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Project title: Personalising Patching for Amblyopia Treatment

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Plain language summary

Why the project was necessary

Reduced vision in one eye as a result of an obstacle to normal visual development occurring in the first 7 years of life is known as amblyopia. Common obstacles to visual development are a squint (misalignment) occurring in one eye or a difference in the focus between the two eyes. Treatment is full-time wear of spectacles for at least 3 months followed by patching of the good eye. Although both treatments are effective, best visual acuity following treatment is subnormal. Treatment regimens range from 30 minutes to all waking hours and the amount prescribed is more dependent on the clinicians beliefs rather than the patients characteristics. These approaches do not accord with a growing realisation in medicine that treatment is best tailored to the individual: the so-called 'personalised dosing strategy' approach (PDS). One problem is that the amount of patching prescribed and that received is often not the same with an average amount received being half of that prescribed.

What we did

Our study comprised two components: laboratory- and clinic-based. The laboratory-based component explored, developed and evaluated a personalised dosing strategy (PDS) approach to amblyopia therapy utilising results from our two previous clinical studies. The clinic-based part sought to use the personalised dosing software created in the lab-based component and evaluate the PDS approach by conducting a trial comparing SDS with PDS in children with amblyopia aged 3 to 8 years.

What we found

We found that personal patient characteristics such as age of the patient at the start of patching, and particularly the level of vision loss in the amblyopic eye had significant impacts on the amount of patching that the child required to get to their best visual acuity. We coined the phrase total effective dose (TED) suggesting that each individual has a personal TED and this can be calculated by taking into consideration the age of the patient, the type of amblyopia and the vision loss at the start of treatment. We found that the PDS was equally effective as the SDS but the time to best vision was shorter by 2 weeks in an average of 9 weeks.

Potential patient benefit

The practical consequences of the PDS approach are that the amount and duration of treatment can be tailored to the individual patient. The TED gives a total number of hours recommended but that can be tailored to the needs of the family, short intensive or long less intensive treatment.

Keywords

Amblyopia, Visual acuity, Occlusion by patching, Personalised dosing strategy, Compliance

Summary of research findings

Background

Amblyopia is a developmental anomaly of human spatial vision in which a deficit of resolution cannot immediately be alleviated by refractive correction in an otherwise healthy eye. Associated risk factors include strabismus (ocular misalignment), anisometropia (a significant difference in refractive power between the two eyes), cataract (lens opacity), and ptosis (eyelid drooping). It is the commonest visual disorder of childhood in the Western world (2-5%) [1] and in the UK accounts for approximately 9 out of every 10 appointments to the NHS Children's Eye Service. [2] Research in the '60s and '70s demonstrated that the developing visual system is highly sensitive to deprivation. [3] This led to the concept of a visual sensitive period, ending at around 6 to 7 years, which if interrupted by any obstacle such as blurred vision and/or strabismus, results in amblyopia. The clinical upshot of this research was the practise that amblyopia should be both identified and treated in early childhood. Consequently, in the UK and the USA national screening for strabismus and amblyopia is recommended between 4 and 5 years [4] and 3 and 4 years [5] respectively. Such a massive investment requires that amblyopia therapy is both effective and efficient.

The predominant treatment method is the degradation of spatial visual input to the dominant eye, either by a patch (occlusion therapy) or pharmacologically (penalization therapy). Its effectiveness was, until very recently, assumed on the basis of clinical experience, until the publication of a systematic review [6] which concluded that "…the evidence [for amblyopia therapy] falls far short of showing that treatment works". This report undoubtedly did much to promote an evidence-based approach to treatment evaluation leading to a series of randomised controlled clinical trials broadly concluding that treatment can improve spatial vision of the affected eye. [7-15]

Aims and objectives

1) To use data from two clinical trials (the monitored occlusion treatment for amblyopia study [MOTAS] and the randomised occlusion treatment for amblyopia study [ROTAS] to generate a model for a dosing strategy — 'the personalised dosing strategy' (PDS) — for occlusion therapy for the treatment of childhood amblyopia. The model will be incarnated as dosing regimens incorporating key patient characteristics of individual patients and be implemented as computer software.

