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Objectively monitored patching regimens for treatment of amblyopia: randomised trial

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ABSTRACT

Objectives To compare visual outcome in response to two prescribed rates of occlusion (six hours a day and 12 hours a day).

Design Unmasked randomised trial.

Setting Research clinics in two London hospitals.

Participants 97 children with a confirmed diagnosis of amblyopia associated with strabismus, anisometropia, or both.

Interventions 18 week period of wearing glasses (refractive adaptation) followed by occlusion prescribed ("patching") for six or 12 hours a day.

Main outcome measures Visual acuity measured by logMAR letter recognition; objectively monitored rate of occlusion (hours a day).

Results The mean age of children at study entry was 5.6 (SD 1.5) years. Ninety were eligible for occlusion but 10 dropped out in this phase, leaving 80 children who were randomised to a prescribed dose rate of six (n=40) or 12 (n=40) hours a day. The mean change in visual acuity of the amblyopic eye was not significantly different (P=0.64) between the two groups (0.26 (95% confidence interval 0.21 to 0.31) log units in six hour group; 0.24 (0.19 to 0.29) log units in 12 hour group). The mean dose rates

(hours a day) actually received, however, were also not significantly different (4.2 (3.7 to 4.7) in six hour group v 6.2 (5.1 to 7.3) in 12 hour group; P=0.06). The visual outcome was similar for those children who received three to six hours a day or more than six to 12 hours a day, but significantly better than that in children who received less than three hours a day. Children aged under 4 required significantly less occlusion than older children. Visual outcome was not influenced by type of amblyopia. **Conclusions** Substantial (six hours a day) and maximal (12 hours a day) prescribed occlusion results in similar visual outcome. On average, the occlusion dose received in the maximal group was only 50% more than in the substantial group and in both groups was much less than that prescribed. Younger children required the least occlusion. **Trials registration** Clinical Trials NCT00274664.

INTRODUCTION

The developing visual system is highly sensitive to visual experience.^{1,2} Interruption by any obstacle, such as blurred vision or strabismus before about 7 years, results in a reduction of visual capacity known as amblyopia.^{1,3} About 90% of work in the children's eye services is related to amblyopia,⁴ and the condition carries an

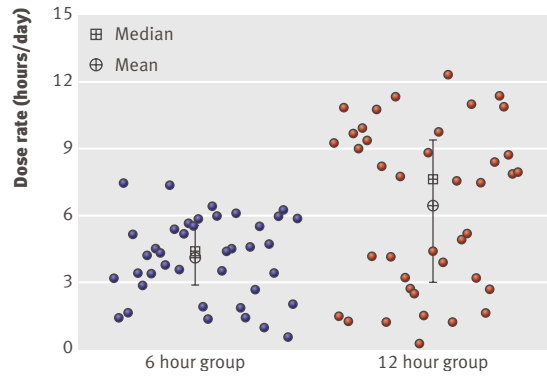


Fig 1 | Achieved dose rate in children allocated to six or 12 hours of occlusion a day. Vertical lines indicate interquartile range. To enhance clarity, dots have been jittered horizontally

increased lifetime risk of serious loss of vision in the other eye.⁵

Treatment of amblyopia has two main components: refractive correction by glasses and occlusion (by “patching”) or “penalisation” (by pharmacological or optical means) of the other eye. The improvement attributable to wearing glasses takes considerable time,^{4,6-8} a process we call “refractive adaptation.”^{7,8} Accurate knowledge of the amount of occlusion a child actually receives is a prerequisite for determining a dose-response relation and is fundamental to evidence based prescribing. We compared two commonly used occlusion regimens—substantial (six hours a day) and maximal (12 hours a day). In this randomised trial of occlusion regimens we fully differentiated the effects of refractive adaptation from those of patching, objectively monitored occlusion, and used recently described methods of quantifying outcome.⁹

