Treatment of Unilateral Amblyopia: Factors Influencing Visual Outcome

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Purpose. To identify factors that influence the outcome of treatment for unilateral amblyopia, as a part of the Monitored Occlusion Treatment of Amblyopia Study (MOTAS).

Methods. This was an intervention study consisting of three nonoverlapping phases: "Baseline", "refractive adaptation" (18 weeks of full-time spectacle wear), and "occlusion" (6 hours of patching per day, objectively monitored). Condition factors: *type of amblyopia*, *age of participant*, *initial severity of amblyopia*, *fixation*, and *binocular vision status*; treatment factors: refractive adaptation and occlusion (*total dose* [hours] and *dose rate* [hours per day]) were assessed for their influence on visual outcome. Visual outcome was expressed in three ways: logMAR (logarithm of the minimum angle of resolution) change, residual amblyopia, and proportion of the deficit corrected.

Results. The study included 85 participants (mean age, 5.1 ± 1.4 years) with amblyopia associated with strabismus ($n = 32$) or anisometropia ($n = 20$) or associated with both anisometropia and strabismus ($n = 33$). Treatment factors: cumulative occlusion dose exceeding 50 hours, and dose rates ≥1 hour per day resulted in ($P \leq 0.01$) lower residual amblyopia and a greater proportion of the deficit corrected. Condition factors associated with poor outcome (high residual amblyopia) were presence of eccentric fixation, severe initial amblyopia, and no binocular vision.

Conclusions. Factors influencing outcome with treatment for amblyopia are occlusion dose (the rate of delivery and cumulative dose worn), the initial severity of the amblyopia, binocular vision status, fixation of the amblyopic eye, and the age of the subject at the start of treatment. (*Invest Ophthalmol Vis Sci.* 2005;46:3152–3160) DOI:10.1167/iovs.05-0357

Amblyopia is the most common (prevalence of 1.6%–3.5% among children)[1] cause of visual morbidity in childhood and is characterized by reduced spatial vision (usually unilateral) in association with one or more sensory obstacles (e.g., ametropia, strabismus, or a form-depriving condition such as cataract) during the visual-sensitive period.[2] It carries an increased lifetime risk (at least three times that of the general population) of serious vision loss in the fellow eye.[3]

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Currently, population screening for strabismus and amblyopia is recommended in the United Kingdom between the ages of 4 and 5 years[4] and in the United States between the ages of 3 and 4 years.[5] Mainstream treatment for unilateral amblyopia has two principal components: refractive correction, usually by spectacles, and occlusion by patching or penalization (atropine cycloplegia) of the fellow eye. Occlusion regimens lack standardization and can range from a few minutes of patching a day to all waking hours, often continuing for many months.[6] Studies that have been conducted to determine the effectiveness of treatment have had a variety of methodological constraints, to which variations in the reported success rates of 19% to 93% can be attributed.[6–14] Recent randomized controlled trials (RCTs) with standardized protocols for visual acuity measurement have reported success rates of ~60% to 70%.[15–17]

Critical to the evaluation of therapeutic effectiveness is a valid definition of treatment outcome. On the basis that binocular vision is best promoted by equal visual input from each eye, the optimum outcome of amblyopia therapy is when the vision of the amblyopic eye equals that of the fellow eye. Calculation of residual amblyopia (interocular difference) and the proportion of the visual deficit corrected, provide measures of treatment outcome accounting for initial severity and response to treatment.[18]

The terminology used in MOTAS is defined as follows:

- Refractive adaptation: period of full-time spectacle wear in which full visual response to spectacle wear is expected.
- Residual amblyopia: the difference between amblyopic and fellow eye visual acuities on completion of treatment.
- Proportion of deficit corrected:

$$\frac{\text{VAas} - \text{VAae}}{\text{VAas} - \text{VAfe}}$$

where VAas is visual acuity of the amblyopic eye at baseline, VAae is visual acuity of the amblyopic eye at the trial's end, and VAfe is the visual acuity of the fellow eye at the end of treatment.

Factors that influence outcome fall broadly into two categories: those that relate to the underlying conditions (condition factors) and those that relate to its treatment (treatment factors). Condition factors often reported to carry an independent risk of poor outcome or unsuccessful treatment are age at or near the end of the visual-sensitive period, presence of both strabismus and anisometropia, and presence of severe amblyopia.[7] However, recent RCTs have suggested that age is a factor that predicts outcome only in severe compared with mild/moderate amblyopia[16,17] and that the type of amblyopia is not a significant factor in determining outcome.[16,17]

A treatment factor most frequently quoted as influencing treatment failure is poor compliance with occlusion therapy,[11,19] but until recently there has been no objective means by which to monitor compliance. However, the development of the occlusion dose monitor (ODM)[20] now permits a quan-

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TABLE 1. Criteria and Tests Used to Categorize Condition Factors Assessed for Influence on Visual Outcome

