Amblyopia treatment outcomes after screening before or at age 3 years: follow up from randomised trial

C Williams, K Northstone, R A Harrad, J M Sparrow, I Harvey, ALSPAC Study Team

Abstract

Objective To assess the effectiveness of early treatment for amblyopia in children.
Design Follow up of outcomes of treatment for amblyopia in a randomised controlled trial comparing intensive orthoptic screening at 8, 12, 18, 25, 31, and 37 months (intensive group) with orthoptic screening at 37 months only (control group).
Setting Avon, southwest England.
Participants 3490 children who were part of a birth cohort study.
Main outcome measures Prevalence of amblyopia and visual acuity of the worse seeing eye at 7.5 years of age.
Results Amblyopia at 7.5 years was less prevalent in the intensive group than in the control group (0.6% *v* 1.8%; P=0.02). Mean visual acuities in the worse seeing eye were better for children who had been treated for amblyopia in the intensive group than for similar children in the control group (0.15 *v* 0.26 LogMAR units; $P < 0.001$). A higher proportion of the children who were treated for amblyopia had been seen in a hospital eye clinic before 3 years of age in the intensive group than in the control group (48% *v* 13%; P=0.0002).
Conclusions The intensive screening protocol was associated with better acuity in the amblyopic eye and a lower prevalence of amblyopia at 7.5 years of age, in comparison with screening at 37 months only. These data support the hypothesis that early treatment for amblyopia leads to a better outcome than later treatment and may act as a stimulus for research into feasible screening programmes.

Introduction

Preschool screening of vision is carried out to detect amblyopia (reduced visual acuity that is not instantly alleviated by wearing spectacles, in an otherwise apparently healthy eye). It is treated by long term wearing of spectacles when appropriate and by temporarily patching the better seeing eye. Preschool screening programmes for amblyopia were developed in response to experimental data in animals, which suggested that treatment given during early development could improve conditions thought to be analogous to human amblyopia, whereas later treatment was ineffective.[1 2] The programmes varied widely in content and coverage.[3] A recent systematic review discussed the poor clinical evidence base underpinning these programmes and emphasised the lack of evidence that treatment for amblyopia is better than placebo or that early treatment is more effective than later treatment.[4] This review recommended discontinuation of existing preschool vision screening programmes and has provoked much discussion.[5–7]

We present the follow up results from a population based randomised controlled trial, which was nested within a birth cohort study. The original hypothesis being tested was that a "de luxe" intensive early screening programme would detect and refer for treatment more children with amblyopia than would routine surveillance (the control programme). The results were assessed when the children were 37 months of age, and the data supported the hypothesis.[8] The hypothesis being tested by the present follow up study was that the children with amblyopia detected by the early intensive screening would have achieved better outcomes after treatment than children with amblyopia in the control group (who had been examined only at 37 months).

Methods

Participants—The participants were part of the ongoing Avon longitudinal study of parents and children (ALSPAC), known as the "children of the nineties" study.[9 10] Box 1 gives further details. The nested randomised controlled trial reported here was open to all children in the cohort born during the last six months of the study period.

Exclusions—We excluded children who were born in the first 15 months of the cohort or whose parents had declined to continue with the study or had more than one participating child.

Routine services provided in the study area—One institution provides hospital eye services for all children in the study area. All children received the usual recommended surveillance by their general practitioners and health visitors and were offered screening for reduced visual acuity by a school nurse at school entry (4-5 years).

Randomisation, assignment, and masking—We allocated children into different arms of the study by a "pseudo-random" process according to the last digit in the day of the mother's date of birth: 1, 3, and 5 for the intensive group, and 2 and 4 for the control group. We

Division of Child Health, University of Bristol, Bristol BS8 1TQ
C Williams *consultant ophthalmologist*
K Northstone *research fellow in statistics*
Bristol Eye Hospital, Lower Maudlin St, Bristol BS1 2LX
R A Harrad *consultant ophthalmologist*
J M Sparrow *consultant ophthalmologist*
School of Medicine, Health Policy and Practice, University of East Anglia, Norwich NR4 7TJ
I Harvey *professor of epidemiology and public health*
Correspondence to: C Williams Cathy.Williams@bristol.ac.uk

