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Putting efficacy into context: do controlled trials on efficacy of myopia control translate to a clinical population?

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INTRODUCTION

Concerns surrounding the global increase in the prevalence of myopia[1] have led to the development of various optical and pharmacological interventions which aim to slow axial elongation within the myopic eye. This is of particular importance when considering that myopia, particularly high myopia, increases the risk of diseases such as maculopathy and subsequent visual impairment.[2]

Children recruited to clinical trials must meet a set of stringent inclusion and exclusion criteria. Typically, children with high amounts of myopia and moderate to high amounts of astigmatism are excluded.[3–5] Additionally, preschool (younger than 6 years) and post primary school (older than 12 or 13 years) children are typically excluded from trials[3–5] as are those with binocular vision issues.[5] This leads to the question of how applicable research trials are to a more diverse clinic population, that is, the real world, particularly when compliance is not monitored as a stringent requirement as within clinical trials, and where motivation and commitment among parents and children may be less than in a clinical trial. The application of clinical trial data in myopia management is a topic which has been investigated within a case series of patients[6] and with a larger clinic population further presented and undergoing further analysis.[7] Here we want to consider how efficacy is portrayed in literature, the variation it results in for treatment effect and the applicability of research on efficacy of intervention from clinical trials to clinical practice.

VARIABILITY IN THE EFFICACY OF MYOPIA MANAGEMENT INTERVENTIONS

When describing efficacy of an intervention, clinical trials traditionally report the average difference in axial elongation and cycloplegic spherical equivalent refraction (SER) progression between the intervention group and the control group over the study period. This is reported as both an absolute value as well as a relative effect between the groups as a percentage. As described by previous authors,[8] the use of percentages can be misleading and lead to a perceived overestimation of treatment effects in the long term as it assumes a continual effect over time. Instead, the absolute reduction in axial elongation and SER should be taken into account more.

Alongside this, average values can be useful in consolidating a large volume of data, but indices of variability including the SD and 95% CIs should also be carefully considered in order to more fully consider the range of expected efficacy of an intervention; not everyone will reach the average expected slowing in progressing with some children achieving a greater slowing and some achieving little slowing if at all. Variability in the efficacy for some examples of commercially available optical interventions in the UK is summarised in table 1.[3 4 9–11]

The SE and CI data presented in table 1 from clinical trials indicate the variability in the estimate of the mean when comparing slowing in progression between treatment and control groups. However, when efficacy of an intervention is considered within the context of a clinic population, our preliminary findings[7] indicated a mean reduction in axial elongation of 0.12 mm and a SD of 0.20 mm (n=44). These values were reported for various optical interventions including defocus incorporated multiple segments (DIMSs), MiSight, orthokeratology and multifocal contact lenses. Although this average reduction of 0.12 mm/year is similar as that reported by the literature (table 1, average slowing in progression per year of 0.13 mm), the SD indicates the variability in efficacy within the clinic population. This highlights the importance of managing expectations with parents and children in that a discussion should be held regarding potential variability

Table 1 Table comparing the variability in absolute treatment effects between commercially available optical interventions in the UK. The average slowing in progression between treatment and control groups in addition to SD, SE and CIs are included

Optical intervention	Study duration	Average slowing in axial elongation over the study duration	Variability	Average slowing in SER over the study duration	Variability
Defocus incorporated multiple segments[4]	2 years	0.34 mm	SE 0.04 mm 95% CI 0.22 to 0.37 mm	0.44D	SE 0.09D 95% CI 0.37D to 0.73D
MiSight[3]*	3 years	0.28 mm	SD 0.04 mm 95% CI 0.20 to 0.36 mm	0.67D	SD 0.09D 95% CI 0.49D to 0.84D
Highly Aspheric Lenslets[9]*	2 years	0.35mm	SE 0.05 mm 95% CI 0.23 to 0.47 mm	0.80D	SE 0.11D 95% CI 0.53D to 1.07D
Multifocal contact lenses (high addition)[10]*	3 years	0.23 mm	SE 0.03 mm† 95% CI 0.17 to 0.30 mm	0.46D	SE 0.09D† 95% CI 0.29D to 0.63D
Orthokeratology[11]	2 years	0.27 mm	SE 0.06 mm 95% CI 0.16 to 0.38 mm	Not applicable	Not applicable

*Values adjusted for multiple factors within the statistical analysis.
†SD not reported in the text. For statistical accuracy, SE instead of SD was calculated from 95% CI.[28 29]
SER, spherical equivalent refraction.

in response when communicating the likelihood of success of intervention. Although the risks of adverse events using interventions are low,[12] costs of optical interventions can pose a significant barrier to parents opting for myopia control as reported by eye care practitioners (ECPs).[13] Because myopia management requires ongoing significant financial investment, discussing potential variability in efficacy would allow parents to make fully informed decisions regarding the potential benefits versus costs of interventions.

