Extended optical treatment versus early patching with an intensive patching regimen in children with amblyopia in Europe (EuPatch): a multicentre, randomised controlled trial

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Summary

Background Amblyopia, the most common visual impairment of childhood, is a public health concern. An extended period of optical treatment before patching is recommended by the clinical guidelines of several countries. The aim of this study was to compare an intensive patching regimen, with and without extended optical treatment (EOT), in a randomised controlled trial.

Methods EuPatch was a randomised controlled trial conducted in 30 hospitals in the UK, Greece, Austria, Germany, and Switzerland. Children aged 3–8 years with newly detected, untreated amblyopia (defined as an interocular difference ≥0·30 logarithm of the minimum angle of resolution [logMAR] best corrected visual acuity [BCVA]) due to anisometropia, strabismus, or both were eligible. Participants were randomly assigned (1:1) via a computer-generated sequence to either the EOT group (18 weeks of glasses use before patching) or to the early patching group (3 weeks of glasses use before patching), stratified for type and severity of amblyopia. All participants were initially prescribed an intensive patching regimen (10 h/day, 6 days per week), supplemented with motivational materials. The patching period was up to 24 weeks. Participants, parents or guardians, assessors, and the trial statistician were not masked to treatment allocation. The primary outcome was successful treatment (ie, ≤0·20 logMAR interocular difference in BCVA) after 12 weeks of patching. Two primary analyses were conducted: the main analysis included all participants, including those who dropped out, but excluded those who did not provide outcome data at week 12 and remained on the study; the other analysis imputed this missing data. All eligible and randomly assigned participants were assessed for adverse events. This study is registered with the International Standard Randomised Controlled Trial Number registry (ISRCTN51712593) and is no longer recruiting.

Findings Between June 20, 2013, and March 12, 2020, after exclusion of eight participants found ineligible after detailed screening, we randomly assigned 334 participants (170 to the EOT group and 164 to the early patching group), including 188 (56%) boys, 146 (44%) girls, and two (1%) participants whose sex was not recorded. 317 participants (158 in the EOT group and 159 in the early patching group) were analysed for the primary outcome without imputation of missing data (median follow-up time 42 weeks [IQR 42] in the EOT group *vs* 27 weeks [27] in the early patching group). 24 (14%) of 170 participants in the EOT group and ten (6%) of 164 in the early patching group were excluded or dropped out of the study, mostly due to loss to follow-up and withdrawal of consent; ten (6%) in the EOT group and three (2%) in the early patching group missed the 12 week visit but remained on the study. A higher proportion of participants in the early patching group had successful treatment (107 [67%] of 159) than those in the EOT group (86 [54%] of 158; 13% difference; p=0·019) after 12 weeks of patching. No serious adverse events related to the interventions occurred.

Interpretation The results from this trial indicate that early patching is more effective than EOT for the treatment of most children with amblyopia. Our findings also provide data for the personalisation of amblyopia treatments.

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Introduction

Amblyopia is the most common visual impairment of childhood, affecting 1–5% of the global population[1] and accounting for over three-quarters of attendance in children's eye clinics.[2] Unilateral amblyopia is caused by unequal inputs to the eyes during visual development, usually because of strabismus, anisometropia, or a combination of both. Untreated, amblyopia can generate lifelong visual motor deficits[3] and severe visual impairment if vision in the unaffected (contralateral) eye is lost at a later point in life.[4] Amblyopia and personal experiences during treatment can also have a psychosocial effect on children and later in life.[5]

