

Methodologies for Interventional Myopia Studies

Chong-Yew Khoo,¹*FRCOphth, FRACS, FAMS*, Richard FS Ng,²*BSc*

Abstract

Myopia studies are notoriously difficult to carry out. Past studies on intervention in myopia progression have given conflicting results. Beside inaccurate and inadequate measurements, the most important cause for this is the very variable nature of myopia, which makes it difficult to achieve baseline comparability between the control and the study group. Although there were inclusion criteria in these studies, for age, sex, race, degree of myopia and stigmatism, the most important variate – the rate of myopia progression – was not included. Randomisation can achieve baseline comparability of the myopia progression rate, provided the sample sizes are large enough. Unfortunately, past studies have been limited to 100 to 200 children only. Studies on twins are more reliable than random groups because myopia progression rates are more likely to be the same in a pair of twins. Studies on the same subject, comparing the right eye and the left eye would be even better, but this method is practicable for some studies only (e.g., we cannot have a spectacle lens for one eye and a contact lens on the fellow eye). There is another method of doing an interventional study on myopia. Because myopia progression is linear in its early stage until the early teenage years, it is possible to observe what happens to the linear progression upon intervention. In this way, we avoid the problem of trying to compare “apples with apples” but use the “same apple” instead.

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Introduction

Past studies on intervention in myopia progression have given conflicting results.¹⁻¹¹ For example, in the past, studies on (PMMA) hard contact lenses took researchers in the past on a roller-coaster ride. Besides inaccurate and inadequate measurements, the most important reason for this was the very variable nature of myopia.

To overcome this problem, we try to achieve the best baseline comparability by devising strict inclusion criteria for the subject, such as age, race, sex, degree of myopia and astigmatism, and by randomising. However, the very variable nature of myopia raises the question of whether we are comparing apples with apples. One group of subjects may have a higher proportion of highly progressive myopias than the other. Another way of trying to overcome this problem is to do a study on twins, which, however, are scarce.

Myopia, like glaucoma, is not one disease (Table 1). This has been amply described by Brian Curtin in his classic text

book on myopia, which he so aptly called “The Myopias”.¹² You would be horrified if we told you that we were doing a study on glaucoma, and did not separate the acute angle-closure glaucomas from the chronic open-angle glaucomas. Again, if you were doing a study on the effectiveness of an anti-obesity drug, you would want to balance the basal metabolic rates of the subjects before starting the trial.

Therefore the most important variable – the rate of myopia progression – should be balanced at baseline. Two children of the same race, sex, age and degree of myopia; say -3.00 D at baseline, can progress very differently; one at 2.00 D every year, ending up with -15.00 D and the other at 0.50 D every year, ending up with -6.00 D. You can randomly pick 2 groups of myopic children, all wearing spectacles, and show after 2 or 3 years that one group’s myopia is progressing more rapidly than the other. Hence, we cannot claim that an intervention works or does not work with 2 random groups.

How can we achieve better baseline comparability in

¹ Private Practice
Raffles Hospital, Singapore

² Former Statistics Consultant

School Health Services, Ministry of Health, Singapore

Address for Reprints: Dr Chong-Yew Khoo, Raffles Hospital, 585 North Bridge Road, #02-00, Singapore 188770.

Table 1. Myopia is Not One Disease

Clinical types of myopia	
1)	Pseudomyopia (due to accommodative spasm)
2)	Stationary (non-progressing)
3)	Physiologic or simple (axial length usually <25.5 mm, no crescent)
4)	Intermediate (axial length usually >25.5 mm, crescent)
5)	Pathologic (has serious degenerative changes)
6)	Curvature and index (due to corneal or lens changes)

myopia studies? Various designs for myopia studies have been adopted in the past, with a view to achieving good baseline comparability, reliability and repeatability. They are:

“Parallel” Studies

Randomised Group Trials

In randomised group studies, 2 groups of myopic subjects are randomly allocated, 1 group as a control, and the other the study group. Inclusion criteria are required here for baseline comparability. However, the most important variate, i.e., the rate of myopia progression, has never been included in the lists of inclusion criteria of past studies. It is possible to do this if we monitor the rate of progression for one year or so before starting the trial proper. We can then specify in the inclusion criteria the range for the myopia progression rates to be considered, e.g., 0.50 D per year to say 1.00 D per year. Alternatively, a stratified analysis can be made, separating the high progressors (more than -0.75 D progression per year) from the normal progressors. This is an important consideration for studies on Asian children, whose myopia progression rates are much more variable than their western counterparts.

