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Designing clinical trials for amblyopia

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ABSTRACT

Randomized clinical trial (RCT) study design leads to one of the highest levels of evidence, and is a preferred study design over cohort studies, because randomization reduces bias and maximizes the chance that even unknown confounding factors will be balanced between treatment groups. Recent randomized clinical trials and observational studies in amblyopia can be taken together to formulate an evidence-based approach to amblyopia treatment, which is presented in this review. When designing future clinical studies of amblyopia treatment, issues such as regression to the mean, sample size and trial duration must be considered, since each may impact study results and conclusions.

1. The need for randomized clinical trials

Randomized clinical trials (RCTs) are considered one of the highest levels of evidence, above cohort studies, case series, and case reports, primarily because the process of randomization minimizes bias, increasing the probability that potentially confounding factors would be equally distributed between treatment groups. These potentially confounding factors include age, gender, race, and severity of disease, and in studies of amblyopia, specifically include baseline refractive error, amblyopia subtype (e.g., anisometropic, strabismic, and combined), and previous treatment.

One illustration of the importance of randomization is to consider the hypothetical situation where one is the treating eye care provider participating in a non-randomized study comparing treatment versus control. It is hard to remain truly dispassionate about the decision to assign each patient to either treatment or control. If the patient's condition is on the severe end of the spectrum, the temptation may be to offer the active treatment rather than the control, whereas if the condition is mild, the temptation may be to offer the control rather than the active treatment. Randomization eliminates this potential bias, maximizing the chance that even unknown confounding factors will also be balanced between treatment groups.

Nevertheless, randomization alone is not sufficient to eliminate all forms of bias. Allocation concealment is important, preventing the investigator from knowing to which group the next patient will be assigned, otherwise the investigator might not offer participation to the next patient for the same reasons that the investigator might assign treatment to one group or the other. Masking of outcome assessment is also preferable, preventing the examiner from knowing the treatment group, so that the examiner does not consciously or subconsciously influence the result of testing. In addition, appropriate sample size is important to reduce the chance of concluding there is no effect (based on study results) when in fact there is an effect (a type II error).

Despite the preference for randomized clinical trials, there is a clear role for non-randomized studies. Preliminary data are needed to obtain an estimate of effect in both the proposed treatment group and the control group. In addition, for some treatments, randomization may not be acceptable to investigators, to patients, or to parents. When conducting a non-randomized cohort study, it is important to have clearly defined inclusion and exclusion criteria, a clear protocol with a defined follow-up schedule, a pre-established primary outcome measure, and standardization of outcome assessment. A control group should also be considered in a non-randomized study design, either concurrently or historically, recognizing that the same objections may exist for a concurrent control group in cohort studies as for RCTs, specifically investigator, patient and/or parent unwillingness to be assigned to "control."

2. Recent evidence from amblyopia treatment studies

The above principles of study design have been applied to clinical amblyopia studies conducted by the Pediatric Eye Disease Investigator Group (PEDIG), a multicenter network of over 200 pediatric ophthalmologists and pediatric optometrists across North America, from private practices and academic institutions (Beck, 1998). The network is funded by the National Institutes of Health to conduct large simple RCTs and observational studies.

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Typically 50–80 investigators participate in each study and all studies are approved by the relevant Institutional Review Boards, obtaining appropriate informed consent from participants and parents.

Regarding amblyopia treatment studies, all PEDIG amblyopia studies thus far pertain to anisometropic, strabismic, or combined amblyopia, not deprivation amblyopia. One hallmark of PEDIG amblyopia studies is the standardization of visual acuity outcome assessment, presenting single surrounded optotypes at logMAR intervals, by using the Amblyopia Treatment Study (ATS) HOTV visual acuity protocol (for 3 to <7 year olds) (Holmes, Beck, Repka, et al., 2001), or by using the eETDRS protocol (for 7 year-olds and older) (Beck, Moke, Turpin, et al., 2003), both presented on the Electronic Visual Acuity tester (Moke, Turpin, Beck, et al., 2001). Importantly, the ATS HOTV visual acuity protocol can be performed as a matching task, which increases testability among younger children, and, typically, visual acuity assessment is performed by masked examiners who do not know the subject's treatment assignment. The way in which PEDIG amblyopia studies have profoundly changed the treatment of amblyopia is described in the following sections.

3. Observational studies of refractive correction alone

In a non-randomized prospective observational study, 84 children 3 to <7 years old with previously untreated anisometropic amblyopia were studied (visual acuity between 20/40 and 20/250) (Pediatric Eye Disease Investigator Group, 2006a). Optimal refractive correction was provided and visual acuity was measured with the new spectacle correction at baseline, confirming the presence of amblyopia and then measured at 5-week intervals until visual acuity stabilized or amblyopia resolved.

Amblyopia improved with optical correction by 2 or more lines in 77% of the subjects and resolved in 27% (Pediatric Eye Disease Investigator Group, 2006a). Improvement took up to 30 weeks before stabilization. Mean improvement was 2.9 lines. Even after apparent stabilization, additional improvement occurred with spectacles alone in 21 (62%) of 34 subjects (Pediatric Eye Disease Investigator Group, 2006a) followed as a control group in a subsequent randomized trial (Pediatric Eye Disease Investigator Group, 2006b), and amblyopia resolved in 6 of those subjects (Pediatric Eye Disease Investigator Group, 2006a, 2006b).