Research in context

Evidence before this study

Amblyopia is the most common childhood visual disease, affecting 1–5% of the global population. If left untreated, amblyopia can lead to life-long serious visual impairment as well as lead to negative experiences for children receiving treatment (eg, bullying), which can affect children psychologically and socially at the time of treatment and even later in life. Optimal treatment regimens for amblyopia are far from established. Before this study, several clinical trials were published by multicentre collaboratives showing the efficacy of an extended period of glasses use only (of 4–6 months or more), called extended optical treatment, in improving vision before start of patching therapy. These studies have led to extended optical treatment becoming a mainstay of treatment for amblyopia. Extended optical treatment is included in clinical guidelines in several countries, including guidelines from the American Academy of Ophthalmology and the UK Royal College of Ophthalmologists. We searched all PubMed research articles, in any language, listed from database inception up to June 12, 2012, using the search terms "amblyopia (tiab)" OR "anisometropia (tiab)" OR "strabismus (tiab)" AND "optical (tiab)" OR "refractive (tiab)" OR "glasses". We found no published randomised controlled trials comparing extended optical treatment to a treatment group in which patching was begun earlier. In addition, a search of clinical trials registries, including ClinicalTrials.gov, the EU Clinical Trials Register, and the International Standard Randomised Controlled Trial Number registry found no planned randomised controlled trials investigating this question. A similar search was also done at the trial's midpoint on June 14, 2016. Subsequently, a similar study prescribing 2-h patching per day was launched by the Pediatric Eye Disease Investigator Group in 2020 (NCT04378790).

Added value of this study

Currently, the use of glasses for 4–6 months or more before children start patching is widely prescribed. This recommendation is based on the assumption that improving vision before patching reduces the overall amount of patching required, improving the treatment experience. This approach, however, could have the opposite effect, resulting in an extended treatment period, reducing motivation, and leading to worse visual outcomes and patient satisfaction. To our knowledge, this study is the first randomised controlled trial comparing extended glasses use before patching for the treatment of amblyopia with a control group for whom patching was begun earlier. Extended glasses use was more successful in younger children with mild amblyopia than in older children and those with more severe amblyopia. In contrast, in most children with severe amblyopia, children with larger differences in refractive errors between the eyes, and older children benefitted from starting patching early because, overall, early patching accelerated improvement in their vision. The attitudes of parents or guardians of children with amblyopia towards patching were more favourable for children patched earlier than those who underwent extended optical treatment.

Implications of all the available evidence

A systematic review and meta-analysis based on 20 publications by Asper and colleagues in 2018 showed unequivocally that vision improves during 4–6 months or more of glasses use, but not whether this improvement is better than that caused by earlier patching. The evidence from our study indicates that a personalised approach to extended glasses use is preferred. In our study, prescriptions of extended glasses use were favourable in younger children with mild amblyopia. Children with severe amblyopia, large differences in refractive errors between the eyes, and older children were less likely to benefit from glasses use alone, and the majority benefitted from early patching. We prescribed intense patching (ie, 10 h/day, 6 days per week) in our study. Future studies, comparing treatments with and without extended glasses use, are needed to establish whether the same conclusions can be drawn for different patching regimens.

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Current outcomes of patching treatment for unilateral amblyopia are poor. In the UK, for example, 30% of children treated with patching do not reach the best corrected visual acuity (BCVA) of 6/12 (ie, the ability to read, at a distance of 6 m, something that someone with no visual impairment can read from 12 m away) in the amblyopic eye, often after several thousand hours of prescribed patching.[6] Poor adherence to patching, which can happen as a consequence of reduced vision while patching the contralateral eye or of social and educational issues, has been identified as an important barrier to the attainment of improvement in BCVA.[7] In addition, personalised approaches for the treatment of amblyopia on the basis of factors such as age, type of amblyopia, and baseline visual deficit are not widely available.[3] Such personalised approaches could potentially increase the likelihood of treatment success and reduce the duration of treatment, costs, and burden of amblyopia on individuals, their families, and health-care services.[8]

Amblyopia is usually treated first with a period of glasses use to correct for refractive errors, followed by patching of the contralateral eye. Several studies, including a meta-analysis, found a moderate to large effect size from the glasses-only period before commencing patching,[9–15] which significantly decreased for children who commenced treatment when they were older.[9] However, whether parameters such as severity of amblyopia or refractive error and type of amblyopia have a role in the success of treatment with glasses is unclear.