METHODS

Study participants

Children were recruited from two London hospitals. All were aged 3-8 years and had anisometropia or strabismus, or both; a significant difference in interocular acuity; no occlusion therapy; and no ocular pathology or learning difficulties. Before study entry, all children had a full ophthalmic assessment including cycloplegic retinoscopy and ophthalmoscopy. The study comprised three phases: baseline, refractive adaptation, and occlusion. In the baseline phase, one author (CES) enrolled participants and the same examiner assessed stability of their visual acuity on at least two occasions. Children who required correction with glasses or who had already been wearing glasses for less than 18 weeks entered the refractive adaptation phase. They were instructed to wear glasses all the time and scheduled to return for assessment of vision every six weeks until 18 weeks of refractive adaptation had been completed.⁷ On completion of refractive adaptation, children who still met the study’s operational definition of amblyopia entered the occlusion phase. Those children who did not require correction with glasses or who had previously worn glasses for 18 weeks or longer entered directly into the occlusion phase. CES allocated children to prescribed dose rates of either 12 hours a day (maximal) or six hours a day (substantial), stratified, but not blocked, by type of amblyopia and implemented by means of a concealed typed allocation list. Neither investigator nor the parents were masked to group allocation.

The occlusion dose monitor¹⁰ recorded episodes of occlusion to the nearest minute. Visual function was recorded every two weeks, at which time we also audited the occlusion dose received between visits. The occlusion phase continued until visual acuity ceased to improve.

Mean (95% confidence interval) visual outcome according to prescribed dose of occlusion (six or 12 hours a day) and actual dose received*

	Change in visual acuity	Proportion of deficit corrected	Residual amblyopia	Cumulative dose (hours)	Dose rate (hours/day)	Time to best visual acuity (days)
Prescribed occlusion dose (hours/day)						
6 (n=39)	0.26 (0.21 to 0.31)	0.67 (0.57 to 0.77)	0.17 (0.11 to 0.23)	225 (183 to 267)	4.2 (3.7 to 4.7)	59 (49 to 69)
12 (n=41)	0.24 (0.18 to 0.30)	0.61 (0.50 to 0.72)	0.22 (0.15 to 0.29)	307 (240 to 384)	6.2 (5.1 to 7.3)	54 (44 to 64)
Difference	0.02 (0.0 to 0.04)	0.06 (0.03 to 0.09)	0.05 (0.03 to 0.07)	82 (63 to 101)	2.0 (1.7 to 2.3)	05 (1.8 to 8.8)
P value	0.64	0.34	0.25	0.30	0.06	0.48
Received occlusion dose (hours/day)						
≤3 (n=21)	0.18 (0.11 to 0.25)	0.33 (0.16 to 0.50)	0.31 (0.25 to 0.37)	87 (51 to 123)	1.6 (1.3 to 1.9)	70 (51 to 89)
>3-6 (n=32)	0.25 (0.18 to 0.32)	0.77 (0.67 to 0.87)	0.10 (0.06 to 0.14)	255 (213 to 297)	4.3 (4.0 to 4.6)	66 (55 to 77)
Difference	0.07 (0.06 to 0.12)	0.44 (0.39 to 0.49)	0.21 (0.19 to 0.23)	168 (153 to 181)	2.7 (2.6 to 2.8)	4 (-2 to 10)
P value	0.04	0.004	<0.001	<0.001	<0.001	0.68
≤3 (n=21)	0.18 (0.11 to 0.25)	0.33 (0.16 to 0.50)	0.31 (0.25 to 0.37)	87 (51 to 123)	1.6 (1.3 to 1.9)	70 (51 to 89)
>6-12 (n=27)	0.33 (0.25 to 0.41)	0.67 (0.55 to 0.79)	0.16 (0.10 to 0.22)	403 (310 to 500)	9.0 (7.8 to 10.2)	50 (40 to 60)
Difference	0.15 (0.12 to 0.18)	0.34 (0.28 to 0.40)	0.15 (0.12 to 0.18)	316 (279 to 353)	7.4 (7.1 to 7.7)	20 (12 to 28)
P value	0.01	0.01	0.004	<0.001	<0.001	0.04
>3-6 (n=32)	0.25 (0.18 to 0.32)	0.77 (0.67 to 0.87)	0.10 (0.06 to 0.14)	255 (213 to 297)	4.3 (4.0 to 4.6)	66 (55 to 77)
>6-12 (n=27)	0.33 (0.25 to 0.41)	0.67 (0.55 to 0.79)	0.16 (0.10 to 0.22)	403 (310 to 500)	9.0 (7.8 to 10.2)	50 (40 to 60)
Difference	0.08 (0.05 to 0.11)	0.10 (0.06 to 0.14)	0.06 (0.04 to 0.08)	148 (122 to 174)	4.7 (4.4 to 5.0)	16 (12 to 20)
P value	0.13	0.08	0.11	<0.001	<0.001	0.18