2) To conduct a randomised controlled trial to compare two dosing strategies 'the PDS approach' and the 'standardised treatment strategy (SDS).'

Research question

Does a personalised dosing strategy of occlusion treatment improve treatment outcome for childhood amblyopia. Specifically, does it improve visual outcome, reduce treatment time or overall cumulative dose received compared to the current clinical approach (standardised dosing strategy).

Methods

The investigation comprised two principal phases: laboratory-based and clinic-based. In the laboratory-based phase the investigator undertook a detailed analysis and appraisal of the results of the MOTAS and ROTAS studies, developing mathematical models and generating patient simulations. This attempted to answer the question, “given a patient of known characteristics (e.g. initial amblyopic deficit, current amblyopic deficit, known concordance with treatment) what are the predicted outcomes for such a patient (e.g. best acuity, time to best acuity) for a given received occlusion dose?” The models and simulations were then formulated into PDS software in which optimum occlusion for a given patient was prescribed (modifiable at defined intervals according to concordance and any change in the amblyopic deficit).

The clinic-based part included a randomised trial of occlusion treatment using PDS and SDS as the two occlusion treatment arms. The clinic-based study comprised three phases: ‘initial assessment’, ‘adaptation’ and ‘occlusion’ depicted in the flow-chart (see Figure 2, Annex 4). This empirical study design has previously been employed and validated by the applicants in a major clinical trial: the Randomised Occlusion Treatment for Amblyopia Study (ROTAS).[16]

Randomised Trial study phases:

1) Initial assessment: This included visual performance testing, orthoptic assessment and cycloplegic retinoscopy. Vision was assessed at least twice in this phase to ensure visual stability (measurements within 0.1 log units) before commencing treatment.

2) Refractive Adaptation phase: This began approximately 14 days after the initial assessment (allowing for delivery of spectacles, where prescribed). Subjects were instructed to wear spectacles (where appropriate) full-time and return to clinic at subsequent 6 weekly intervals until 18 weeks of spectacle adaptation has occurred. However if a significant gain in visual acuity was observed between weeks 12 and 18 in this phase then additional six weekly assessments were made until a plateau of the response occurred.

3) Occlusion phase: Subjects remaining eligible (i.e. meet the study’s operational definition of amblyopia) were randomised (using a random number generator) to receive either a PDS or SDS regimen. If allocated PDS their personal characteristics were input into the personal software and a regimen in the range of 2.5 hours/day to 12/hours/day was prescribed for a 12-week period in the first instance. If they were allocated the SDS then the

amount prescribed depended on visual acuity of the amblyopic eye; 2 hours/day for mild amblyopia; 3 hours/day for moderate amblyopia and 5 hours/day for severe amblyopia.

Key findings

Component 1 Modelling the data

Data from MOTAS and ROTAS were successfully merged. Statistical modelling was undertaken on a combined dataset of the Monitored Occlusion Treatment of Amblyopia

Study (MOTAS) and the Randomized Occlusion Treatment of Amblyopia Study (ROTAS). Occlusion data for 149 study participants with amblyopia; anisometropic in 50, strabismic in 43, and mixed in 56 were analysed. Median time to best observed visual acuity was 63 days (25% and 75% quartiles; 28 and 91 days). Median visual acuity in the amblyopic eye at start of occlusion was 0.40 logMAR (quartiles 0.22 and 0.68 logMAR)and at end of occlusion was 0.12 (quartiles 0.025 and 0.32 logMAR). Median lower and upper estimates of TED were 120 hours (quartiles 34 and 242 hours), and 176 hours (quartiles 84 and 316 hours). The data suggest a piecewise linear relationship between patching dose-rate (hours/day) and TED ($p = 0.008$) with a single breakpoint estimated at 2.16 (standard error 0.51) hours/day suggesting doses below 2.16 hours/day are less effective. We introduce the concept of total effective dose (TED) of occlusion. Predictors for TED are visual acuity deficit, amblyopia type, and age at start of occlusion therapy. Dose-rates prescribed within the model range from 2.5 to 12 hours/day and can be revised dynamically throughout treatment in response to recorded patient compliance: a personalized dosing strategy.