These reported results have led to the notion that all children with amblyopia should be prescribed an extended period of glasses use (also called extended optical treatment [EOT] or refractive adaptation) before the start of the patching treatment.[12] The rationale behind this approach is to improve vision before patching, reduce difficulties during patching, or (in some children) avoid the need of patching altogether. Current guidelines from various countries, including from the American Academy of Ophthalmology and the UK Royal College of Ophthalmologists, recommend EOT until visual improvement plateaus, or up to 16–22 weeks before patching.[16,17]

See Online for appendix

However, extending the overall treatment period with a lengthy phase of only wearing glasses could result in reduced motivation and reduced adherence to patching and glasses use during later treatment, potentially slowing the overall improvement in vision. Younger children are more responsive to patching than older children; therefore, delaying the start of patching through EOT might also reduce visual improvements.[18]

To date, no trials have directly compared patching treatment with and without EOT. In addition to improvement in vision, outcome measures that should be studied include: the required amount of patching for improvement, as prescribed by the clinician or as administered by parents or guardians; improvements in stereovision; attitudes of the children and parents or guardians towards treatment; and the cost and duration of treatment (especially because different durations of treatment can affect study dropout rates unequally, which would need to be accounted for).

We aimed to perform the first randomised controlled trial to assess the effects of an intensive patching regimen with and without previous EOT. This regimen was planned on the basis of results from our previous two studies[19,20] comparing five treatment regimens across a 12-week patching period in which patching was electronically monitored; we found that the best visual improvements were seen in participants prescribed patching for 10 h/day, 6 days per week, supported with an educational intervention. We also aimed to explore success after 18 weeks and 24 weeks of patching, adherence to glasses use and patching, and the parent's or guardian's and child's perception of the treatments.

Methods

Study design and participants

EuPatch was an unmasked, parallel, two-armed, randomised controlled trial comparing amblyopia treatment with and without EOT (figure 1), conducted at 30 hospital sites across the UK, Greece, Austria, Germany, and Switzerland between 2013 and 2020 (appendix pp 2–3). The UK sites received national ethics approval, and all continental European sites received ethical approval from their local ethics committees. Because the regimens in both treatment groups are current clinical practice, the ethics committee (National Research Ethics Service Committee East Midlands, Derby, UK) confirmed that a data safety monitoring board was not required. The study adhered to the tenets of the Declaration of Helsinki. The trial protocol is available online.[21]

Eligible participants were children aged 3–8 years with newly diagnosed, untreated amblyopia, defined as an interocular difference at least 0·30 logarithm of the minimum angle of resolution (logMAR) BCVA at baseline, caused by anisometropia, strabismus, or a combination of both (mixed amblyopia). Other eligibility criteria included a clinically significant refractive error (ie, ≥1·5 dioptres spherical equivalent in at least one eye, or ≥1·0 dioptre of anisometropia); ability to perform the logMAR Crowded test of visual acuity (Keeler, Windsor, UK); and no previous use of glasses or other amblyopia treatment; full inclusion and exclusion criteria are listed in the appendix (p 4). Participants were initially screened for eligibility at each recruiting site through the reviewing of participant notes made by clinicians at the local site before the glasses prescription was available. After participants received their new glasses prescription, eligibility of participants was confirmed by the local site coordinator via a detailed screening assessment performed at the baseline visit, at which point participants were randomised. Information from each recruiting site was then reviewed centrally to reconfirm eligibility by the study coordinator. The child's sex was reported by the parent or guardian. Written informed consent was

