Modeling Dose-Response in Amblyopia: Toward a Child-Specific Treatment Plan

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PURPOSE. This article describes an empirically derived mathematical model of the treatment dose-response of occlusion therapy for amblyopia based on outcome data obtained from the Monitored Occlusion Treatment for Amblyopia Study (MOTAS).

METHODS. The MOTAS protocol comprised three discrete phases: baseline, refractive adaptation, and occlusion. Only data from the occlusion phase were used in this dose-response model. Seventy-two participants, 3 to 8 years of age, mean ± SD age 5.2 ± 1.4 years (anisometropia [n = 18]; strabismus [n = 22]); both anisometropia and strabismus [n = 32]) completed the occlusion phase. All participants were prescribed 6-h/d patching, which was objectively monitored by an occlusion dose monitor (ODM).

RESULTS. Simple normal linear regression modeling of the data on an interval-by-interval basis (interval between clinic visits) indicates that increasing cumulative dose within interval (hours) yields an increase in visual acuity (R² = 0.918; 684 data points). Most of the children achieved their best visual acuity with 150 to 250 hours' cumulative dose. Specific patient characteristics (especially age) modify the steepness of this function. For example, a 0.20-logMAR (2-line logarithm of the minimum angle of resolution) gain in visual acuity requires a cumulative dose of 170 hours for children at age 48 months and 236 hours at age 72 months.

CONCLUSIONS. Mathematical modeling of amblyopia therapy is a novel approach that elucidates the kinetics of the therapeutic response in humans. This response is age-influenced so that older children require a greater dose to achieve the same outcome—evidence of altered plasticity of the visual system. Fine-tuning the dose-response in amblyopia therapy will facilitate the development of child-specific, evidence-based treatment plans. (Invest Ophthalmol Vis Sci. 2007;48:2589–2594) DOI:10.1167/iovs.05-1243

Understanding that the developing visual system is highly plastic in infancy and early childhood has led to the concept of a sensitive period during which any obstacle to clear vision (refractive error, monocular deprivation, and/or strabismus) results in amblyopia. This concept has generated the firmly held clinical tenet that to achieve optimum outcome, children with amblyopia should be identified and treated as soon as possible within this sensitive period. Thus, screening for amblyopia of all children is recommended at between 4 and 5 years of age in the United Kingdom and at between 3 and 4 years of age in the United States. Even though teenagers and adults have been reported to respond to treatment in some cases, there is no justification for delaying treatment, because improvement later on is less assured.

The mainstay of amblyopia treatment is occlusion by patching. However, most children who undergo patching also require refractive correction; both interventions individually generate a visual improvement. In addition, although pragmatic clinical trials have established that occlusion therapy has a positive effect, the nature of the dose-response remains poorly defined, because in almost all trials, the amount of occlusion has not been monitored. The two studies in which objective occlusion monitoring was used have shown that compliance with prescribed treatment is rarely total and is also variable across the treatment course, emphasizing the importance of differentiating between treatment clinically prescribed and treatment actually received by the child. Thus, current practice does not permit evidence-based prescribing to meet the specific requirements of the individual child.

Understanding the dose-response relationship in amblyopia therapy necessitates identifying several potentially confounding factors that contribute to treatment outcome. In this article, we explore the use of an empirically derived mathematical model of the treatment dose-response, based on data from the Monitored Occlusion Treatment for Amblyopia Study (MOTAS) in which the variables contributing to outcome have been fully differentiated.

METHODS

MOTAS comprised three discrete phases—baseline, refractive adaptation, and occlusion—and is described in detail elsewhere. The flow of participants through the study is depicted in Figure 1. Before study entry, all children had a full ophthalmic assessment including funduscopy and cycloplegic retinoscopy. The baseline phase comprised a minimum of two consecutive assessments to be certain that the first measure of function was robust. Children who required spectacle correction entered the refractive adaptation phase. Those individuals not requiring spectacle correction entered the occlusion phase. Children were instructed to wear spectacles (where prescribed) full time and were scheduled to return for vision assessment at 6-week intervals from week 0 (onset of spectacle wear) until 18 weeks of refractive adaptation was completed—a period that our previous research indicated would allow for all significant improvement attributable to spectacle wear to have occurred. Refractive adaptation required four visits. Children who were already wearing spectacles before study enrollment and had done so for >18 weeks did not require further
refractive adaptation and, provided visual acuity measurements were stable on two consecutive visits, entered the study directly in the occlusion phase. Children who had worn spectacles for <18 weeks, entered the refractive adaptation phase and continued for at least two consecutive visits until a minimum of 18 weeks of total spectacle wear was reached. Children remaining eligible for occlusion (inclusion criteria described in the next paragraph), entered the occlusion phase and were prescribed 6 hours of occlusion per day. Occlusion episodes received were recorded to the nearest minute by an occlusion dose monitor (ODM). The ODM, a device developed and extensively piloted by ourselves, consists of an eye patch with two small electrodes attached to its undersurface connected to a battery-powered data logger by a plastic encapsulated wire lead. Both visual function and the monitored occlusion dose received were recorded at 2-week intervals, until visual acuity ceased to improve (two inflections on a visual acuity versus time plot or measurements not exceeding \( \pm 0.02 \) log units difference on three consecutive visits). On completion of the occlusion phase, participants left the study and were returned to standard clinical care. Only data from the occlusion phase was used in the dose-response model reported here. No patient had any other ophthalmic intervention, such as surgery, during the study period.