If the sample groups are large enough, however, randomisation should achieve baseline comparability of the myopia progression rates. Unfortunately, past studies have been limited to 100 to 200 children only. What is not often appreciated is that there is a high drop-out rate in children, particularly in the group with intervention (such as with contact lenses). Therefore, at the end of the study (usually 2 to 3 years) the study group is much smaller than the control group (the drop-out rate with contact lens wear in children is 30% to 40%). Only 1 study (the CLAMP study in USA) was designed to overcome this problem by using only children who were successful contact lens wearers.

Twin Studies

Two groups of myopic subjects who are twins can be compared. They should preferably be monozygotic twins.

Here we achieve much better baseline comparability than in (1), as myopia progression rates are more likely to be the same in a pair of twins.

Same-subject Studies (Randomised)

We can compare the right eye versus the left eye of the same subject; e.g., we can use atropine ointment in the right eye and a placebo (vehicle ointment) in the left eye, and compare the myopia progression rates of the 2 eyes. This is provided there is no anisometropia. The baseline comparability is much better than that in (1) and (2).

For contact lens studies, however, we cannot have spectacle lens for one eye and contact lens for the other. We can do studies with children wearing a soft contact lens on one eye and a rigid contact lens on the fellow eye, or a rigid contact lens on one eye and an orthokeratology contact lens on the fellow eye.

“Cross-Over” Studies (Randomised)

Same-eye Studies

Cross-over allows each person to act as his/her control. We can study the effect of an intervention on an eye whose myopia progression rate has been monitored and is known. As myopia progression is linear in children¹²⁻¹⁵ (up to the early teenage years), it is possible to see the direct effect of the intervention on the linear progression. This is unique for myopia; in no other medical condition is there a measurable linear progression. The authors personally confirmed the linear progression by tracing the myopia progression of 60 children (120 eyes). All showed linear progression. Figures 1 to 3 show some of these cases.

From the point of view of baseline comparability, the above 4 methods are listed in ascending order of reliability. For example, twin studies are better than random group studies. Studies on the same subject are even better than twin studies, and studies on the same eye would be best. With studies on the same eye, we would not have the problem of “comparing apples with apples”, as we would be using the “same apple”.

Other Pitfalls in Myopia Studies

Age of Subjects

It has been shown that myopia stabilises somewhere between 18 and 23 years of age. The subjects for myopia studies should therefore be much younger. Otherwise, when control of myopia occurs, it is possible that it could have been due to the natural ageing process. In Singapore, recent studies have shown that the onset of myopia is now earlier than before, and that the earlier the onset, the more highly progressive the myopia. This was confirmed in my personal review of 60 children (120 eyes). Figures 1 to 3 show samples of the cases.

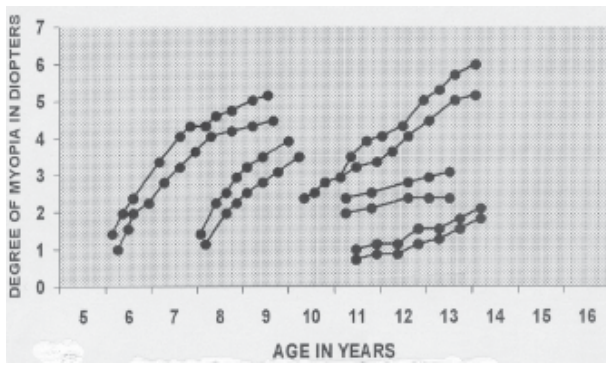


Fig. 1. Spectacle wearers: observed values of myopia progression.