In the trial participants in the personalising dosing strategy (PDS arm) had their total effective dose estimated on an assumed fixed follow-up period of 12 weeks which results in manageable dose-rates.

Component 2: Randomised controlled trial

The randomised occlusion dosing strategy (RODs) study recruited 96 subjects, 57 anisometropia, 10 with strabismus only and 27 with mixed amblyopia. We have 68 completed occlusion phases; 37 in the PDS group and 31 in the SDS group. The PDS group started the occlusion phase with 0.64 ± 0.36 visual acuity improving to 0.36 ± 0.26; SDS group started 0.50 ± 0.26 improving to 0.26 ± 0.17. Mean visual acuity improvement was 0.27 log units in the PDS group, compared to 0.23 in the SDS group which was not significantly different ($p=0.25$) Suggestive that visual acuity at the start of treatment is the most important factor to consider when choosing the occlusion regimen. The mean ± sd time to achieving best visual acuity for the first time was 63 ± 45 days for the PDS compared to 76 ± 65 days for the SDS group. Although this was not significantly different ($p=0.06$) it is showing a trend for shorter treatment periods for the PDS approach. The actual dose worn to achieve best visual acuity was significantly less ($p=0.04$) for the PDS group 189 ± 76 hours compared to 251 ± 141 hours for the SDS group.

Expected impact

We expect that in the future clinicians will be using occlusion dose-monitors and personalised dosing software on a routine basis to better inform the patient and their family

of the expected time-frame and prognosis with the treatment. It is envisaged that this will make the treatment more cost-effective and more enjoyable for the patient with short intensive periods of patching.

[1] Attebo et al. Ophthalmology 1998;105:154-9. [2] Stewart CE et al. Invest Ophthalmol Vis Sci 2004;45:3048-54. [3] Hubel DH, Wiesel TN. J Physiol (London) 1970;206:419-36. [4] Hall DMB. Screening for vision defects. In: Hall DM, Elliman D, eds. Health for all children. 4th ed. Oxford, England: Oxford Medical Publications, 2003:230-44. [5] Hartman EE et al. Ophthalmology 2001; 108:479-486. [6] Snowdon S, Stewart-Brown S. Report No 9. York: NHS Centre for Reviews and Dissemination, University of York. [7] PEDIG. Arch Ophthalmol 2003;121:60 [8] PEDIG. Ophthalmology 2003;110:2075-87. [9] Clarke et al. BMJ 2003;327:1251-6. [10] PEDIG Arch Ophthalmol. 2002;120:268-78. [11] Fielder et al. Lancet 1994;343:547. [12] Fielder et al. Br J Ophthalmol 1995;79:585-9. [13] Stewart et al. Br J Ophthalmol 2002;86:915-9. [14] Stewart et al. Invest Ophthalmol Vis Sci 2007 48, 2589-94. [15] Stewart CE et al.Invest Ophthalmol Vis Sci 2005;46:3152-60. [16] Stewart et al. BMJ 2007;335:707-711.

Patient and public involvement

We frequently asked the study patients for their opinion on the study design and design of the occlusion dose monitors. Responses have been input into future designs of the occlusion dose monitor. For instance a patient aged 7 said 'what will the occlusion dose monitor do when I have done the 2 hours patching that you have asked me to do'. The response to that question was 'Currently the occlusion dose monitor does not have any instant feedback to but the next step in development of the occlusion dose monitor is to incorporate a watch type system that reports when milestones in patching have been made. Feedback from the parents have been positive and they have favoured frequent visits with the same professional each time. We will feed this back into mainstream to clinic to keep patients on the same clinic day with the same professional ware possible especially when in the treatment phase as it aids encouragement of continuing when children are becoming despondent with the treatment.

Data sharing statement

See link [https://www.nihr.ac.uk/documents/nihr-position-on-the-sharing-of-research-data/12253] for the NIHR position on the sharing of research data. The NIHR strongly supports the sharing of data in the most appropriate way, to help deliver research that maximises benefits to patients and the wider public, the health and care system and which contributes to economic growth in the UK. All requests for data should be directed to the award holder and managed by the award holder.

Disclaimer

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