Factors	Criteria	Tests Used
Type of amblyopia		
Anisometropic	≥1.00 D interocular difference and no manifest squint.	Refractive error: cycloplegic retinoscopy
Strabismic	Manifest squint, near or distance, and/or eccentric fixation and ≤0.75 D interocular difference.	Strabismus: cover/uncover and alternate cover test
Mixed (anisometropic and strabismic)	Manifest squint, near or distance, and/or eccentric fixation and ≥1.00 D interocular difference.	Eccentric fixation: ophthalmoscope (see below)
Initial severity		
Mild	0.1–0.3 logMAR	LogMAR visual acuity: ETDRS, crowded
Moderate	>0.3–0.6 logMAR	LogMAR, uncrowded logMAR.
Severe	>0.6 logMAR	Test used dependent on age and capacity to undertake test.
Fixation		
Central	Steady foveal	Ophthalmoscope with Linksz star[27]
Eccentric	Unsteady or eccentric	
Binocular Functions		
Binocular	Stereopsis and/or motor fusion	Stereopsis: Frisby test
Non-binocular	No motor fusion and no stereopsis	Motor fusion: Prism fusion range test Sensory fusion: Bagolini glasses Simultaneous perception: Bagolini glasses

titative approach, as exemplified by the Monitored Occlusion Treatment of Amblyopia Study (MOTAS) in which average compliance was found to be ~50%[21]—a level in accord with those reported for prescribed medicines.[22] In this article, we considered objectively recorded occlusion in two ways: cumulative total dose (in hours) and dose rate (in hours per day). The purpose of the study was to identify factors that influence visual outcome in the treatment of unilateral amblyopia.

METHODS

Study Design

The design of this prospective study (MOTAS) has been reported in detail elsewhere.[23] The quantitative relations between occlusion and visual acuity (dose–response) have been published.[21]

The MOTAS comprised three phases: "baseline," "refractive adaptation," and "occlusion." Before study entry, all children had a full ophthalmic assessment, including cycloplegic retinoscopy, fundoscopy, fixation behavior, and assessment of binocular function. The baseline phase comprised a minimum of two consecutive visual acuity assessments to establish that the first measure of function was robust. Children who needed spectacle correction entered the refractive adaptation phase. Those who did not need spectacle correction entered the occlusion phase directly. In the refractive adaptation phase, children were instructed to wear spectacles (where prescribed) full time for 18 weeks—a period that our published research indicated would allow for all significant improvement attributable to spectacle wear to occur.[24] Children remaining eligible (i.e., by still meeting the study's operational definition of amblyopia; see the next section), entered the occlusion phase and were prescribed 6 hours of occlusion per day. Occlusion episodes were recorded to the nearest minute by an ODM.[20,25] Both visual function and monitored occlusion dose were recorded at 2-week intervals until acuity ceased to improve (two reversals of visual acuity or identical measurements on three consecutive visits).[23] On completion of the occlusion phase, participants returned to standard clinical care.

Study Participants

Children were recruited from two London hospitals between January 2000 and December 2001. Eligibility criteria were 3 to 8 years of age, anisometropia and/or strabismus, an interocular acuity difference of at least 0.1 logMAR (e.g., 20/20; ≤20/25, logarithm of the minimum angle of resolution), and no history of previous occlusion therapy, ocular disease, or learning difficulties.[23] Written parental consent was a prerequisite for enrollment. The study was administered according to the Helsinki Declaration II and approved by Hillingdon and St. Mary's Hospital NHS Trusts' Local Research Ethics Committees.

Outcome Measures

Assessment of Visual Function. The primary visual outcome was logMAR visual acuity. Three logMAR visual acuity charts were used: ETDRS (Early Treatment Diabetic Retinopathy Study; Precision Vision Ltd., Aurora, CO), crowded (Keeler Ltd., Windsor, UK), and uncrowded (Keeler Ltd.).[26] Standard protocols for visual acuity testing were used and were scored 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 session for each individual was used throughout the study period; however, when children were able to perform a more difficult test, it was added to their test battery.

Factors Influencing Outcome. Factors assessed for their possible influence on visual outcome were classified into condition and treatment factors. Condition factors included: *type of amblyopia*, *age at treatment*, *initial severity of amblyopia*, *fixation*, and *binocular vision status* (Table 1). Treatment factors include the relative contributions of refractive adaptation and occlusion, and occlusion specific factors: *total dose* (in hours) and *dose rate* (in hours per day).

Definition of Optimum Outcomes. Visual outcome was expressed in three ways: the change in visual acuity of the amblyopic eye, residual amblyopia (acuity difference between the amblyopic and fellow eye at outcome), and the proportion of deficit corrected (proportion of the visual deficit corrected). All measurements were in logMAR units.

Statistical Analysis

The Kruskal-Wallis one-way analysis of variance (ANOVA) on ranks was conducted to test for significant differences in final visual outcome for study participants according to their age, type of amblyopia, initial severity, fixation, binocular vision, and occlusion dose. Multiple hypothesis testing demanded a stringent $P < 0.01$ for rejection of the null hypothesis. The statistical power of the analyses ranged from 0.6 to 0.9, to detect a 0.20 difference in logMAR units between groups (for ranges of $n = 17–37$; $\alpha = 0.01$). Data are in mean logMAR units (range), unless stated otherwise.

TABLE 2. Baseline Refractive Error for Each Participant by Type of Amblyopia

	All Groups (n = 85)	Anisometropic (n = 20)	Strabismic (n = 32)	Mixed (n = 33)
AE				
Sphere, mean	+4.24 (3.1)	+4.76 (1.70)	+3.36 (2.20)	+4.75 (3.9)
Sphere, range	+9.00 to −10.25	+7.50 to +1.00	+9.00 to 0	+9.00 to −10.25
Cylinder, mean	−1.15 (0.96)	−1.27 (1.26)	−0.90 (0.76)	−1.29 (0.92)
Cylinder, range	0 to −4.00	0 to −3.75	0 to −3.50	0 to −4.00
FE				
Sphere, mean	+3.00 (2.00)	+2.31 (1.39)	+3.12 (1.91)	+3.29 (2.33)
Sphere, range	+8.50 to −1.75	+4.75 to 0	+8.00 to 0.00	+8.50 to −1.75
Cylinder, mean	−0.85 (0.75)	−0.67 (0.61)	−0.93 (0.72)	−0.86 (0.89)
Cylinder, range	0 to −3.75	0 to −2.25	0 to −3.50	0 to −3.75

Data are expressed as the mean ± SD. AE, amblyopic eye; FE, fellow eye.