Inclusion eligibility criteria were: 3 to 8 years of age; anisometropia and/or strabismus; an interocular acuity difference of at least 0.1 logMAR, written parental consent, no previous occlusion, and the absence of either ocular disease or learning difficulties. Seventy-two participants at a mean age of 5.2 ± 1.4 years at first visit (anisometropia \( n = 18 \)); strabismus \( n = 22 \); both anisometropia and strabismus \( n = 32 \) ) completed the occlusion phase. The study was administered according to the Helsinki Declaration II and was approved by Hillingdon and St. Mary’s Hospital National Health Service (NHS) Trusts’ Local Research Ethics Committees. The primary visual outcome measure was logMAR visual acuity employing three charts: Early Treatment Diabetic Retinopathy Study (ETDRS; Precision Vision, Bloomington, IL), crowded (Keeler Ltd., Barnsley, UK), and uncrowded (Keeler Ltd.) charts. Standard protocols for visual acuity testing were used including scoring by letter. The chart used depended on the reading ability of the child and was generally age dependent. The visual acuity test used at the first study visit for each individual was used throughout the study period; however, when children were capable of undertaking a more difficult test this was added to their test battery. Only data obtained from the primary visual acuity test were used in the analysis reported herein.
Statistical Analysis and Model Identification

For a detailed explanation of the statistical methods, see the Appendix (http://www.iovs.org/cgi/content/full/48/6/2589/DC1) or the Moodie et al.19 technical report.

In our analysis, the ODM data were available on a dose-by-dose basis—that is, the total dose received in each separate treatment period, was recorded, but we restrict attention to simple functions of the cumulative dose ($D_c$; total hours of occlusion received up to the current clinic visit). Specifically, the cumulative change in visual acuity from inclusion in the study was modeled as a function of cumulative dose.

In the analysis, covariates (e.g., age, initial visual acuity, time on study, as outlined later) were considered as potential influential factors, in a multiple linear regression model. We considered both the repeated-measures nature of the data (longitudinal), and the multivariate models that allowed for different correlation structures between the residual errors. The selection of influential covariates was achieved by using a standard model selection mechanism, the Bayesian Information Criterion (BIC); this approach also allowed comparison of the various correlated error models fitted (see the Appendix online for full details). In the second phase of the analysis, the linear regression model was extended to a general linear additive model by using semiparametric components to model the influence of covariates. For example, flexible functional forms replaced linear terms involving dose. The flexible regression models were implemented using spline models and a linear mixed-effect model approach, as outlined in Ruppert et al.20 Finally, mixed-effects models were also used in the analysis of the visual acuity data themselves. All the aspects of the analysis (fitting, testing, and model selection) were implemented by using standard libraries in the statistical package R. For a complete survey of (fitting, testing, and model selection) were implemented by using the Appendix online.

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An alternative and equally plausible analysis could be based on the interval-by-interval change in visual acuity, modeled as a function of the occlusion dose received within the between-clinic-visit interval. Such an analysis has been performed and reveals similar results comparing the effect of occlusion to those presented in this article. This analysis is omitted here for brevity, but is included in the Appendix online.

Many factors may influence treatment dose-response, and these covariates are incorporated into the model. We classified these as condition and treatment factors. Condition factors were type of amblyopia ($T$), age at treatment ($A$), and severity of amblyopia ($S$). Treatment factors were occlusion required ($O$), time in occlusion ($t_o$), and cumulative dose ($D_c$). The interaction between these factors was considered. Type of amblyopia had three categories; anisometric, strabismic, and mixed. All other factors had continuous scales and were not grouped.

Terminology

Refractive adaptation phase: a period during which an improvement in vision of the amblyopic eye may occur in response to optical correction alone. Sometimes referred to as ‘spectacle adaptation.’

Occlusion phase: the period in which patching of the fellow eye for 6 h/d in this study was prescribed.