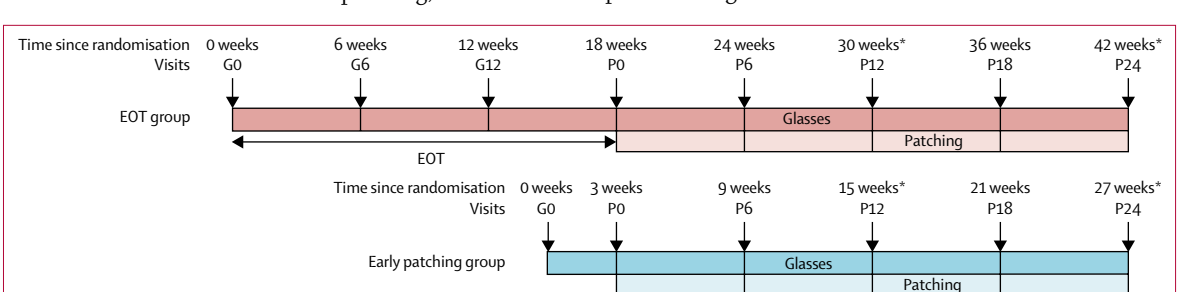


Figure 1: **Study design**

Arrows indicate orthoptic examination timepoints. G0 to G12 indicate the number of weeks of only glasses use and P0 to P24 indicate the numbers of weeks of patching. The primary outcome was assessed at P12 (ie, after 12 weeks of prescribed patching in the two treatment groups). Secondary outcome assessments were performed at P18 and P24. EOT=extended optical treatment. *Timepoints at which questionnaires were administered.

obtained from each participant's parent or guardian and assent was obtained from children whenever applicable (ie, usually on children older than 4 years).

Randomisation

Participants meeting the inclusion criteria were randomly assigned (1:1) to the EOT group (ie, use of glasses for 18 weeks followed by patching and use of glasses for 24 weeks) or to the early patching group (use of glasses for 3 weeks followed by patching and use of glasses for 24 weeks), with a stratified, balanced block design with a block size of four (ie, EOT with electronic monitoring of patching or glasses use; EOT without monitoring; early patching with monitoring; and early patching without monitoring). 50% of participants in each treatment group were randomly allocated electronic dose monitors for assessment of adherence to glasses use and patching. Stratification was done according to type (anisometropic, strabismic, or mixed) and severity (severe [ie, amblyopic eye BCVA ≥0·60 logMAR] or mild to moderate [ie, <0·60 logMAR]) of amblyopia. Randomisation was not stratified on the basis of the centre due to the small number of participants in some centres.

Randomisation was done by the local investigator using a secure online randomisation service (Sealed Envelope, London, UK) that assigned participants to treatment groups and could be accessed locally at sites. The local investigator communicated the assigned group information to the participants and was responsible for subsequent examinations and treatment. Participants, parents or guardians, assessors, and the trial statistician were not masked to study treatments.

Procedures

Before enrolment, potential participants received a full ophthalmological examination, including a cycloplegic refraction. At this examination, participant information for the study was provided and the glasses prescription was issued but not yet worn. After informed consent was obtained, participants were enrolled in the study, randomly assigned to a treatment group, and requested to wear glasses during all waking hours from the date of first examination (time G0; figure 1). Both groups were prescribed an intensive patching regimen, supplemented with motivational materials to improve adherence to the use of glasses and patching. Participants in the EOT group were assigned 18 weeks of full-time glasses use, followed by 24 weeks of combined patching and glasses use. Participants in the early patching group were assigned 3 weeks of full-time glasses use followed by 24 weeks of combined patching and glasses use.

Patching was initially recommended for 10 h per day, 6 days per week (with one non-occluding day chosen by families), with the patching hours modified at the discretion of the orthoptist or ophthalmologist after improvement of visual acuity, if the treatment endpoint was reached, or if adverse effects occurred. In participants assigned electronic monitoring, electronic dose monitors were placed on the frame of glasses or between two occlusion patches (Ortopad Elite, Pietrasanta Pharma, Lucca, Italy) to monitor glasses use and patching.[22] All data from electronic dose monitors were analysed in the University of Leicester (Leiceister, UK); feedback from the monitors was not provided to participants or treating orthoptists at any time.