RESULTS

Of the 126 eligible participants, 94 (75%) of their parents gave consent. Nine participants withdrew partway through the study. We report on the remaining 85 participants (mean ± SD age, 5.1 ± 1.5 years), who had amblyopia associated with anisometropia (n = 20; 5.6 ± 1.2 years), strabismus (n = 32; 4.7 ± 1.2 years), or both anisometropia and strabismus (mixed; n = 33; 5.3 ± 1.5 years). Classification of refractive error and ocular alignment for the group are shown in Tables 2 and 3. Seventy-eight (91%) had significant refractive errors (≥1.50 Ds bilateral hypermetropia, ≥ 1.50 Ds bilateral myopia, ≥ 0.75 Dc bilateral astigmatism and/or anisometropia ≥ 1.00 Ds)[23] and underwent full refractive adaptation. In the refractive adaptation phase, visual acuity in amblyopic eyes improved from 0.65 ± 0.41 (1.6–0.14) to 0.43 ± 0.37 (1.3 to −0.08)—an improvement of 0.22 ± 0.18 (0.0–0.6). In the refractive adaptation phase, visual acuity in fellow eyes improved from 0.15 ± 0.13 (0.30 to −0.10) to 0.07 ± 0.07 (0.2 to −0.14)—an improvement of 0.08 ± 0.08 (0.0–0.16). After refractive adaptation, 13 study participants no longer had amblyopia, according to the study definition.

Seventy-two participants entered the occlusion phase. 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), a change of 0.35 ± 0.19 (0.0–1.2). Mean compliance with the prescribed occlusion dose rate (6 h/d) was 2.8 h/d (48%).

The overall improvement (including both refractive adaptation and occlusion phases) of visual acuity increased significantly with decreasing age: under 4 years (n = 23), 0.57 ± 0.32 (0.05–1.475); 4 to 6 years (n = 34), 0.44 ± 0.34 (0–1.55); older than 6 years (n = 28), 0.24 ± 0.18 (0–92; $P < 0.0001$). After age had been accounted for (two-way ANOVA to account for interactions), the change in visual acuity (log units) was not significantly different (P = 0.03) for amblyopia associated with anisometropia (n = 21; 0.28 ± 0.20; 0–0.75), strabismus (n = 32; 0.39 ± 0.34; 0.05–1.55), or both (n = 32; 0.46 ± 0.32; 0.08–1.475).

Visual Outcome

Residual amblyopia was nil in 30%, within <0.1 logMAR of the fellow eye in 57%, <0.2 logMAR in 69%, <0.4 logMAR in 83%, and <0.6 logMAR in 90%. The proportion of deficit corrected was full in 30% of participants, 75% to <100% in 24%, 50% to <75% in 23%, and 25% to <50% in 13%; whereas in 10%, <25% of the amblyopic deficit was corrected.

TABLE 3. Baseline Classification of Visual Alignment

	Corrected		Uncorrected	
Classifications	PCT (Near)	PCT (Distance)	PCT (Near)	PCT (Distance)
Fully accommodative esotropia (n = 4)	7 ± 3Δ BO; 4–10Δ BO	5 ± 2Δ BO; 2–6Δ BO	16 ± 3Δ BO; 14–20Δ BO	11 ± 2Δ BO; 10–12Δ BO
Partially accommodative esotropia (n = 19)	21 ± 14Δ BO; 4–50Δ BO	16 ± 12Δ BO; 0–40Δ BO	33 ± 15Δ BO; 18–60Δ BO	25 ± 13Δ BO; 8–50Δ BO
Microtropia with identity (n = 8)	1 ± 3Δ BI; 4Δ BI–6Δ BO	0 ± 3Δ BI; 4Δ BI–6Δ BO	2 ± 5Δ BI; 4Δ BI–12Δ BO	2 ± 4Δ BI; 2Δ BI–10Δ BO
Microtropia without identity (n = 7)	5 ± 5Δ BO; 2Δ BI–12Δ BO	4 ± 2Δ BO; 0–10Δ BO	7 ± 3Δ BO; 4–12Δ BO	5 ± 3Δ BO; 2–10Δ BO
Acquired nonaccommodative esotropia (n = 18)	29 ± 12Δ BO; 14–50Δ BO	24 ± 13Δ BO; 6–45Δ BO	33 ± 12Δ BO; 16–50Δ BO	28 ± 13Δ BO; 8–45Δ BO
Nonspecific exotropia (n = 3)	9 ± 1 BIΔ; 8–10Δ BI	7 ± 4 BIΔ; 4–10Δ BI	19 ± 18 BIΔ; 8–40Δ BI	18 ± 19 BIΔ; 4–40 BI
Distance exotropia (n = 3)	11 ± 4 BIΔ; 6–16 BI	20 ± 8 BIΔ; 10–45Δ BI	11 ± 4 BIΔ; 20–60Δ BI	30 ± 11 BIΔ; 25–50 BI
Latent deviation (n = 11)	2 ± 3Δ BI; 6Δ BI–4Δ BO	1 ± 2Δ BI; 4Δ BI–4Δ BO	1 ± 4Δ BO; 6Δ BI–10Δ BO	0 ± 3Δ BI; 4Δ BI–8Δ BO
Orthophoric (n = 12)	—	—	—	—
Total (n = 85)	10 ± 16Δ BO; 16Δ BI to 50Δ BO	8 ± 14Δ BO; 30Δ BI to 45Δ BO	15 ± 20Δ BO; 40Δ BI to 60Δ BO	11 ± 18Δ BO; 40Δ BI to 50Δ BO

Data are expressed as the mean ± SD; range, of angle of deviation at near and distance fixation, with and without refractive correction. The corrected column represents all children in their emmetropic state.