In a subsequent prospective observational study (Pediatric Eye Disease Investigator Group, 2012) of 146 children 3 to <7 years old with previously untreated strabismic amblyopia ($n = 52$) or combined amblyopia ($n = 94$), optical treatment alone was provided as spectacles based on a cycloplegic refraction (allowing plus sphere to be cut by up to +0.50 D). At 18 weeks, amblyopic eye visual acuity improved a mean of 2.6 lines, with 75% of children improving $\geqslant$2 lines. Resolution of amblyopia occurred in 32% of the children and visual acuity improved regardless of whether eye alignment improved (Pediatric Eye Disease Investigator Group, 2012).

Independent of PEDIG, Moseley, Neufeld, McCarry, et al. (2002), Stewart, Moseley, Fielder, and Stephens (2004a), Stewart, Moseley, Stephens, and Fielder (2004b) and Clarke et al. (2003) have also provided evidence that marked improvement in amblyopic eye visual acuity can be obtained with spectacles alone, in both strabismic amblyopia and anisometropic amblyopia. In many cases, treatment with spectacles alone eliminated the need for patching or atropine. Taken together, the practical implication of these studies is that it is very reasonable to start with spectacles first in the management of anisometropic, strabismic, and combined amblyopia. If spectacles alone are insufficient treatment, then there are three primary subsequent options; patching, atropine, and Bangerter filters, discussed in the next sections.

4. Studies of patching dose

If patching is chosen as the next step, then the eye care provider must decide what dose of patching to prescribe. In a patching dose study, prescribed full-time patching (all or all but 1 waking hour a day) was compared with prescribed 6 h of daily patching in 175 children, 3 to <7 years old, with severe amblyopia (best-corrected visual acuity 20/100–20/400) (Pediatric Eye Disease Investigator Group, 2003a). Both groups were also prescribed at least 1 h of near visual activities during patching. Visual acuity in the amblyopic eye improved by a similar amount in both groups at the 17-week primary outcome exam, averaging 4.8 lines in the 6-h group and 4.7 lines in the full-time group ($P = 0.45$).

In a parallel patching dose study in moderate amblyopia (best-corrected visual acuity 20/40–20/80), 189 children were randomized to either prescribed 6 h of daily patching or prescribed 2 h of daily patching (Pediatric Eye Disease Investigator Group, 2003b). Both groups were also instructed to perform at least 1 h of near visual activities during patching. Visual acuity improvement of the amblyopic eye was similar in each group at the 17-week outcome visit, averaging 2.4 lines (Pediatric Eye Disease Investigator Group, 2003b).

These patching dose studies concluded that, in children 3 to <7 years of age, 6 h of prescribed daily patching produces an improvement in visual acuity that is of similar magnitude to prescribed full-time patching in severe amblyopia, and 2 h of prescribed daily patching produced improvement in visual acuity of similar magnitude to prescribed 6 h of daily patching in moderate amblyopia. It was also noteworthy that there was no difference in the rate of improvement between different doses of patching (Pediatric Eye Disease Investigator Group, 2003a, 2003b).

Independent of PEDIG, Stewart, Stephens, Fielder, and Moseley (2007) also conducted an RCT comparing 12 h per day with 6 h per day of patching and used an occlusion dose monitor to measure the actual wearing time. They found that actual patching time was similar between groups (4.2 h versus 6.2 h, $P = 0.06$), suggesting that one reason for the lack of superiority of more intense regimens might be reduced compliance with intense patching, and the fact that children and families find it very difficult to wear a patch for many hours a day. Nevertheless, the study of Stewart et al. (2007) confirmed that many children who actually wore the patch for only 2 h per day do in fact respond. What remains unexplained is why a few children who actually wore the patch for 12 h a day showed very little response, and further work is needed to identify such children earlier in their treatment course and to develop new treatments that might address this type of resistant amblyopia.

In a subsequent PEDIG RCT of prescribed 2 h a day of patching with near activities versus 2 h a day with distance activities (Pediatric Eye Disease Investigator Group, 2008a), no difference was found in treatment effect between types of activities performed when patched. Nevertheless, some children with severe amblyopia (20/100–20/400) responded to 2 h a day of prescribed patching, and so even in severe amblyopia a dose of 2 h a day is a reasonable option. Based on these RCTs of patching dose, if visual acuity fails to improve completely with spectacles alone, it is reasonable to initiate prescription of 2 h of daily patching for all children with anisometropic, strabismic, or combined amblyopia, regardless of severity of amblyopia.

5. Atropine versus Patching

In the first RCT conducted by PEDIG (Pediatric Eye Disease Investigator Group, 2002; Pediatric Eye Disease Investigator Group, 2005a), atropine 1% (one drop each morning to the fellow eye) was compared with patching of the fellow eye (prescribed