A Randomized Controlled Trial of Unilateral Strabismic and Mixed Amblyopia Using Occlusion Dose Monitors to Record Compliance

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PURPOSE. To investigate compliance with patching therapy and the dose–effect relationship in occlusion therapy in amblyopia by recording the effective patching time using occlusion dose monitors (ODMs).

METHODS. Fifty-two children with strabismic or mixed amblyopia (Snellen equivalent, 6/12–6/48) were given optimal refractive correction and randomly allocated for 12 weeks into three treatment groups: group 1, no patching; group 2, prescribed patching for 3 hours; and group 3, prescribed patching for 6 hours. The effective time of occlusion was monitored with ODMs continuously. Visual acuity (VA) was measured every 3 weeks with LogMAR (logarithm of the minimum angle of resolution) Crowded Tests.

RESULTS. In the 3- and 6-hour groups, mean (SD) compliance was 57.5% (30.8%) and 41.2% (30.9%), respectively, and mean effective patching time per day was 1 hour 43 minutes (55 minutes) and 2 hours 33 minutes (1 hour 52 minutes), respectively. The mean (SD) improvement in logMAR VA of amblyopic eyes was 0.24 (0.17), 0.29 (0.14), and 0.34 (0.19) in groups 1, 2, and 3, respectively. There was no significant difference in compliance with the prescribed patching between the 3- and 6-hour groups. VA outcomes in the 3- and 6-hour groups were not significantly better than 0-hour patching. However, the VA of patients with eyes effectively patched for more than 3 hours improved significantly. A dose–effect relationship was observed. Age at treatment did not influence the visual outcome.

CONCLUSIONS. Poor compliance with prescribed occlusion explains discrepancies in previous studies. No differences in the effect between the different prescribed patching periods were found. The dose–effect relationship observed should encourage development of methods such as educational intervention to improve visual outcome by increasing effective patching time. (Invest Ophthalmol Vis Sci. 2005;46:1435–1439) DOI: 10.1167/iovs.04-0971

The visual system has a vulnerable period of development in which amblyopia, a cortical form of visual impairment, can be caused by deficient visual stimulus. This is most commonly due to misalignment of the eyes (strabismus) and/or refractive error (anisometropia).1–3 Amblyopia is the most common disease affecting visual acuity (VA) in childhood, with prevalence estimated between 2% and 4%.3 Amblyopia commonly affects one eye, reducing binocular vision and stereopsis and causing considerable disability if the other eye loses vision.4 There is a strong clinical belief that patching the fellow eye is successful during a sensitive period that lasts up to ~8 years of age. This has led to preschool vision-screening programs and treatment of thousands of patients every year. However, there are no guidelines regarding the amount of treatment required, and the outcome is often mediocre (Awan MB, et al. IOVS 2004;45:ARVO E-Abstract 499B). Our survey of practices and outcomes of amblyopia treatment in Europe shows extensive variation between and within countries.6 A major review has concluded that no study has yet provided sufficient evidence that patching treatment is beneficial and recommends discontinuing preschool screening for amblyopia.7 It states that dose–effect and adherence to occlusion have not been adequately investigated. Since then, one recent study has shown that glasses and/or patching significantly improve vision in moderate VA, 6/36–6/18 anisometropic amblyopia compared with no intervention.8 This is the first study to have used a nonintervention group. Other recent large multicenter amblyopia treatment studies (ATSs) have shown no differences in VA improvement between the prescription of 2 and 6 hours of patching in moderate amblyopia or 6 hours versus full-time patching in severe amblyopia.9,10 These studies question whether a dose–effect relationship exists in amblyopia and suggest that less intensive patching might be preferable. However, the success of visual rehabilitation has not been optimal in these studies11 and patients’ adherence to treatment has not been taken into account. Occlusion dose monitors (ODMs) are devices placed over the patch to measure the effective wearing time of the patch. Evidence is emerging, using ODMs, that different compliance rates may explain the discrepancies noted between prescribed patching and improvement in VA.12–20

Our objectives were to explore the role of compliance in explaining visual outcomes in a randomized controlled study comparing different patching regimens and to investigate whether there is a dose effect relationship. Our hypotheses were (1) that in amblyopia there is poor compliance with patching therapy; (2) that poor visual outcomes for patching therapy can be explained by poor compliance; and (3) that, when compliance is accounted for, there is a dose–effect relationship between effective hours of patching and improvement in vision.