PCT, prism cover test (using alternate prism cover testing); BO, base out; BI, base in.

TABLE 4. Distribution of Age, Initial Severity, Fixation and Binocular Vision within the Amblyopic Groups

Factors Assessed for Influence on Outcome	Type of Amblyopia			
	Anisometropic *n* = 20	Strabismic *n* = 32	Mixed *n* = 33	Total *n* = 85
Age (y)				
>4	2 (10)	12 (38)	7 (21)	21 (25)
4 to <6	8 (40)	12 (38)	14 (42)	34 (40)
>6	10 (56)	8 (25)	12 (36)	30 (35)
Initial severity (logMAR)				
Mild (0–0.3)	5 (25)	7 (22)	6 (18)	18 (21)
Moderate (>0.3–0.6)	13 (65)	14 (44)	8 (24)	35 (41)
Severe (>0.6)	2 (10)	11 (34)	19 (58)	32 (38)
Fixation				
Central	20 (100)	26 (81)	14 (42)	60 (71)
Eccentric	0 (0)	6 (19)	19 (58)	25 (29)
Binocularity				
Binocular	20 (100)	17 (53)	15 (45)	52 (61)
Nonbinocular	0 (0)	15 (47)	18 (55)	33 (39)

Data are expressed as the number in each category (percentage of the total group).

Visual Outcome: Condition Factors

The distribution of participants by type of amblyopia was categorized according to the condition factors age, initial severity of amblyopia, fixation, and binocular vision status (Table 4). Of the participants with eccentric fixation, 76% had mixed-type amblyopia and 24% had strabismus. A summary of residual amblyopia and proportion of deficit corrected according to condition factors is shown in Table 5.

Type of Amblyopia. Residual amblyopia was not significantly different ($P = 0.10$) for each type of amblyopia: anisometropic ($n = 20$), 0.14 ± 0.13 (0–0.44); mixed ($n = 33$), 0.29 ± 0.30 (0–0.98); and strabismic ($n = 32$), 0.16 ± 0.22 (−0.02–0.7). However, if participants with mixed amblyopia were categorized by eccentric or central fixation, the former ($n = 19$) had significantly ($P = 0.003$) greater residual amblyopia than the latter ($n = 14$) (mixed with eccentric fixation, 0.36 ± 0.29, 0.025–0.98; mixed with central fixation, 0.12 ± 0.19, 0–0.68). The proportion of the deficit corrected was not significantly different ($P = 0.30$) for each type of amblyopia: anisometropic, 0.61 ± 0.33 (0.04–1.16); mixed, 0.60 ± 0.32 (0.0–1.0); and strabismic, 0.73 ± 0.32 (0.04–1.14). Although there was a difference in proportion of deficit corrected for mixed amblyopes with or without eccentric fixation—mixed with eccentric fixation, 0.52 ± 0.33 (0.07–1.0), and mixed with central fixation, 0.73 ± 0.33 (0 to 1.0)—it was not significant ($P = 0.02$) when the stringent criteria of $P < 0.01$ was applied.

TABLE 5. Residual Amblyopia and Proportion of Deficit Corrected by Condition Factors

Factors Assessed for Influence on Outcome	Residual Amblyopia (Log Units)	Proportion of Deficit Corrected
Type of amblyopia		
Anisometropic ($n = 20$)	0.14 ± 0.13	0.61 ± 0.35
Strabismic ($n = 32$)	0.16 ± 0.22	0.73 ± 0.32
Mixed ($n = 33$)	0.29 ± 0.30	0.60 ± 0.32
Age (y)		
>4 ($n = 23$)	0.13 ± 0.16	0.80 ± 0.24
4 to <6 ($n = 34$)	0.21 ± 0.23	0.60 ± 0.34
>6 ($n = 28$)	0.23 ± 0.28	0.61 ± 0.33
Initial severity (logMAR)		
Mild (0–0.3) ($n = 18$)	0.04 ± 0.06	0.78 ± 0.30
Moderate (>0.3–0.6) ($n = 35$)	0.14 ± 0.14	0.66 ± 0.31
Severe (>0.6) ($n = 32$)	0.35 ± 0.30	0.58 ± 0.34
Fixation		
Central ($n = 60$)	0.13 ± 0.18	0.70 ± 0.34
Eccentric ($n = 25$)	0.36 ± 0.29	0.53 ± 0.28
Binocularity		
Binocular ($n = 52$)	0.31 ± 0.30	0.63 ± 0.30
Non-binocular ($n = 33$)	0.13 ± 0.15	0.66 ± 0.33
Total ($n = 85$)	0.20 ± 0.24	0.66 ± 0.33

Data are expressed as the mean ± SD.

Age. Residual amblyopia was not significantly different ($P = 0.30$) as a function of age: <4 years ($n = 23$; 0.13 ± 0.16; 0–0.58), 4 to 6 years ($n = 28$; 0.21 ± 0.23; −0.02–0.8), and >6 years ($n = 23$; 0.23 ± 0.28; 0–0.98). The proportion of the deficit corrected was not significantly different ($P = 0.11$) as a function of age: <4 years (0.80 ± 0.24; 0.04–1.0), 4 to 6 years (0.62 ± 0.33; 0.08–1.14), and >6 years (0.61 ± 0.33; 0.04–1.14). Although when outcome is considered by overall change in visual acuity, age is a factor (described earlier).