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Box 1: Avon longitudinal study of parents and children

- This is a World Health Organization initiative and is an ongoing, geographically based, population birth cohort study. Sister studies in other European countries (collectively known as ELSPAC) are also in progress[9]
- The cohort study was open to all pregnant women with an estimated date of delivery between 1 April 1991 and 31 December 1992, who were resident in the area formerly known as Avon, in southwest England
- Approximately 14 000 women were recruited (85% of those eligible) while they were still pregnant
- Demographic data for the sample are very similar to data from the 1991 UK census for Avon, but the sample contains fewer very deprived families, families of Asian extraction, and families in which the mother was a teenager when her child was born
- Data collection is prospective and by diverse means, including self completion questionnaires to the mothers, their partners, and (after age 5) the children; physical samples such as mother's antenatal blood, cord blood, teeth, nails, placentas, and blood on subsets of the children; environmental samples; linkage to the hospital and educational records; and a recently established DNA library and cell lines (for the children, the mothers, and their partners)
- The results of a variety of physical and psychometric examinations are available for a random sample of children who were examined between 4 months and 5 years of age and for the whole cohort who have been invited to yearly examinations since the age of 7 (examinations at age 9 are currently taking place)
- Substudies (including the one reported here) covering a range of outcomes in the children have been nested within the main study, and further projects are ongoing

sent invitations to eligible children during recruitment until all available clinic slots were filled. Administrative staff carried out allocation of the children into groups and invitation to the clinics. The orthoptists carrying out the vision tests had no knowledge of the mothers' dates of birth, the rules determining allocation into the different groups, or the screening history of the children. Different orthoptists carried out the screening and final assessment parts of the study.

Protocols—In the intensive group, children were invited to attend a research clinic at 8, 12, 18, 25, 31, and 37 months, where an orthoptist examined them and carried out a battery of tests appropriate to the age of the child (box 2). The children in the control group were offered similar testing by an orthoptist at 37 months only. Any child failing the acuity test or cover test in either of the groups was referred to the hospital eye service.

Final assessment—We invited all children to a vision assessment at 7.5 years (box 2), including measurement of visual acuity both with and without a pinhole (with pinhole as a proxy for correction by spectacles). We sent out a questionnaire on family history and previous treatment with patching beforehand.

Sample size—The long term follow up study had approximately 80% power, calculated retrospectively ($P<0.05$, two tailed test), to detect a minimum difference in mean acuity of the amblyopic eyes of 0.65 standard deviations (1.7 lines or eight letters on a LogMAR chart[20]) between children in the two groups, given that approximately 4% of children were treated for amblyopia.

Statistical analysis—We analysed the data according to the principle of intention to treat. The outcomes were the prevalence of amblyopia and the visual acuity in the worse seeing eye for children after treatment with patching at 7.5 years. The visual acuity result used for each eye was the better of the results obtained with and without pinhole. We defined amblyopia in advance in two ways to allow comparisons with other studies: amblyopia A, where the interocular difference in acuity was 0.2 LogMAR (two lines on the chart) or more[21]; and amblyopia B, where the visual acuity in the amblyopic eye was worse than 0.3 LogMAR.[22] We compared proportions with the χ^2 test or Fisher's exact test. We analysed continuous data by using analysis of variance or multivariate analysis with SPSS version 10. We regarded a P value of <0.05 as significant. Results are given as proportions, mean visual acuities in LogMAR units, or odds ratios.

Box 2: Details of interventions used in intensive and control groups

Strabismus testing

Cover testing was carried out each time a child was seen, including at the final assessment. Failure on cover testing (any manifest strabismus, any latent convergent strabismus, or a latent divergent strabismus of 10 prism dioptres or more) led to referral to the hospital eye service for full evaluation, including cycloplegic refraction and fundoscopy. Any new cases of strabismus discovered at the final assessment were also referred.