The EOT group received eight orthoptic assessments over 42 weeks and the early patching group received six assessments over 27 weeks (figure 1). A deviation of 1 week for each orthoptic assessment was permitted. Each 6-weekly assessment included measurements of uniocular BCVA with the logMAR Crowded test and stereoacuity (a measure of depth perception) with the Frisby Near Stereotest (Stereotest, Thame, UK). Many participants were unable to resolve the 6 mm plate at 30 cm (ie, the lowest stereoacuity measurement, equivalent to 600"), especially for early examinations, and were assigned a value of 1200" to enable statistical analysis. After the trial, children returned to clinical care if further treatment was required.

The Amblyopia Treatment Index questionnaire, developed by the Pediatric Eye Investigator Group (PEDIG), was administered after 12 weeks and 24 weeks of prescribed patching to record the attitudes towards treatment of parents or guardians (appendix pp 16–19).[23] Some questions were modified to include perspectives on the use of glasses in addition to patching. The children's perspectives were recorded with the Smiley Face Likert scale. Data were recorded at each site and collated and analysed centrally at the University of Leicester, UK.

Outcomes

The primary outcome was the proportion of successfully treated children (ie, reaching ≤0·20 logMAR interocular difference in BCVA) after 12 weeks of prescribed patching. A threshold of success of logMAR of less than or equal to 0·10 was originally planned, as stated in the protocol. However, this threshold falls within the normal variability of BCVA measurements in children.[24] Hence, a decision was made by lead investigators to adjust this threshold to less than or equal to 0·20 on May 13, 2021. This amendment was made before the statistician viewed the data and commenced statistical analysis. Children who dropped out of the study were recorded as not having responded to treatment without data imputation. Prespecified secondary exploratory outcomes were the proportion of successfully treated children after 18 weeks and 24 weeks of prescribed patching; total hours of prescribed patching required; electronic dose monitor-measured compliance to glasses use and patching; and responses of parents, guardians, and children to questionnaires about the treatment. Post-hoc secondary exploratory outcomes were the proportion of successfully treated children according to other definitions of

treatment success (ie, ≤0·10 and ≤0·30 logMAR interocular difference in BCVA); the proportion of successfully treated children after imputation of missing values by use of multiple imputation methods for study dropouts or missed visits; time to reach successful treatment, assessed with a time-to-event analysis; the determination of characteristics of participants most likely to respond to EOT treatment without patching by constructing a decision tree with a recursive partitioning method; and changes in stereopsis between baseline and after 12 weeks of patching.

Statistical analysis

The sample size was based on our previous studies[19,20] recording BCVA outcomes over a 12-week patching timeframe. In Pradeep and colleagues' study,[20] success after 12 weeks of patching without EOT (10 h/day, 6 days per week) was 23% (≤0·10 logMAR interocular difference in BCVA). Accordingly, a 15% difference in success—the same difference in success observed between the two patching regimens in Awan and colleagues[19]—required 173 participants in each arm (two-sided α of 0·05, power 80%, and a 15% dropout rate).

The primary analysis was done in a modified intention-to-treat (mITT) population consisting of all randomly assigned participants, including those who dropped out, but excluding those who were deemed ineligible after randomisation. A full ITT analysis of all randomised participants was initially planned; however, we did not anticipate the randomisation of several ineligible participants after glasses had been prescribed and worn. Hence, a decision was made by the lead investigators on May 13, 2021, to use the mITT design outlined here, performed both with and without imputation of missing values. The main primary analysis was performed in all participants in the mITT population for whom data were available for the primary outcome visit with no imputation for missing values (treatment was deemed unsuccessful in participants who dropped out of the study), and another analysis was performed including all participants in the mITT population, imputing missing data with the multiple imputation by chained equations approach for missing values. Pearson's χ^2 tests were used to compare success rates for the primary outcome after 12 weeks of prescribed patching, after 18 weeks and 24 weeks of prescribed patching, and with other definitions of success (ie, ≤0·10 and ≤0·30 logMAR interocular difference in BCVA).