Severity of the Amblyopic Deficit. Participants were subcategorized according to the severity of their initial amblyopic deficit (mild, <0.3 logMAR; moderate, 0.3–0.6 logMAR; and severe, >0.6 logMAR). Residual amblyopia differed significantly ($P < 0.001$) between the mild and severe group and the moderate and severe group: mild, 0.04 ± 0.06 (0.0–0.16); moderate, 0.14 ± 0.14 (0–0.58); and severe, 0.35 ± 0.30 (−0.02–0.98). However, the proportion of the deficit corrected was not significantly different ($P = 0.06$) as a function of severity: mild, 0.78 ± 0.30 (0–1.0); moderate, 0.66 ± 0.31 (0.04–1.16); and severe, 0.58 ± 0.34 (0.07–1.14).

Fixation of the Amblyopic Eye. Participants with eccentric fixation had significantly greater residual amblyopia ($P < 0.0001$) than did those with central fixation: residual amblyopia, 0.36 ± 0.29 (0–0.98) versus 0.13 ± 0.18 (−0.02–0.70). However, the proportion of deficit corrected was not significantly different ($P = 0.03$): proportion of deficit corrected 0.53 ± 0.27 (0.07–1) versus 0.69 ± 0.34 (0–1.14).

Binocular Status. Participants were subcategorized according to their binocular function status (binocular, motor fusion and/or stereopsis; and nonbinocular: no stereopsis, no fusion; Table 1). Nonbinocular participants had signifi-

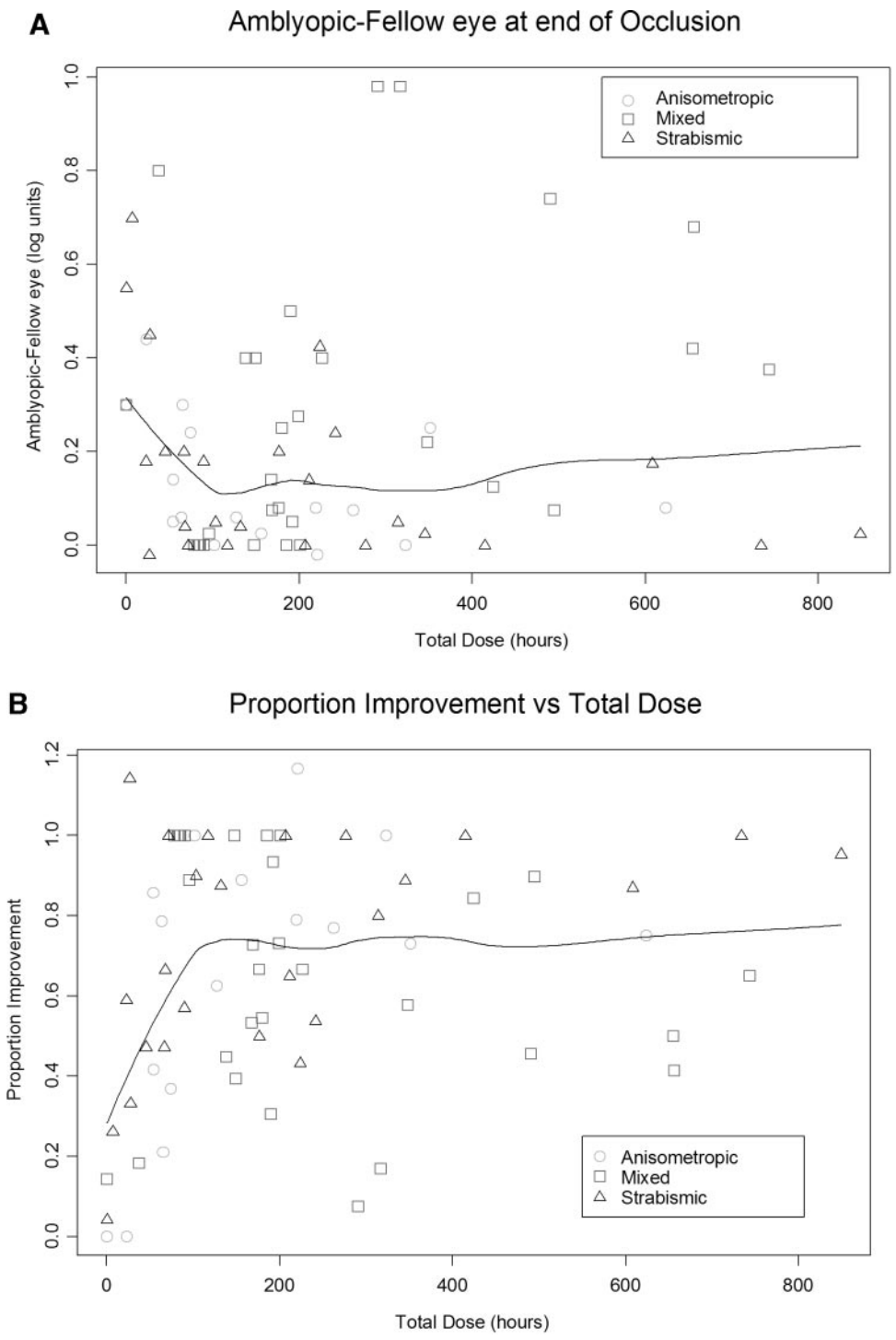

FIGURE 1. Total dose to achieve (**A**) the lowest residual amblyopia and (**B**) the greatest proportion of deficit corrected. Fitted lines are default LOWESS (locally weighted smoothed) line of best fit.

cantly greater residual amblyopia ($P = 0.0001$) than did binocular participants: residual amblyopia, 0.31 ± 0.30 (0.0–0.98) versus 0.13 ± 0.15 (−0.02–0.68). However, the mean proportion of deficit corrected was not significantly different ($P = 0.31$): 0.63 ± 0.33 (0.04–1.0) versus 0.66 ± 0.33 (0–1.16).