*One child received dose rate of only 0.2 hours (12.5 minutes a day), an amount with doubtful therapeutic value. Significance values are unchanged with or without this data point.

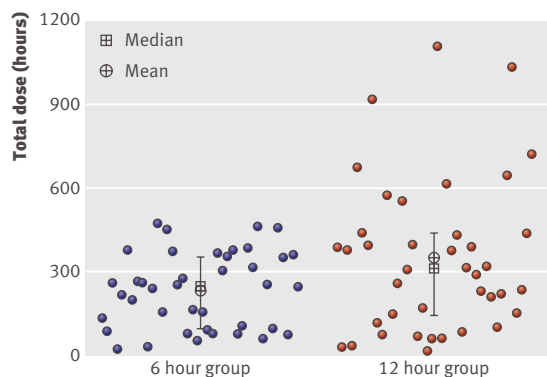


Fig 2 | Total dose of occlusion actually received in children allocated to six or 12 hours of occlusion a day. Vertical lines indicate interquartile range. To enhance clarity, dots have been jittered horizontally

Outcome measures

Our primary outcome measure was logMAR visual acuity.¹¹ We expressed visual outcome in three ways: firstly, by calculating the change in visual acuity of the amblyopic eye; secondly, by calculating the amount of residual amblyopia (acuity difference between the amblyopic and fellow eye at outcome); and, thirdly, by calculating the proportion of the visual deficit corrected (proportional improvement).⁹

Statistical analysis

We used Wilcoxon signed rank analysis to test for significant differences in outcome and dose between the groups and Kruskal-Wallis one way analysis of variance on ranks to test for significant differences in outcome for participants by objectively monitored dose rate.

RESULTS

Ninety seven children with a mean age of 5.6 (SD 1.5) years entered the study (see bmj.com).

Refractive adaptation phase

The mean (SD) visual acuity of amblyopic eyes improved from 0.55 (0.28) to 0.38 (0.34) logMAR; a mean improvement of 0.17 (95% confidence interval 0.12 to 0.22). In 40 children who had undergone partial refractive adaptation before study entry, the mean change in acuity was 0.11 (0.05 to 0.17). The mean change in acuity in the 44 children who underwent full refractive adaptation monitored in our study was significantly greater ($P=0.03$) (mean 0.22 (0.16 to 0.28) log units).

During refractive adaptation, visual acuity in seven children improved to an extent that they were no longer eligible to enter the occlusion phase, with mean logMAR visual acuity 0.00 (−0.07 to 0.07) in the amblyopic eye and −0.04 (−0.10 to 0.02) in the fellow eye.

Occlusion phase

Though 90 children were eligible for occlusion, 10 left the study. The 80 remaining were randomised to a prescribed occlusion dose rate of six ($n=40$; age 5.4, SD 1.7

or 12 hours a day ($n=40$; age 5.6, SD 1.4) (see bmj.com). In the six hour group, the mean (SD) visual acuity in the amblyopic eye improved from 0.45 (0.30) to 0.19 (0.19) logMAR, a change of 0.26 (95% confidence interval 0.21 to 0.31) log units. In the 12 hour group, the improvement was from 0.44 (0.30) to 0.20 (0.24) logMAR, a change of 0.24 (0.19 to 0.29) log units (table). There was no significant difference between the two groups for any outcome measure (visual acuity at start and end, magnitude of change in acuity, amount of residual amblyopia, or proportion of the amblyopia deficit corrected) (table).