Several secondary analyses were decided post-hoc because a formal statistical analysis plan was not included at the time the trial was originally planned. A Kaplan–Meier analysis was used to estimate median time from the initiation of patching (ie, start and origin) to time of treatment success or end of follow-up (at week 24 of patching). The analysis included all participants, from both study groups, who provided measurements at the visit at which patching commenced (ie, P0; figure 1), along with at least one follow-up visit, but excluded participants who had already reached success by P0. The median time to treatment success between groups was compared with the log-rank test. The probability of treatment success was calculated with the formula recommended by Spruance and colleagues[25] (ie, probability=HR/[1+HR]), with HR being the hazard ratio from a Cox regression model, adjusted for age at baseline, sex, type of amblyopia (ie, anisometropic, strabismic, or mixed), and amblyopic eye BCVA at baseline. The proportionality assumption behind the Cox model was evaluated with Schoenfeld residuals and met.

To assist clinical decision making for future amblyopia treatment, we constructed a decision tree for responses to EOT based on children's demographic and clinical characteristics. We included data only from the EOT group after 18 weeks of glasses use before start of patching. The recursive partitioning method[26] was used through identification of the optimal split of predictor variables that would partition the data into outcome groups (treatment success *vs* treatment failure). Finally, we calculated the sensitivity and specificity of the decision tree for prediction of treatment success during the EOT period. External validations of the decision tree were performed with data provided by three study groups: the US PEDIG collaborative,[10,15] the UK Monitored and Randomised Occlusion Treatment of Amblyopia Studies (MOTAS and ROTAS) collaborative,[14,27,28] and a previous study by the Ulverscroft Eye Unit, Leicester, UK.[22] The same criteria for the main trial were used to include data, with a BCVA assessment required at 18 weeks (plus or minus 1 week) after use of glasses commenced.

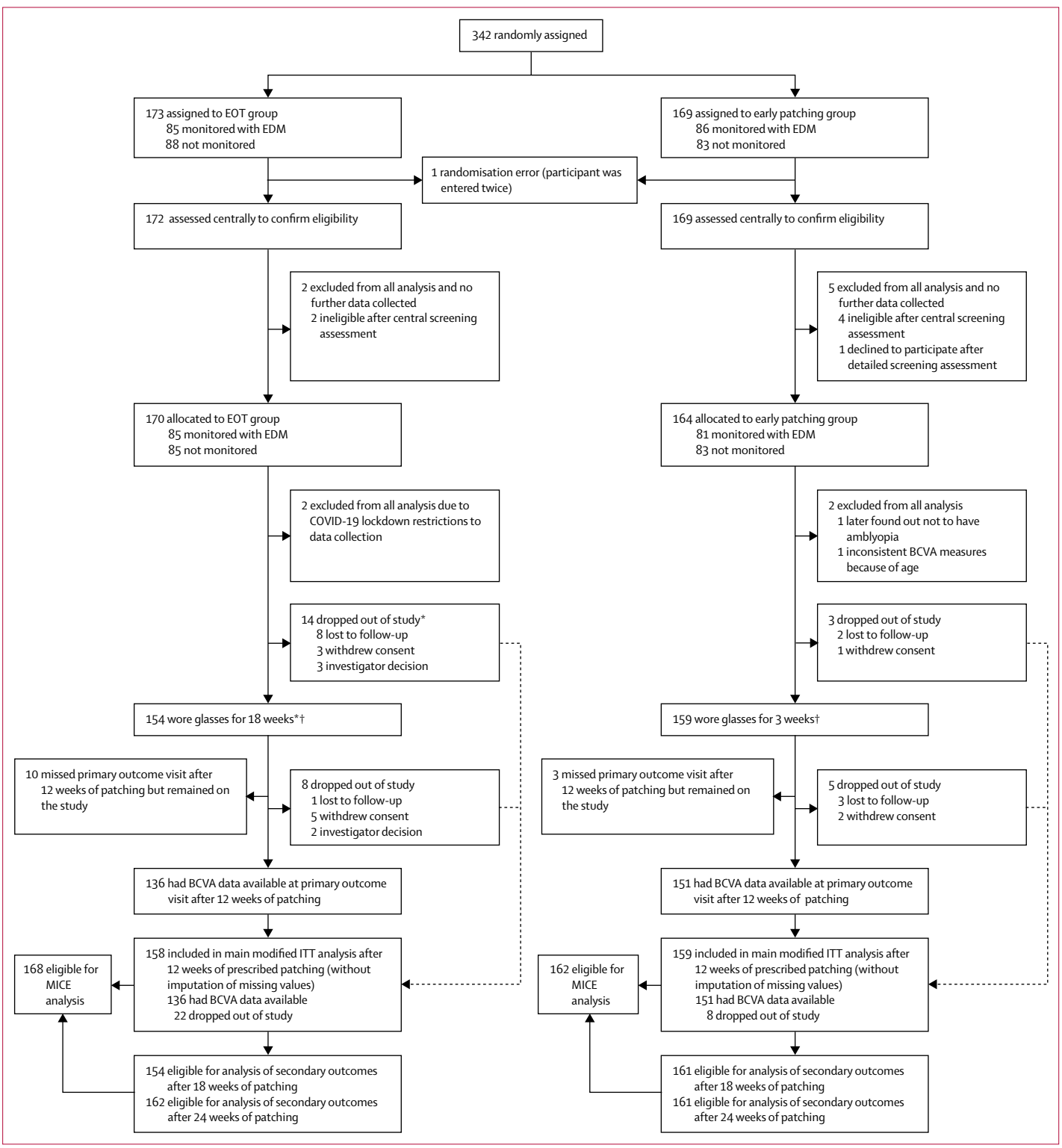
Change in prescribed patching hours throughout the patching period was compared with generalised linear estimating equations, adjusted for type and severity of amblyopia and centre, and including an interaction