Visual Outcome: Treatment Factors

Cumulative Dose. Residual amblyopia was significantly greater ($P = 0.0009$) in those who had less than 50 hours of occlusion: 0–49 hours, 0.42 ± 0.20; and ≥50 hours, 0.23 ± 0.25; Fig. 1A). The proportion of deficit corrected was significantly less ($P = 0.01$) in those who had less than 50 hours of occlusion: 0–49 hours, 0.37 ± 0.35; ≥50 hours, 0.74 ± 0.26; Fig. 1B).

Dose Rate. Residual amblyopia (mean logMAR ± SD) was significantly greater ($P = 0.006$) in those who had less than 0.5 h/d of occlusion: 0.36 ± 0.21; or ≥0.5 h/d: 0.11 ± 0.17 (similar residual amblyopia for all dose rates 0.5–6 h/d; Fig. 2A). The proportion of deficit corrected was significantly less ($P = 0.01$) in study participants wearing occlusion for less than 1 hour per day: <1 hour, 0.52 ± 0.35; ≥1 h/d, 0.74 ± 0.26 (similar proportion of deficit corrected for all dose rates 1 h/d to 6 h/d; Fig. 2B).

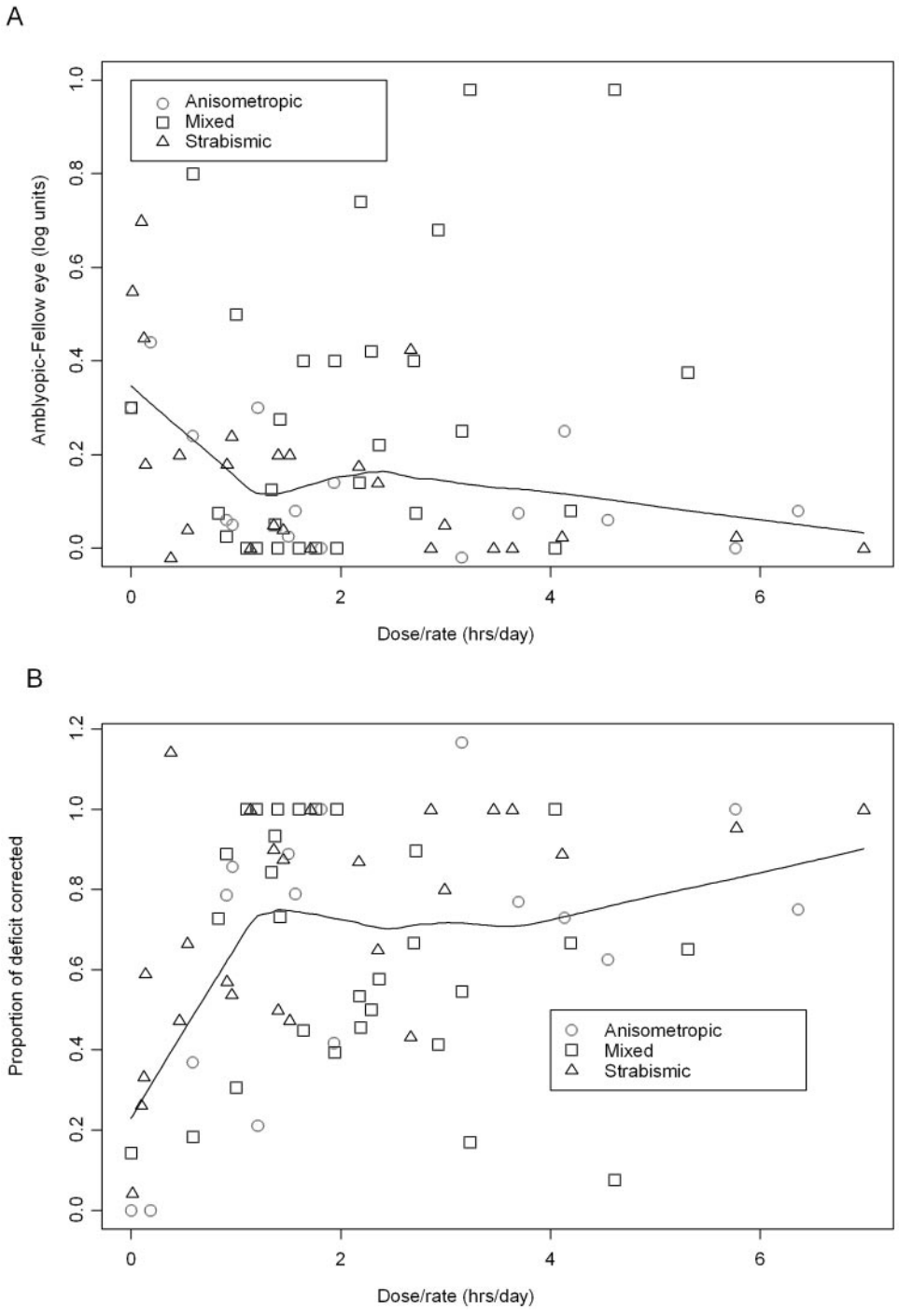

FIGURE 2. Dose rate versus (**A**) residual amblyopia and (**B**) proportion of deficit corrected. Fitted lines are default LOWESS (locally weighted smoothed) line of best fit.