Further research is required to explore why some children respond better to interventions than others. The term 'non-responder' indicates a child who has not sufficiently slowed in progression while using myopia intervention. The difficulty lies in defining which children can be termed 'non-responders' as they must be clearly differentiated from those who are 'fast progressors', and may inadvertently appear to be showing a reduced respose.[14] Arbitrary cut-off values have been proposed, including progression of >0.11mm/year[15] for axial length and <−0.50D/year[16] for SER, despite use of intervention. However, these values have not considered the previous individual progression rates of those children. For example, a child who is progressing at a fast rate for example, 0.40 mm/year may achieve significant slowing with intervention yet still progress faster than the cut-off value of 0.11 mm/year. This leads to the question of how to evaluate treatment success within a clinic population for individual patients, particularly where there is no control group to act as a comparison.

EVALUATING TREATMENT SUCCESS

Research has started to explore how best to evaluate treatment success,[17] but there is no guidance on how this could be incorporated into clinical practice. Some approaches which could be considered within clinical populations[6 7] and within clinical practice are considered below. Please note that these methods use axial length. This is because of the limitations of using refraction to evaluate treatment success; primarily because it is not as sensitive a measure as axial length.[18] Additionally, SER may not provide the optimum and most appropriate method of defining refractive error.[19 20]

Percentile method

Definition

This method uses axial length growth curves[21] to determine if a child's eye growth has slowed to the rate of growth in a lower percentile. For example, a child following along the 98th percentile before starting intervention should slow in eye growth to match the growth rate within the 95th percentile or lower.

Limitations

This method considerably overestimated treatment success as the difference in growth rates between percentiles is, at times, clinically insignificant ranging from 0.01 to 0.04 mm[6] and not detectable using modern biometry.[22] Taking the example above of a child following along the 98th percentile and slowing in growth to match the 95th percentile, this slowing in progression is small (0.02 mm)

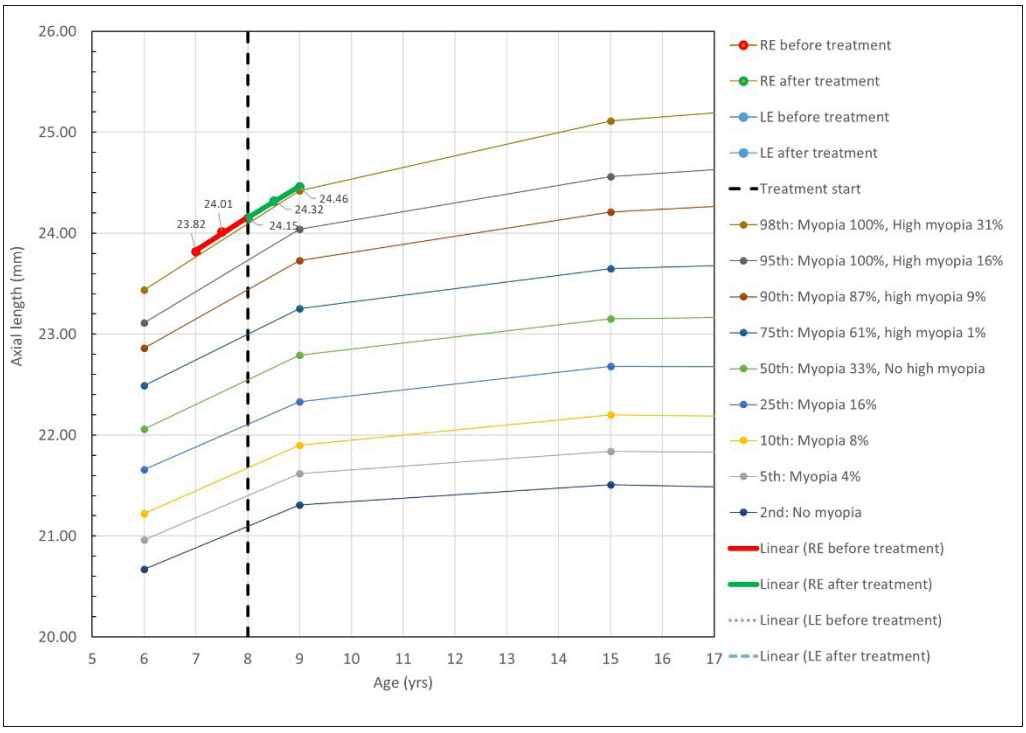

Figure 1 A child following along the 98th percentile before starting intervention who has slowed in eye growth to match the growth rate within the 95th percentile, figure adapted from Tideman *et al* 2017. The black dashed line indicates when intervention was commenced. This slowing in progression is small (0.02 mm) and not able to be detected visually. LE, left eye; RE, right eye.

and not able to be detected visually as depicted in figure 1, adapted from Tideman *et al* 2017.[21]

Emmetropic growth method

Definition

The rate of progression after starting intervention was compared with the expected age matched rate of growth of a typical emmetrope.[23] Emmetropic growth values have also been applied to develop an 'Emmetropic Progression Ratio' to evaluate treatment success within a recent clinical trial.[24]

Limitations

This method of comparing the rate of progression after starting intervention to the expected age matched rate of growth of a typical emmetrope considerably underestimated treatment success.[6] Achieving the same growth rate as an emmetrope may be overly ambitious depending on the rate of progression prior to starting intervention.