Protocols for vision testing

Children in the intensive group only were tested at 8 months and 12 months with Cardiff cards at 1 m.[11 12]
At 18, 25, and 31 months children in the intensive group only were tested with Cardiff cards at 1 m and with Kays picture test at 6 m.[13 14] At 37 months children in both groups were tested with Kays picture test at 3 m or 6 m and with single HOTV letters, with and without crowding bars,[15] displayed on a computer monitor at 6 m.[16]
Failure on any vision test led to referral to the hospital eye service, where cycloplegic refraction was carried out and treatment instituted if needed.
At all ages non-cycloplegic autorefraction was carried out,[17] but referrals to the hospital eye service were not made on the basis of this until the 37 month clinic.
At 7.5 years LogMAR ($\log_{10}$ minimum angle of resolution, using ETDRS charts) at 4 m was measured in the child's habitual state (that is, with glasses if worn) both with and without a pinhole.[18 19] If the better (smaller LogMAR score) acuity obtained either with or without pinhole for either eye was 0.2 or worse or if there was a difference between the best acuity of the two eyes of 0.2 or more, the child was seen again in a further research clinic where cycloplegic retinoscopy and fundoscopy were carried out. Glasses, referral to the hospital eye service, or both were offered if needed. If the best visual acuity of either eye was better than 0.2 but improved by 0.2 or more with the pinhole, the child's carer was advised to see an optician and given a referral note describing the study findings.

Results

Of the 3490 children in the trial, 1929 attended the final examination. Fifteen children had organic ocular pathology or were developmentally delayed and were excluded from further analysis, leaving 1914 children—1088/2029 (54%) of the intensive group and 826/1490 (55%) of the control group as originally randomised.

Comparison of children who did and did not provide outcome data

Children who attended for the final assessment were more likely to have mothers with education to at least A level, to live in owner occupied rather than council or rented accommodation, to have been breast fed for at least three months, and to have a family history of strabismus or sight problems, in comparison with children who did not attend. Children who attended were less likely to have been born to a teenage mother or to have weighed less than 2500 g at birth (data not shown, all $P<0.001$).

Prevalence of amblyopia at 7.5 years of age

Amblyopia was found less often at 7.5 years in the intensive group than in the control group. The prevalence of amblyopia A was 1.45% (95% confidence interval 0.89% to 2.35%) in the intensive group and 2.66% (1.76% to 4.00%) in the control group ($\chi^2=3.4$, df=1, P=0.06). The prevalence of amblyopia B was 0.63% (0.30% to 1.32%) in the intensive group and 1.81% (1.10% to 2.98%) in the control group ($\chi^2=5.6$, df=1, P=0.02).

Four children with amblyopia A in the intensive group and six children with amblyopia A in the control group had not had previous patching treatment. All but one child (in the control group) had defaulted from all previous invitations to the study vision screening clinics. The difference in the proportions of untreated amblyopia in the intensive and control groups was not significant (Fisher's exact test, P=0.42).

Cumulative incidence of amblyopia

No significant differences existed in the proportions of children previously treated with patching in the two groups. In the intensive group 40/1088 (3.7%; 2.71% to 4.97%) were given patches compared with 40/826 (4.8%; 3.56% to 6.52%) in the control group ($\chi^2=1.31$, df=1, P=0.25). When the children with untreated amblyopia were added in, the difference between the groups in the total number of treated or untreated children with amblyopia was still not significant: 4.0% (3.02% to 5.39%) compared with 5.6% (4.09% to 7.22%) ($\chi^2=2.1$, df=1, P=0.14). These data show that the cumulative incidence of amblyopia in each group was similar.

Prevalence of residual amblyopia at 7.5 years after patching treatment

Residual amblyopia was more likely to be present despite previous treatment in the control group (10/40) than in the intensive group (3/40). The difference for amblyopia A was not significant (odds ratio 1.56, 95% confidence interval 0.62 to 3.92), but for amblyopia B the difference was more marked (4.11, 1.04 to 16.29).