Visual Outcome: Treatment Condition Factor Interactions

To analyze the contribution to the proportion of deficit corrected by intervention (refractive adaptation and occlusion), participants who had undergone some refractive adaptation before entering the study ($n = 12$) and those who did not attend the occlusion phase ($n = 5$) were excluded, leaving 68 participants (anisometropia, $n = 16$; mixed, $n = 27$; and strabismus, $n = 25$). The relative contributions of refractive adaptation and occlusion to correction of the deficit for participants subcategorized according to condition factors (as above) are shown in Figure 3 and Table 6. Factors found to be significant included: initial severity of amblyopia, fixation, and binocularity.

Participants with mild amblyopia had a significantly greater ($P = 0.002$) proportion of their deficit corrected by refractive adaptation than did those with severe amblyopia (0.57 ± 0.38 vs. 0.26 ± 0.27). Participants with central fixation had a significantly greater ($P = 0.0008$) proportion of the deficit corrected by refractive adaptation than did those with eccentric fixation (0.47 ± 0.36 vs. 0.19 ± 0.21). Binocular participants had a significantly greater ($P = 0.005$) proportion of the deficit corrected by refractive adaptation than did the nonbinocular participants (0.48 ± 0.31 vs. 0.24 ± 0.29).

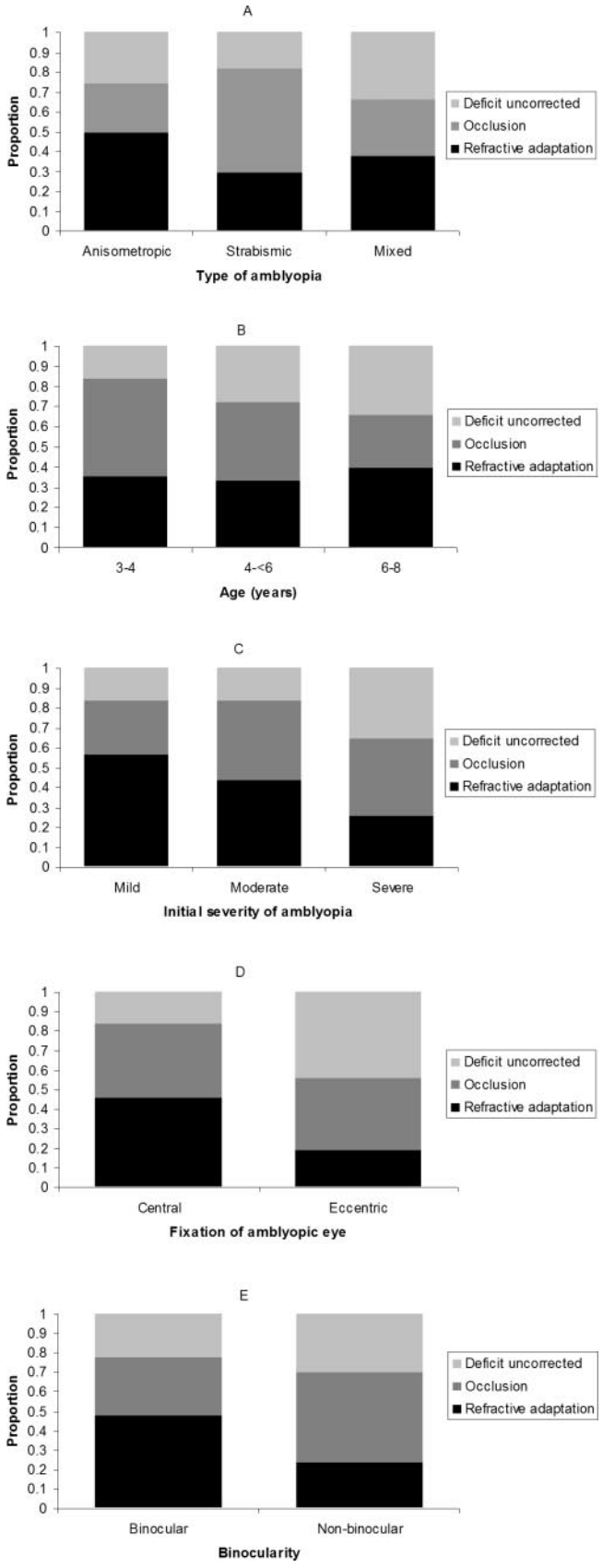

FIGURE 3. Proportion of deficit corrected by improvement during refractive adaptation and occlusion phases as by factors assessed for influence on outcome: (**A**) type of amblyopia, (**B**) age of subject at start of treatment, (**C**) initial severity of amblyopia, (**D**) fixation, and (**E**) binocular vision.

DISCUSSION

In this study, we examined factors that may influence visual outcome after treatment for unilateral amblyopia. Factors found to be significant were age, occlusion dose worn (cumulative and dose rate), the initial severity of amblyopia, fixation of the amblyopic eye, and binocular vision status.

In current practice, dose rates prescribed range from 10 min/d to all waking hours.[8,13,16–18,28] For the first time we have been able to quantify outcome in terms of the actual dose: dose rate and cumulative dose worn to achieve best outcome. Actual dose rates exceeding 1 h/d contribute to successful outcomes. Therefore, low compliance—less than 17% of the prescribed 6-h/d dose is likely to be associated with poor outcome. This suggests that occlusion regimens of ≅1 h/d (actual dose hours) would have similar effects on outcome as moderate amounts—a finding that has also emerged from a recent randomized trial of 2 versus 6 h/d prescribed occlusion for moderate amblyopia.[16] However, care should be exercised when prescribing small doses, as compliance is on average half the dose prescribed.