Interval-by-interval analysis: interval refers to the time between consecutive clinic visits. The analysis was based on 684 data points obtained from 72 participants (mean number of visits, 9.5).

Type of amblyopia ($T$): associated risk factors for amblyopia, strabismic, anisometric, mixed.

Age at treatment ($A$): age in months at each clinic visit.

Severity of amblyopia ($S$): logMAR visual acuity of the amblyopic eye recorded at each clinic visit.

Occlusion required ($O$): participant eligible for occlusion after the refractive adaptation phase is completed.

Time in occlusion ($t_o$): the number of days spent in the occlusion phase.

Cumulative dose ($D_c$): total amount of occlusion worn (hours) in the occlusion phase.

Optimum dose: the minimum dose a child needs to achieve the best VA.

RESULTS

Profile plots for each participant of visual acuity as a function of time (grouped by age) are provided in Figure 2, downward-sloping trajectories predominated indicating a general beneficial effect of occlusion therapy. In the children under 4 years there was an initial steep increase in vision followed by a plateau. With increasing age, this initial steep trajectory lessened so that the overall response became flatter. Note that the amount of dose worn during the period is not depicted, and therefore this is an indication of response and not dose-response.

The mean ± SD improvement in visual acuity (log units) was significantly less ($P = 0.0014$) in those older than 6 years compared with those younger than 4 years: <4 years ($n = 17$), 0.43 (0.25); 4 to 6 years ($n = 31$), 0.29 (0.19); >6 years ($n = 24$), 0.19 (0.12). It is important to note, however, as Figure 2 shows, that the degree of improvement possible for those over 6 years was less, because they had a milder degree of amblyopia at the start of the occlusion phase.

Combining across age, within the occlusion phase, mean (SD; range) visual acuity in the amblyopic eye improved from 0.50 (0.36; 1.6–0.0) to 0.15 (0.25; 1.02 to −0.15) logMAR, a change of 0.35 (0.19; 0.0–1.2). The mean (SD; range) visual acuity in the nonamblyopic eye improved from 0.09 (0.08; 0.28 to −0.1) to 0.06 (0.07; 0.23 to −0.2) logMAR, a change of 0.03 (0.04; 0.0–0.1) demonstrating that a simple practice effect does not account for the improvement in vision observed in the occlusion phase. The median cumulative dose ($D_c$) of occlusion was 205.2 hours (7.1–1037.0).

Linear Regression Modeling

The 72 participants attended, in total, 684 visits, a fairly large data sample (~10 data points for each participant). To understand the influence of covariates on visual acuity, we analyzed changes in visual acuity by using a univariate normal linear regression model (with independent errors). Inspection of variables related to dose in the fitted model revealed that cumulative dose received ($D_c$), interactions between cumulative dose and age ($D_c.A$) and cumulative dose and time in occlusion ($D_c.T_o$), all significantly modified the improvements in visual acuity ($P_d$: $D_c < 0.0001$, $D_c.A < 0.0001$, $D_c.T_o < 0.0001$; Table 1). Thus, it appears that visual acuity improved with increasing cumulative dose, but was moderated by the age of the child and the duration of occlusion. Children who were younger at the start of occlusion, and at the start of each occlusion interval, all improved further with the same occlusion dose ($D_c$) compared with older children. The simple linear regression model fits the data well ($R^2 = 0.918$), and the sample size is quite large; thus, the inferences appear to be reliable.

We used the linear model to examine the effect of age on the occlusion dose requirements for children with amblyopia of 1.0-logMAR severity. The effect of age was striking—for example, simulation (Monte Carlo) indicates that a 0.20-log-
MAR (2-line) gain in visual acuity required 170 hours and 236 hours of cumulative occlusion dose in children aged 48 and 72 months, respectively.

**Modeling Extensions: Multivariate and Semiparametric Analysis**

The linear model analysis is readily comprehensible, but is deficient, as it does not reflect the repeated-measures nature of the data. Strictly therefore, a model that allows for the possibility of correlated residual errors should be used. For these data, we have also fitted a multivariate linear model with a variety of correlation structures; this model did fit better overall, but the estimates of regression coefficients did not change significantly, and so we have omitted that analysis.

A further, more sophisticated approach utilizes semiparametric modeling, in which the dependence of the response on the covariates is modeled with a flexible function. These models are becoming standard in statistical analysis (see Ref. 20 for example), and can be readily implemented in the statistical package R (http://www.r-project.org). As an illustration of this powerful approach, the dependence on cumulative dose $D^c$ fitted in a semiparametric fashion (using regression splines) is depicted in Figure 3. This shows an approximately linear function between cumulative dose ($D^c$) and improvement in visual acuity up to 400 hours of occlusion. Age at treatment (A), severity of amblyopia (S), required occlusion (Occ), and time in occlusion ($t_O$) were accounted for in this model.