Cumulative absolute reduction in axial elongation (CARE)

Definition

When applying this method to a clinic setting in the absence of a control group, the annual rate of axial elongation before treatment initiation is first calculated. The rate of axial elongation at each 12-month time point after the initiation of treatment is then calculated and subtracted from the annual rate of axial elongation before treatment initiation. The CARE value for the child can then be compared with the expected CARE value for that specific intervention for example, 0.27 mm over a 3-year period for orthokeratology.[11]

Limitations

The CARE method may better account for age and rate of progression.[8] Initial application of this method to a case series[6] suggests similar results as for the mean efficacy method, detailed below, and further application of this to a larger population would confirm this finding. From a clinical perspective, the time required to manually calculate the CARE for a patient may be difficult to incorporate into a busy clinical practice, and therefore its application may be more realistic within a research setting. However, the difference in study durations may make it difficult to directly compare CARE values between research studies.

Mean efficacy method

Definition

This was found to be the most clinically appropriate method of determining treatment success.[6] It is based on the premise that the child's pre-intervention rate of axial elongation should slow by the average amount reported in literature for that specific intervention. For example, a child progressing at 0.28 mm/year prior to starting intervention slows to 0.08 mm/year after starting intervention. The slowing in progression of 0.20 mm/year would then be compared with the expected slowing in literature for that intervention. For example, a child wearing DIMS spectacles may expect an average slowing of 0.17 mm/

year.[4] Based on this value, the child has a successful treatment effect and could be deemed a responder.

Limitations

There are strengths and limitations to this approach. There may be reluctance by parents and ECPs to withhold intervention for this monitoring period of up to 12 months while the myopia may continue to progress. However, in the authors' opinion, the amount of progression that will occur over such a short period of time (on average 0.23 mm/year[23]) may not significantly change the prevalence of associated conditions such as myopic maculopathy for the majority of axial lengths.[25] Additionally, this period of time would provide confirmation that axial elongation is progressing at a significant rate to warrant intervention. Subsequently, we believe that the advantages of monitoring for up to 12 months prior to starting an optical myopia management intervention outweighs the potential disadvantages, and may provide more valuable individual-level data to help determine treatment success.

One limitation of this mean efficacy method is that it may not fully account for slowing in axial elongation with age. The average target value may go some way to accounting for slowing with age as it is taken from clinical trials which include children of a wide age range (6–12 years)[3 4 9] who will have a range of different growth rates and take place over 2–3 years[3 4 9] where some slowing of progression with age will have occurred. This may not be as much of a concern when evaluating short term changes over a year or two as the average slowing with age is reported to be 0.03 mm on average in untreated myopes[23] which is within the repeatability of modern biometry instruments.[22] However, when evaluating longer term changes over many years, there may be more of a notable cumulative change.

The mean efficacy method relies on the assumption that previous progression predicts future progression. Research exploring this topic is so far limited to two studies.[26 27] The first study explored SER only, and found that one year previous progression predicted subsequent 2 years of myopia progression in a dose dependent manner.[26] However, the authors also noted that prior progression in isolation cannot fully predict future progression due to the multifactorial nature of myopia, and there was considerable variability within the data. Another study has explored whether previous axial elongation predicts future axial elongation using a modelling approach[27]; results indicated that despite low correlation, axial elongation and SER progression in the previous year predicted progression in the subsequent year. Other factors such as age and ethnicity were more effective in reducing the 95% limits in comparison to the inclusion of previous progression alone in predictive modelling. However, a-scan ultrasonography was used to measure axial length which is approximately eight times more variable than modern biometry when evaluating changes in axial length over time in children (95% limits of agreement for repeatability: −0.052 to 0.073 mm for optical biometry and −0.57 to 0.49 mm for ultrasound biometry).[22] This suggests that previous progression should not be immediately dismissed as a predictive factor, and that further research exploring previous axial elongation measured using modern biometry should be of merit.

CONCLUSION

Further research into the success of interventions within real-world clinic populations is required to determine the relevance of average and variability data taken from controlled research trials. Research from our clinic so far suggests that treatment effects can be variable in practice-based studies, and further work looking at larger populations is warranted. The variability of patients presenting with myopia within a diverse clinic population highlights the need for research into groups excluded from clinical trials to determine whether there is any benefit for use, particularly those with high myopia, and young myopic children at greatest risk of visual impairment from associated pathologies.

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