Dose–response appears to plateau beyond 100 cumulative hours generating on average no further treatment gains. We were able to analyze the occlusion dose (worn) required for optimum outcomes. In a previous study documenting cumulative prescribed hours rather than dose actually worn,[13] investigators concluded that no benefit was observed after 400 hours of occlusion, and inspection of their data reveals little benefit (5%–10% of total improvement) beyond 200 prescribed hours.

Children with eccentric fixation were found to have considerably greater residual amblyopia than those with central fixation, as documented previously.[13,29] However, the proportion of deficit improvements gained are independent of eccentric fixation, suggesting that the amblyopic component of the deficit has responded, and the visual deficit remaining is dependent on the physiological consequence of using an eccentric point of fixation.

TABLE 6. Relative Contribution of Treatment Factors to Proportion of Deficit Corrected for the Groups within Condition Factors Analyzed for Their Effect on Outcome

Factors Assessed for Influence on Outcome	Refractive Adaptation	Occlusion
Type of amblyopia		
Anisometropic (n = 16)	0.51 ± 0.33	0.28 ± 0.30
Strabismic (n = 20)	0.30 ± 0.39	0.52 ± 0.42
Mixed (n = 32)	0.34 ± 0.30	0.36 ± 0.28
Age (y)		
>4 (n = 20)	0.36 ± 0.37	0.49 ± 0.38
4 to <6 (n = 32)	0.34 ± 0.30	0.39 ± 0.37
>6 (n = 17)	0.40 ± 0.38	0.26 ± 0.25
Initial severity (logMAR)		
Mild (0–0.3) (n = 9)	0.57 ± 0.38	0.27 ± 0.45
Moderate (>0.3–0.6) (n = 24)	0.44 ± 0.37	0.41 ± 0.36
Severe (>0.6) (n = 35)	0.26 ± 0.278	0.39 ± 0.31
Fixation		
Central (n = 43)	0.47 ± 0.36	0.39 ± 0.39
Eccentric (n = 21)	0.19 ± 0.21	0.37 ± 0.27
Binocularity		
Binocular (n = 35)	0.47 ± 0.34	0.31 ± 0.34
Nonbinocular (n = 33)	0.24 ± 0.30	0.47 ± 0.33
Total (n = 68)	0.37 ± 0.34	0.38 ± 0.35

N.B. Seventeen of the 85 patients were excluded from this analysis because they either had partial refractive adaptation before study entry or did not have a significant refractive error, leaving 68 participants. Data are expressed as the mean ± SD.

Initial severity of amblyopia is a prognostic factor of outcome.[6] In our study, those with severe amblyopia (defined as >0.6 logMAR) had significantly greater residual amblyopia than did those with lesser degrees of amblyopia. However, there was no difference with respect to the proportion of the deficit corrected in this group (an analysis that was independent of initial severity). Although it is perhaps not surprising that those with severe amblyopia had greater residual amblyopia, since they had farther to improve, it is intriguing that the proportion of the deficit corrected was independent of initial severity, with average values being similar for each group. This may suggest that a proportion of the deficit is correctable. This matter needs further clarification with more detailed psychophysical testing revealing second-order deficits as well as larger numbers of patients, to increase the power and certainty of the results.

Overall, type of amblyopia was not shown to be a significant factor affecting outcome. However, the presence of eccentric fixation that was predominantly present in those with mixed amblyopia (58% of mixed amblyopia, 22% of strabismic amblyopia, and 0% of anisometropic amblyopia) is a significant factor indicative of poor outcome. Assessment of fixation although subjectively determined appears to be informative.

Although it is a long-held clinical belief that amblyopia therapy is more successful during early visual development,[9,30] the evidence is equivocal. Indeed, Hiscox et al.[6] and others[15,16,31–34] reported no significant difference in the effectiveness of occlusion treatment commencing at any time between 3 and 7 years of age. Cobb et al.[34] studied the age range up to 12 years with children with anisometropic amblyopia and found no age effect. However, others[7,17] have demonstrated greater gains in visual acuity in those younger than 5 years. We have provided further evidence that age *is* a factor in the effectiveness of occlusion; however, this is not without caveat, as the effect depends on the manner in which outcome is expressed. Age is a factor when considering simple change in visual acuity; however, if outcome by residual amblyopia and proportion of deficit corrected are considered, the effect of age ceases to be significant. In this analysis, children older than 6 years had significantly milder initial amblyopia than did the other two age groups, therefore limiting the possible change in visual acuity. Defining outcome by residual amblyopia and proportional amblyopia eliminates this bias. Therefore, in the majority of children, age was not a factor in obtaining optimum outcome. Pediatric Eye Disease Investigator Group (PEDIG) studies have reported significant age-dependent outcomes only when the initial amblyopia was severe. This may suggest that the effective timing of treatment could be influenced by the nature of the amblyopic deficit.[35]

The presence of binocular vision appeared to be a prognostic factor for favorable outcome; however, it had no influence on the proportion of the deficit corrected. This finding may reflect the onset and severity of the deficit.

Because of the relatively small number of participants when divided into groups, the analysis of the data was limited to one factor at a time and therefore did not benefit from interaction analysis between factors. However, this is the first study that has been able to interpret the effect of occlusion compliance throughout a whole course of occlusion with respect to outcome.

In summary, factors influencing outcome with treatment for amblyopia are occlusion dose (the rate of delivery and cumulative dose worn), the initial severity of the amblyopia, binocular vision, fixation of the amblyopic eye, and the age of the subject at the start of treatment. These findings enable clinicians to discuss how the components of treatment (spectacle wear and occlusion) contribute to outcome and the likely prognosis based on the child's clinical characteristics. Increasing evidence suggests that small doses of occlusion are as beneficial as substantial or maximum doses.

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