We consider that the optimum outcome of amblyopia therapy for unilateral amblyopia is the achievement of equal visual acuity in both eyes, on the basis that binocular vision is best promoted by equal visual input from each eye. However, the average child starts the occlusion phase with 0.5 logMAR visual acuity in the amblyopic eye and achieves an outcome of 0.15

**FIGURE 2.** Longitudinal changes in visual acuity for each patient in the occlusion phase of the MOTAS study for those aged under 4 years, 4 to 6 years, and 6 years or more. The number of days refers to days since the study began.

**TABLE 1.** Summary of the Influence of Patient and Treatment Characteristics on the Dose-Response Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>$t$-Statistic</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occlusion (Occ)</td>
<td>−0.22</td>
<td>0.06</td>
<td>−3.89</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time in occlusion ($t_O$)</td>
<td>0.00015</td>
<td>0.00023</td>
<td>0.64</td>
<td>0.52</td>
</tr>
<tr>
<td>Severity of amblyopia (S)</td>
<td>−0.12</td>
<td>0.039</td>
<td>−3.04</td>
<td>0.002</td>
</tr>
<tr>
<td>Age (A)</td>
<td>0.0027</td>
<td>0.00069</td>
<td>−3.92</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cumulative dose ($D^c$)</td>
<td>−0.0010</td>
<td>0.00017</td>
<td>−5.68</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cumulative dose and age ($D^c.A$)</td>
<td>$1.1 \times 10^{-5}$</td>
<td>$2.6 \times 10^{-6}$</td>
<td>4.24</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cumulative dose and time in occlusion ($D^c.t_O$)</td>
<td>$1.5 \times 10^{-6}$</td>
<td>$3.3 \times 10^{-7}$</td>
<td>4.53</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time in occlusion and severity of amblyopia ($t_O.S$)</td>
<td>−0.0018</td>
<td>$2.6 \times 10^{-4}$</td>
<td>−6.86</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
logMAR, a change of 0.35 log units. Reading directly from the model shown in Figure 3, it is obvious that a change in visual acuity of 0.35 log units is to be expected from a cumulative dose (D^c) in the region of 150 to 250 hours.

**Discussion**

Fully differentiating the factors that contribute to outcome permits the modeling of the dose–response function of occlusion therapy. This reveals a positive and predominantly linear relationship between cumulative dose and response over at least the first 400 hours, after which the curve appears to flatten. However, as so few children required doses beyond this time, there are insufficient data (n = 9) to apply the model beyond 400 hours. As an approximate guide, we suggest that most children, irrespective of the type of amblyopia, must accumulate 150 to 250 hours of occlusion. Parents should be advised of this and encouraged to monitor doses worn. Specific patient characteristics (especially age) modify the steepness of this function. Thus, for older children, a greater occlusion dose is required per increment visual acuity gain compared with their younger counterparts. For example, a 0.20 logMAR (2-line) gain in visual acuity requires 170 hours and 236 hours of occlusion at 4 and 6 years, respectively. (These data were computed by using Monte Carlo simulation from the estimated model. We took the parameter estimates and standard errors from the model and simulated forward hypothetical patient patterns of improvement for fixed occlusion dose regimens, and then recorded the sample averages of the simulations.) These data provide evidence of reduced visual plasticity toward the end of the sensitive period for recovery.

It is a long-held clinical tenet that amblyopia therapy is more successful in the earlier stages of visual development.22 However, rather than the treatment’s being less successful (outcome similar for all age groups) it appears that the deficit becomes more resistant to treatment thus requiring a greater dose to achieve a favorable outcome toward the end of the period for visual development. A study by the PEDIG (Pediatric Eye Disease Investigator Group)9 did not reveal any differences between 2- or 6-h/d occlusion for the whole group or as a function of age. However, the PEDIG trial did not monitor occlusion dose and this is a possible reason for the discrepancy. The different dose requirements of an individual as a function of age could explain the large discrepancies and confusion in the literature23–28 regarding the effective age to treat (previous studies have not measured concordance—that is, the ratio of dose actually worn compared with that prescribed), because the degree of concordance has more impact on the older child.

Mathematical modeling of amblyopia therapy is a novel approach that elucidates the kinetics of the sensitive period in humans. By fine-tuning the model further, it will be possible to develop patient-specific, evidence-based treatment plans and will reduce the burden of amblyopia treatment for the child and family and, ultimately, the health service providers.

**Acknowledgments**

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**References**