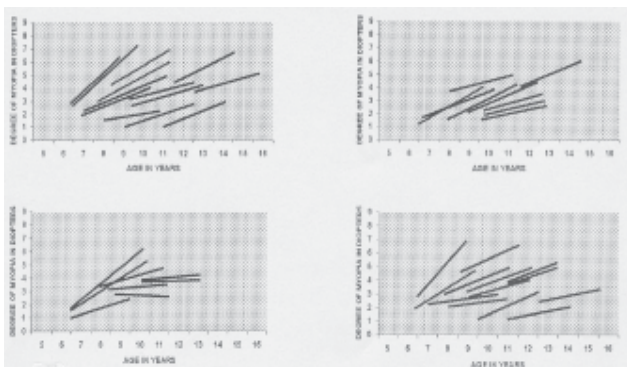


Fig. 2. Spectacle wearers >3 years: graduated lines of myopia progression.

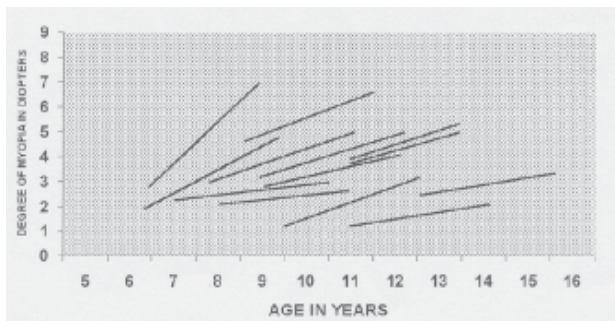


Fig. 3. Myopia progression of spectacle wearers: observations.

1. Wide variation in the progression of rates.
2. Myopia progression is linear, beyond 3 years.³⁻⁷
3. The earliest onset the more highly progressive the myopia.⁸⁻¹¹
4. Three “stationary” myopias, out of 120 (2.5%).
5. Two eyes’ regression, out of 120 (1.6%).

Randomisation

There should be randomisation for the mode of intervention, e.g., whether the subject should be in the study or control group. If subjects are allowed to choose, there will be a tendency for more highly progressive myopes to opt for the study group. For right/left eye studies, there should also be randomisation for what process is carried out in which eye, as in atropine/placebo gel studies.

Overcorrection/Undercorrection

Great care should be taken to ensure that there is no overcorrection or undercorrection with glasses or contact lenses. Cycloplegic autorefraction should be done. There should be no overcorrection for astigmatism with the contact lenses.

Accuracy of Refraction

To obtain accurate refractive readings, and to eliminate pseudomyopia, refraction should be done under complete cycloplegia. It has not been shown which is more reliable: cycloplegic manifest refraction or cycloplegic autorefraction. If the cycloplegia is complete, autorefraction should be more reliable as it is not subjective. Autorefraction should also be more reliable than retinoscopy, which is dependent on the expertise and accuracy of the examiner. Whichever method is used, the same procedure should be used throughout the study. In practice, it is difficult to standardise the refraction procedure. For example, the duration of cycloplegia must be the same (45 minutes) every time to achieve complete cycloplegia.

Reliability of Tests

Keratometry has been shown to be reliable to the order of +0.25 D.¹⁶ The accuracy of A-Scan ultrasound measurements with a hand-held probe has been found to be 0.2 mm.¹⁷

All measurements should be done at least 3 times and the average reading taken. The same equipment should be used, and the number of observers limited.

Choice of Contact Lenses

PMMA hard contact lenses were used in past studies, until 1985, when RGP lenses became available. It is well-known that PMMA contact lenses, which are not gas-permeable, can cause corneal hypoxia in the form of “Sattler’s Veil”, “spectacle blur” and “overwearing syndrome”. Such corneal changes alter the refraction of the eye and will give errors in the refraction test, causing increased myopia readings. These changes are temporary and variable, and a true reading can be obtained if the lenses are removed for a few days before the tests are done. This variable factor is difficult to control, and would have contributed to the fact that past studies with PMMA lenses gave conflicting results. Similarly, soft contact lenses also cause corneal hypoxia, and are not suitable for such studies. They also have a higher risk of infection, and do not correct astigmatism so well.