Table 1 Ages when first seen in the hospital eye service, for children subsequently treated with occlusion (data from hospital notes)

Age (months)	Intensive group (n=40)	Control group (n=40)
Under 12	6	0
12-23	7	4
24-36	6	1
37	10	25
Over 38	11	10

Visual acuity in the worse seeing eye after patching treatment

Visual acuity in the worse seeing (amblyopic) eye was significantly better for treated children in the intensive group than for similar children in the control group: mean acuity 0.15 (95% confidence interval 0.085 to 0.215) compared with 0.26 (0.173 to 0.347). The corresponding acuities for children who had not had patching treatment were -0.02 (-0.024 to -0.016) and -0.01 (-0.016 to -0.004) in the two groups (two factor univariate analysis of variance, $P<0.001$ for effect of group and $P<0.001$ for interaction between group and whether given patch or not).

Age at first referral to hospital eye service

A higher proportion of children who received patching treatment were first seen in the hospital eye service before the age of 3 years in the intensive group (19/40) than in the control group (5/40), as shown in table 1 ($\chi^2=10.06$, df=1, P=0.002). No difference existed between the groups in the proportions of children referred after the study interventions had finished—that is, between 37 months and school age (13/40 *v* 10/40; $\chi^2=0.24$, df=1, P=0.62).

Adjustment for confounding variables

Table 2 shows variables other than the exposure of interest that were associated with the outcome data. Only maternal education remained significantly associated with the outcome in a multivariate analysis. Maternal education may be a proxy for socioeconomic status, which is associated with the likelihood of adherence to treatment for amblyopia in young children.[23] Adjustment for maternal education within the multivariate model made little difference to the results: the adjusted mean acuities in the worse seeing eyes of children treated with patching were again 0.15 (0.083 to 0.217) in the intensive group and 0.26 (0.170 to 0.350) in the control group ($P<0.001$).

Discussion

The results of this study support the hypothesis that offering the "de luxe" early screening programme resulted in a better outcome for the children with amblyopia than offering the control programme and reduced the population prevalence of amblyopia. Compared with the intensively screened group, children treated for amblyopia in the control group were four times more likely to have a post-treatment visual acuity worse than 0.3 in their worse seeing eye and were correspondingly more at risk of major incapacity if they were to lose the sight in their better eye. A national study investigating the frequency of this event is under way, but an interim report suggests that it happens more often than was previously assumed

Table 2 Variables investigated as potential confounders (associated in univariate analyses with visual acuity in worse seeing eye) and their distributions in children who attended for final outcome assessment. Values are numbers (percentages) unless stated otherwise

Variable*	Mean (SD) LogMAR† acuity in worse seeing eye	Distribution in intensive group	Distribution in control group
Birth weight (g):			
<2500	0.025 (0.15)	49 (4.5)	37 (4.5)
2500-3999	−0.006 (0.10)	880 (80.9)	667 (80.8)
⩾4000	−0.015 (0.08)	158 (14.5)	122 (14.8)
	(F=6.3; P=0.002)		
Duration of breast feeding:			
Never	0.004 (0.12)	212 (20.8)	136 (17.6)
<3 months	−0.004 (0.10)	341 (33.5)	232 (30.1)
⩾3 months	−0.013 (0.09)	465 (45.7)	403 (52.3)
	(F=4.09; P=0.017)		
Maternal education:			
Vocational/CSE	0.003 (0.13)	217 (20.6)	176 (21.9)
O level	−0.001 (0.10)	386 (36.6)	270 (33.5)
A level or above	−0.011 (0.095)	453 (42.9)	359 (44.6)
	(F=4.51; P=0.034)		
First degree relative with strabismus or amblyopia:			
Yes	0.009 (0.11)	165 (15.2)	143 (17.3)
No	−0.008 (0.09)	923 (84.8)	683 (82.7)
	(F=8.11; P=0.004)		
Sex:			
Male	−0.009 (0.10)	576 (52.9)	414 (50.1)
Female	−0.001 (0.09)	512 (47.1)	412 (49.9)
	(F=4.21; P=0.040)		
Use of car:			
Yes	−0.007 (0.10)	1002 (93.5)	759 (94.2)
No	0.014 (0.09)	70 (6.5)	47 (5.8)
	(F=5.29; P=0.022)		