METHODS

The power of the study was approximated from previous preliminary estimates of the correlation between adherence and visual outcome (see Ref. 20). Given a correlation coefficient of at least 0.5 and a dropout rate of 10%, we estimated that an overall sample size of approximately 60 should be sufficient to determine a significant correlation with 90% power (two-tailed, P < 0.01).

Seventy-seven patients were referred by orthoptists or ophthalmologists in Leicestershire and assessed for the study (Fig. 1), of which 17

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were not recruited (7 parents did not want their child enrolled in the study, 3 children failed to attend appointments, 2 were too young to comply reliably with VA test, 2 had /H11021 2 lines difference in VA between both eyes, 1 had no manifest strabismus, 1 had previous occlusion therapy, and 1 improved in VA during the initial preadaptation period of glasses wearing, resulting in /H11021 2 lines differences between the two eyes).

Sixty newly diagnosed children with amblyopia were recruited between December 2001 and November 2003 from ophthalmology and orthoptic clinics in Leicestershire. The study ended in January 2004. Thirty-seven children had strabismic amblyopia, and 23 had mixed amblyopia (combined strabismus and anisometropia; difference of refractive error sphere /H11350 1.00 D; astigmatism /H11350 1.50 D in any meridian between amblyopic and fellow eye). Inclusion criteria were the ability to perform a vision test with the Glasgow acuity cards, 8 years of age or under and 2 lines difference in Snellen VA. Thirty-two males and 28 females with logMAR (logarithm of the minimum angle of resolution) VA between 0.3 and 0.9 (Snellen equivalent, 6/12–6/48) were included.

The research adhered to the provisions of the Declaration of Helsinki. The Leicestershire Ethics Committee approved the study. After explanation of the nature and possible consequences of the study, informed consent was obtained from all parents and guardians of enrolled subjects.

Participating children were randomly allocated into three treatment groups by the research orthoptist, who opened numbered sealed envelopes with allocation tickets that had been prepared by a researcher not involved in the study. Randomization was stratified by age for children under and over 4 years of age. Participants and the research orthoptist were aware of the intervention.

The three treatment groups were: group 1, no patching; group 2, 3-hour patching; and group 3, 6-hour patching. Once allocated to treatment, parents and the patients who required patching were fully instructed and shown how to use the ODM and apply the patches. The ODM was placed between two patches, to ensure consistent adherence to the skin, reducing the chance of losing the monitor and making it cosmetically acceptable for the child to wear. Children were asked to wear glasses, if needed, for 6 weeks before the study started. After cycloplegic retinoscopy, spectacles with the strength of full retinoscopic refraction were prescribed. All children but two in the 3-hour group and three in the 6-hour group had refractive errors and were dispensed glasses.

In groups 2 and 3, adherence to occlusion was measured continuously over the entire 12-week patching period during the study by the ODMs12,14 (developed in the public domain, Department of Medical Technical Development, Academic Medical Centre, Amsterdam, The Netherlands) by recording the temperature difference between the front and back of the ODM at 5-minutes intervals with two thermistors (Fig. 2). Figure 3 shows original recordings of ODM measurements. Parents were given an insulated lunch box in which to store the ODM when not used, to ensure that the temperature equilibrium of the ODM was consistently maintained and to prevent the loss of the ODMs. The reliability of the ODMs was tested before the study by performing 34
recordings in which investigators accurately recorded application of an ODM patch to their own children (mean, 53.4 minutes). The mean difference between ODM and investigator-recorded times (SD) was −0.85 minute (3.1) giving an accuracy of 99.4% (7.9%). In addition, eight investigators were instructed to make an accurate recording of the wearing times of the ODM on their arms over a 21-day period between 1 and 8 hours a day (mean, 5 hours 7 minutes). The mean error was 5.7 minutes (3.5) over the whole 21-day period.

LogMAR VA was measured by the research orthoptist (LogMAR Crowded Test, Keeler, Windsor, UK) in all groups every 3 weeks for the 12-week duration.

The primary outcome was compliance with patching, determined by the percentage of the prescribed time during which the subject was wearing the patch measured by the ODM. The mean ± SD of compliance was determined for groups 2 and 3 and the two groups compared by using an intention-to-treat analysis.