The mean dose rates (hours a day) actually received were not significantly different in the six hour group (4.2 (3.7 to 4.7)) from those in the 12 hour group 6.2 (5.1 to 7.3) ($P=0.06$) (fig 1). Correspondingly, there was no difference in the total (accumulated) dose received by children in either of the two groups ($P=0.03$) (fig 2). Only nine (23%) and three (7%) children in the two groups, respectively, achieved an average concordance within 10% of their prescribed dose rate. Concordance was 3.6 times more variable in the 12 hour group than in the six hour group.

The mean dose rate and the mean percentage concordance with the prescribed regimen did not differ significantly with age (see bmj.com). Also, the mean dose rate of occlusion did not differ significantly with type of amblyopia and remained so, even when we stratified by prescribed dose rate ($P=0.05$).

We also analysed the data by objectively monitored dose rate (received rather than prescribed). Children were categorised into three groups according to the dose rate received: <3 hours/day ($n=21$), ≥ 3 –<6 hours/day ($n=32$), and ≥ 6 –12 hours/day ($n=27$). We found a significant difference in visual outcome between participants in the <3 hour group compared with those in the other two groups, with no difference between the latter (table).

Duration of occlusion therapy

The mean time to achieve best visual acuity was nine weeks (SD 5, range 2–26 weeks). Only 12 children (eight in the six hour group; four in the 12 hour group) required more than 14 weeks of occlusion. The mean time to achieve best visual acuity did not differ significantly between the prescribed groups (10 weeks (SD 6, range 2–26) in the six hour group *v* 8 weeks (SD 5, range 1–18) in the 12 hour group). Most of the improvement occurred in the first six weeks (53% by two weeks, 68% by four weeks, 78% by six weeks, 85% by eight weeks).

Factors affecting outcome as a function of dose rate

The proportion of the deficit corrected and residual amblyopia was not significantly different ($P=0.46$ and $P=0.42$, respectively) for each type of amblyopia. There was a significant difference in the dose rate required to obtain maximum proportional improvement with respect to age (see bmj.com).

DISCUSSION

Substantial (six hours a day) and maximal (12 hours a day) prescribed occlusion regimens provide equivalent

WHAT IS ALREADY KNOWN ON THIS TOPIC

Occlusion therapy (patching) is the main treatment for amblyopia

It is an unpleasant procedure and compliance with treatment is often poor

Given the inability to record objectively the amount of occlusion a child actually receives, many practitioners prescribe large doses, above six hours a day

WHAT THIS STUDY ADDS

Results of occlusion do not differ in groups prescribed six or 12 hours of occlusion a day

Objective monitoring shows that the amount of occlusion a child actually receives is substantially less than that prescribed, irrespective of dosing regimen

visual outcome for the treatment of unilateral amblyopia in children aged 3-8. By objectively monitoring occlusion we showed that the maximal group received only about 50% more occlusion a day, despite being prescribed twice the amount of the substantial group. Furthermore, analysis of dose-response showed that the average amount of occlusion received in each group was sufficient to achieve best outcome.

Optimum dose rate

We carried out exploratory analyses on the effect of received dose rate and on dose rate and age. The relation between dose rates and outcome showed that outcome was similar in children receiving between four and 12 hours a day. We observed a linear relation between improved outcome and increased dose rate for dose rates up to four hours a day, and our analysis suggests that achieving an initial dose rate of three to four hours a day should be a clinical priority. The response depends on age, however, so that for those under 4 years this could be reduced. Higher dose rates achieve the best outcome more rapidly but at a risk of accumulating excessive non-therapeutic hours of patching. Thus, patching for all waking hours is almost certainly excessive.

We consider that the observed effect of dose prescribed was not compromised by potential confounding of other variables (for example, type of amblyopia, age of child, visual acuity at start of study). The imperfect adherence to assigned treatment, however, implies that an observational analysis that inspects the effect of dose received may be subject to confounding. A carefully constructed multiple regression analysis or causal inference methods would therefore be required to analyse the data on dose received.¹²

Concordance

Eye patching can cause considerable distress for both the child and family.^{13,14} Full concordance with prescribed dose rates is rare; children in our study received on average 66% and 50% of their prescribed occlusion of six and 12 hours a day, respectively. This suggests that these prescribed regimens imposed a considerable burden on our participants and would be expected to do so in routinely treated patients. We observed a plateau of improvement

in outcome at about four hours a day (see bmj.com). Prescriptions of occlusion should take this into account, minimising the amounts necessary for best expected outcome.

