the progression to pathological myopia.

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