Visual outcome was the secondary measure, calculated from the percentage change in amblyopia = (VA_{as} - VA_{de})/(VA_{as} - VA_{ae}) × 100% where VA_{as} and VA_{ae} represent VA in the amblyopic eye at the start and end, respectively. VA_{de} is VA of the dominant eye at the end. This formula has been proposed by Stewart et al.\textsuperscript{15} to measure treatment outcome in amblyopia because it grades improvement of the amblyopic eye as the proportion of change in VA with respect to the absolute potential of improvement (i.e., VA of the dominant eye at the end of treatment). The result is 100% if VA of the amblyopic and of the dominant eye are equal at the end of treatment. The visual outcomes were calculated for all three groups and compared using an intention-to-treat analysis. The correlation of the absolute patching time and visual outcome was calculated (per protocol analysis) to determine whether a dose-response relationship exists for patching treatment.

In addition, an exploratory analysis was performed comparing effective patching of 3 to 6 hours (n = 8) with no patching.

Statistical analysis was performed using a univariate general linear model, with group comparisons made using Bonferroni post hoc analysis. Prescribed patching time, gender, and age were included as explanatory variables for adherence. Prescribed patching time or absolute patching time, gender, and age were introduced as explanatory variables for visual outcome. Prescribed and absolute patching times were not introduced concurrently in the analysis, as they are not independent variables.

**RESULTS**

Of the 60 recruited children (20 in each group), 52 children completed the study (n = 18 in group 1; n = 17 in group 2; and n = 17 for group 3). Eight patients dropped out of the study: five because the parents could not keep the frequent appointments requested for the study (two in group 1, two in group 2 and one in group 3) and three with parents who did not think it worth continuing the study because their children would not adhere to treatment (one in group 2 and two in group 3). In groups 1, 2, and 3, respectively, mean (SD) ages were 4.6 years (1.5); 4.4 years (1.0), and 4.7 years (1.3); and, respectively. VA improvement in amblyopic eyes over the 12-week period was 0.24 (0.17), 0.29 (0.14), and 0.34 (0.19) [approximate Snellen equivalents: 1.6 lines (0.12), 1.9 lines (1.0), and 2.3 lines (1.2)] for groups 1, 2, and 3, respectively. VA improvement in amblyopic eyes was steady in the three groups over the 3-month period, with a slightly larger increase in the first 3 weeks in the 6-hour group (Fig. 5). The visual outcomes for groups 1, 2, and 3 were 34.5% (27.7%), 46.0% (19.8%), and 51.8% (27.6%), respectively. Recorded patching was a strong predictor of visual outcome (P = 0.0002), whereas there was no influence of age (P = 0.77) or gender (P = 0.86). Initial amblyopia (VA_{as} - VA_{ae}) was a strong predictor for greater improvement in the amblyopic eye (VA_{as} - VA_{ae}, P = 0.0002).

Figure 6 shows ODM-monitored patching time plotted against the percentage of change in amblyopia. The relationship between effective hours patched and the percentage of change in amblyopia was highly significant (F = 17.1, P = 0.00013, r = 0.50) with VA increasing by 8.3% (SE 2.0%) for each hour patched per day over the 12-week period. There were no significant differences in the percentage of change in amblyopia between groups 1 and 2 (P = 0.43), 1 and 3 (P = 0.16), or 2 and 3 (P = 0.99). However, effective patching of 3 to 6 hours (n = 8) was significantly better than no patching (n = 18, P = 0.02), whereas 2 to 3 hours of effective patching (n = 10) was not (P = 0.1).

None of the patients had a major adverse effect, such as inverse amblyopia or patch allergy in this study.

**DISCUSSION**

We found low compliance with patching therapy in amblyopia, with a mean of 57.5% for the 3-hour prescribed patching (1 hour 43 minutes mean effective patching time per day) and
41.2% for 6-hour prescribed patching (2 hours 33 minutes mean effective patching time per day). VA increase was not different whether patients were asked to wear only glasses or to wear the patches 3 or 6 hours per day. Poor compliance explains our findings that prescribed regimens of 3 or 6 hours of patching did not significantly differ in effectiveness compared with no patching.

However, if the effective hours patched per day were taken into account there was a highly significant dose relationship between hours patched per day and increase in VA. A similar dose–effect relationship has also been found by other studies using the ODM.19,20 Poor compliance with occlusion treatment for amblyopia is supported by previous ODM studies.12–20 It has been attributed to poor parental understanding of the rationale and urgency of amblyopia treatment and poor belief in its effectiveness. Intensified education of parents with written information has been shown to change their attitude and significantly increase adherence to treatment, when measured with diaries.21,22

Only one randomized controlled study has compared “no treatment” with “glasses only” and “glasses combined with patching” in mainly anisometropic amblyopic children. They found that treatment with glasses and/or patching had little effect in children with moderate amblyopia.21,22 It is difficult to compare the findings in this study with our results, since all of our subjects in the treatment groups were strabismic patients prescribed full cycloplegic refraction if required. Also, all our patients in the “no treatment” group were prescribed glasses.