The authors examined the keratometric readings of 45 children (90 eyes) who wore RGP contact lenses, ranging from a few to 10 hours a day.^{13,14} The lenses were fitted on-k (alignment fitting). The effect of the RGP lenses on the

cornea was minimal for the duration of 3 years. As most of the children had with-the-rule astigmatism, and fitting was on-k, there was a subtle shift in the against-the-rule direction due to a spherisation effect on the corneal curvature.

Previous studies done on the effect of contact lenses on the corneal curvature were on orthokeratology—i.e., altering the shape of the cornea by fitting flatter than the flattest K reading.¹⁸⁻²² A lesson learnt from these studies is that it is not easy to change the shape of the cornea with a contact lens unless it is fitted 1 D to 2 D flatter than the flattest K-reading. In fact, a reverse-geometry shaped lens is now used in accelerated orthokeratology. This short-term corneal change is different from the long-term “corneal warpage” caused by wearing contact lenses for many years.

Method of Recruitment

Recruitment for trial subjects by advertisement in the news media tends to attract more highly progressive myopes. Recruitment by referrals from the schools would give a more accurate representation of the student population. Different studies would therefore give different results if the methods of recruitment are different.

Drop-out Rate

With contact lens studies, there is the added problem of a high drop-out rate, which can be as high as 40% in children. This is because of a lack of motivation—there is no cosmetic motivation to wear the lenses and they do not understand the purpose of the study. Therefore, at the end of the study, the study (contact lens) group will be much smaller than the control (spectacle) group. It would not only be the quantity but the quality of the study group that has changed, because the drop-outs could be less highly progressive myopics, who are less motivated to use contact lenses. To reduce drop-outs, there should be measures such as attentive clinic staff, and incentives to participants, such as “birthday” cards and free screening at visits.

Compliance

Another problem with contact lens studies is whom to include or exclude from the contact lens group? Is a child wearing the contact lenses for 3 hours a day only or on weekdays only to be included as a contact lens wearer? Is he to be included as a successful contact lens wearer, if he wears them 7 hours a day at the beginning of the study and then 3 hours a day towards the end of the study? Compliance should be monitored, such as asking the child to complete a diary, or sending a reminder “sms” to the child/parent to check that the subject is wearing contact lenses, or reviewing the subjects more frequently.

Significance

Results may show a “statistical significance” of, say, 0.25 D but a difference of 0.25 D has no “clinical significance”. What would be the minimum rate of change to indicate that myopia is progressing? In fact, more important than “progressing myopia” is “progressive myopia”, as this is the group that can give rise to blinding complications and therefore needs to be controlled.

Conclusion

If 2 randomised groups are used for comparison, it is important to have inclusion criteria for the myopia progression rate as well. This means monitoring the progression rates of the subjects for 1 year or so before the trial starts, and including only those who fall within the desired range for the study.

As myopia progression is linear in the early stages (up to the early teenage years), it is possible to study the effect of intervention on the progression rate of the same eye. In this way, many of the variates will be eliminated, and the problem of “comparing apples with apples” is avoided. In fact, we will be using the “same apple”. It is hoped that this method of studying intervention in myopia progression will bring the consistency and reliability which conventional studies have lacked for decades.

As myopia progression is linear, there is no need to do 3-monthly assessments, which makes such studies very laborious. In fact, 6-monthly, or yearly assessments should be adequate. However, you might want to see the subject more frequently to check on compliance.

It is hoped that we will have more comfortable contact lenses soon, so that the drop-out rate will be reduced. The most convenient lens would be one which can be worn safely by the child on an extended-wear basis. Many children drop out because of the inconvenience of having to insert the lenses in the morning before rushing off to school.

There is a paucity of studies on intervention in myopia progression in children as they are difficult to carry out. It is hoped that a better understanding of myopia progression will lead to easier methods for carrying out such studies.

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