The conventional clinical approach in a child whose vision does not improve with part time occlusion therapy is to prescribe a more intense regimen,¹⁵ thus increasing the burden of treatment on the child and family.^{4,12-14} Knowledge of concordance with treatment permits detailed evaluation of treatment strategy. For example, if compliance was low initially then this could be the reason for poor outcome, in which case education¹⁶ or different patching strategies may facilitate best outcome. If concordance was high, however, additional occlusion will probably not be beneficial.

Objective monitoring of occlusion

Our study highlights the potential benefits of objective monitoring of occlusion within routine clinical practice. Firstly, clinicians no longer have to rely on subjective and qualitative feedback from children and parents as to the amount of patching achieved. Secondly, the availability of an objective quantitative record of the occlusion dose and dose rate allows the clinician to tailor advice and prescription to an individual patient. In practical terms, this will reduce the number of patching hours prescribed and clinic visits required. This should result in an improvement in cost effectiveness and potentially a better experience for the child and his or her family.

Although treatment for amblyopia is thought to be more successful at earlier stages of visual development,¹⁷ the evidence is unconvincing and contradictory.¹⁷⁻²³ We have provided further evidence that age can influence the dose-response relation of occlusion treatment.

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Accuracy of electrocardiography in diagnosis of left ventricular hypertrophy in arterial hypertension: systematic review

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ABSTRACT

Objective To review the accuracy of electrocardiography in screening for left ventricular hypertrophy in patients with hypertension.

Design Systematic review of studies of test accuracy of six electrocardiographic indexes: the Sokolow-Lyon index, Cornell voltage index, Cornell product index, Gubner index, and Romhilt-Estes scores with thresholds for a positive test of ≥ 4 points or ≥ 5 points.

Data sources Electronic databases ((Pre-)Medline, Embase), reference lists of relevant studies and previous reviews, and experts.

Study selection Two reviewers scrutinised abstracts and examined potentially eligible studies. Studies comparing the electrocardiographic index with echocardiography in hypertensive patients and reporting sufficient data were included.

Data extraction Data on study populations, echocardiographic criteria, and methodological quality of studies were extracted.

Data synthesis Negative likelihood ratios, which indicate to what extent the posterior odds of left ventricular hypertrophy is reduced by a negative test, were calculated.

Results 21 studies and data on 5608 patients were analysed. The median prevalence of left ventricular hypertrophy was 33% (interquartile range 23-41%) in primary care settings (10 studies) and 65% (37-81%) in secondary care settings (11 studies). The median negative likelihood ratio was similar across

electrocardiographic indexes, ranging from 0.85 (range 0.34-1.03) for the Romhilt-Estes score (with threshold ≥ 4 points) to 0.91 (0.70-1.01) for the Gubner index. Using the Romhilt-Estes score in primary care, a negative electrocardiogram result would reduce the typical pre-test probability from 33% to 31%. In secondary care the typical pre-test probability of 65% would be reduced to 63%.

Conclusion Electrocardiographic criteria should not be used to rule out left ventricular hypertrophy in patients with hypertension.

INTRODUCTION

Left ventricular hypertrophy is an important risk factor in patients with hypertension, leading to a fivefold to 10-fold increase in cardiovascular risk.¹⁻⁵ Decisions about treatment should be based on assessments of hypertensive target organ damage and overall cardiovascular risk. The appropriate diagnostic work-up of suspected left ventricular hypertrophy in patients with hypertension is less clear, however. More than 30 electrocardiographic indexes for the diagnosis of left ventricular hypertrophy have been described. Many of the proposed indexes have remained anecdotal, but others are commonly used.⁶⁻¹⁰ Debate about their comparative diagnostic value continues.¹¹⁻¹³ We did a systematic review to clarify the accuracy of different electrocardiographic indexes.