In another recent large randomized controlled ATS,9 it was found that a prescription of 2 hours of patching produces a VA improvement of a magnitude similar to that produced by 6 hours of patching for moderate amblyopia. Also, with a prescription of 6 hours, they found visual improvement similar to that resulting from full-time patching for severe amblyopia.10 Possible explanations of these results are that there is no dose–effect relationship between the time of patching and the increase in VA or that patching is only effective for a certain amount of hours per day and then reaches saturation. Because these studies did not have a group of patients treated with glasses only, the effect of patching cannot be separated from the effect of optical correction. In our study, we found an increase of 0.24 logMAR lines with glasses only, which is similar to the increase described for children prescribed 2- and 6-hour patching for moderate amblyopia in an ATS.9 Because our subjects had a slightly lower VA at the beginning of the study compared with the ATS (0.59 vs. 0.48 mean logMar VA) these numbers are not directly comparable. Stewart et al.18 found a similar effect increasing VA in a preadaptation phase with glasses only before commencing patching.

Another possible explanation that there was no difference in VA change between the different periods of patching prescribed in the ATSs9,10 is poor adherence to treatment. This is supported by our results showing no difference between effective hours patched, whether 3 or 6 hours were prescribed. In fact, the diaries of the patients indicated less adherence if more hours were prescribed in both ATSs.9,10 Because no objective monitoring of effective patching time was performed, dose–effective relationships could not be calculated.

An alternative explanation of the lack of significant difference in change in VA between the 3- and 6-hour groups would be that the effect of patching is saturated after, for example, 3 hours’ patching per day. The results in the eight subjects who effectively patched for >3 hours daily suggest that there is no plateau effect up to 6 hours’ patching per day, although more data for between 3 and 6 hours patching per day are needed to substantiate this finding. To determine whether a dose–effect response continues beyond 6 hours per day of effective patching, it would be informative in a future study, to increase the effective hours of patching per day by increasing the prescribed hours as well as improving compliance.

**Figure 5.** Mean VA of amblyopic and fellow eyes in each treatment group at each examination time. Lower LogMAR acuities indicate better vision.

**Figure 6.** Percentage change in amblyopia [(VAe – VAa)/(VAa – VAae) × 100%] versus mean hours effectively patched (measured with ODMs) in the 3 groups showing a significant relation between effective hours patching and improvement in amblyopia. Only one patient achieved 6 hours of effective patching.
In our study, there was no influence of age on visual outcome. Similarly, Clarke et al. did not find an influence of age at the start of treatment and found that deferring treatment for 1 year from age 4 until age 5 results in the same VA at the start of treatment and found that deferring treatment for moderate amblyopia, possibly because only patients with relative good VA were included.

Consistent with our data, in most studies, patients who started with worse amblyopia showed a larger improvement in VA. This effect has not been found in the ATS with moderate amblyopia, possibly because only patients with relative good VA were included.

In conclusion, we present for the first time, a randomized controlled trial including a nonpatching group, in which effective patching was monitored. We found poor adherence to treatment but a significant dose–effect relationship if effective patching hours are taken into account.

Our recent survey showed that the mean duration of patching prescribed in the United Kingdom is ~3 hours per day. The results of the present study indicate that only the group of patients who effectively used the patches for >3 hours significantly improved in VA, compared with no patching. Therefore, if ≤3 hours are prescribed, the current practice should be changed by increasing effective patching times through longer prescribed patching hours and improved compliance. Surveys of clinical treatment of amblyopia in North America and the United Kingdom have shown poor outcome despite lengthy treatments, often over several years (Awan MB, et al. JOVS 2004;45:ARVO E-Abstract 4998). Because it has been shown recently that the major effect of occlusion treatment occurs in the first weeks to months of treatment, a more intense treatment in a shorter period could prevent psychological and psychosocial problems of families and reduce health economic costs. It is important to devise methods that improve compliance, such as educational programs. In the future, ODMs could be used routinely to monitor occlusion treatment for amblyopia.

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