*Also tested and not associated with study outcome: admission to special care baby unit in first month of life, gestation, ethnicity, smoked in first trimester, smoked in second trimester, alcohol in first trimester, alcohol in second trimester, use of illicit drugs during pregnancy, housing tenure, overcrowding in home, financial difficulties, maternal age at birth of child.
†LogMAR is $\log_{10}$ minimum angle of resolution: 0.0 corresponds to 6/6 on a Snellen chart (normal vision), 1.0 corresponds to 6/60 (poor vision), and -0.18 corresponds to 6/4 (excellent vision).

and that subsequent improvement in acuity in the amblyopic eye is uncommon.[22]

The mechanisms underlying the improved results in the intensive group cannot be ascertained from this study. Potential explanations include greater effectiveness of treatment due to age dependent plasticity, referral at an earlier stage in the course of the visual defect, greater adherence to treatment, and perceptual learning due to repeated testing. More of the children who were given patches in the intensive group than in the control group had been seen in the hospital eye service when aged less than 37 months, but these referrals were made at a variety of ages (table 2). The earlier report from the present study suggested that screening using only photorefraction at the ages of 8, 12, 18, 25, or 31 months alone could have increased the yield of children with amblyopia compared with the actual yield from the intensive programme, which used acuity and cover testing.[8] The specificity of such an approach would have been poor initially but would have increased to over 95% when the children were aged 31 months and older; these data may help in the design of potentially feasible programmes.

Other studies have investigated the effectiveness of preschool vision screening. Three historical comparison studies have described a lower prevalence of amblyopia after the introduction of such screening than was present before.[24–26] A multicentre retrospective review compared results for over 900 children treated for amblyopia throughout the United Kingdom and did not observe any associations between age at referral and treatment outcome.[27] However, a pooled analysis using these data and data from other studies found that a younger age at start of treatment was predictive of success.[28] A prospective UK cohort study found no difference in the prevalence of amblyopia between children who had been offered primary orthoptic screening at 3 years and children offered only surveillance by a health visitor.[29] The difference between the results of that study and those presented here may be due to differences in methods. Our study included screening offered before the age of 3 years, the groups were randomised, the outcome data were detailed and prospectively collected, and additional data were available to control for confounding variables.

The limitations of this study stem from the fact that it was opportunistic and designed to fit in with the ALSPAC study. The groups were unevenly sized for pragmatic reasons. Only approximately half the children were followed up, which may have biased the results, so caution must be exercised when interpreting these data. However, the effect of the intervention was undiminished when the results were adjusted for the only potential confounder detected after investigating several known and suspected factors. The bias towards more frequent breast feeding and fewer low birthweight babies in those who attended the final assessment would be expected to improve the visual status in these children,[30 31] whereas the greater likelihood of a family history of strabismus or eye problems would be expected to have a deleterious effect on their visual status,[32 33] compared with the children who did not attend for follow up. The overall effect of these biases is uncertain, but there is no reason to assume that they would invalidate the study findings.

To our knowledge, no other randomised study has investigated treatment outcome for children with amblyopia and shown clear improvements associated with very early vision screening and treatment in comparison with screening at the age of 37 months. An important question is whether feasible programmes could deliver the same benefits as the intensive programme without repeated testing, which would be extremely expensive. Future research needs to investigate whether cost effective strategies can be designed that produce similar results. A separate report from this study will compare screening at 37 months with screening at school age. These data and those from other studies will be needed to inform decisions about the advisability of population screening for amblyopia. However, the data presented here support the hypothesis that treatment given for amblyopia is more effective if it starts as early as possible and may contribute to the debate on the management of amblyopia.

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What is already known on this topic

Observational studies have produced conflicting results about whether early treatment for amblyopia gives better results than later treatment

A recent systematic review highlighted the lack of high quality data available and recommended the cessation of preschool vision screening programmes

This has led to fierce debate and to confusion about the provision of vision screening services

What this study adds

Children treated for amblyopia are four times more likely to remain amblyopic if they were screened at 37 months only than if they were screened repeatedly between 8 and 37 months

Children screened early can see an average of one line more with their amblyopic eye after treatment than children screened at 37 months

Early treatment is more effective than later treatment for amblyopia, supporting the principle of preschool vision screening

variety of medical research charities and commercial companies. The ALSPAC study is part of the WHO initiated European longitudinal study of pregnancy and childhood.

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