Figure 2: **Trial profile**

Since screening for participant eligibility consisted of reviewing several tens-of-thousands of clinical notes, the number of participants screened was not recorded. BCVA=best corrected visual acuity. EDM=electronic dose monitor. EOT=extended optical treatment. ITT=intention-to-treat. MICE=multiple imputation by chained equations approach for missing values. *A total of 163 children were included in a post-hoc analysis to assess characteristics of responders and non-responders to EOT after 18 weeks of glasses use alone (before start of patching) by constructing a decision tree using a recursive partitioning method: 147 children who completed 18 weeks (±1 week) of glasses use with available BCVA data, one child who completed 23 weeks, one child who completed 24 weeks of glasses use and had available BCVA data at 18 weeks (±1 week), and 14 children who dropped out of the study before completing 18 weeks of glasses use. †Eight participants deviated from the glasses-use protocol but were included in both modified ITT analyses, including four children in the EOT group who received 23–36 weeks of glasses use and four children in the early patching group who received 7–11 weeks of glasses use. Four participants in the EOT group and two in the early patching group missed the visit after 18 weeks of glasses use but received the correct duration of glasses use and remained on the study; due to missed visits, these participants commenced patching later than stated in the protocol.

term between time (in 6-week intervals) and group. Electronically monitored glasses use and patching were compared with χ^2 tests.

The between-group differences in the change in the number of octaves of stereoacuity (a measure of depth perception analysed in octave changes—distinct from



visual acuity measured in logMAR) for each participant between baseline and after 12 weeks, 18 weeks, and 24 weeks of patching were compared with Kruskal's γ statistic.

Questionnaire data from parents or guardians and children were analysed by aggregating individuals' responses into a single score, reflecting an overall perception of the intervention (appendix pp 16–19). This score was then dichotomised into positive (including positive and strongly positive responses) and negative (including strongly negative, negative, and neutral). We compared the difference in the proportion of individuals in the two categories at the primary timepoint and the final visit between groups using the χ^2 test.

For all randomly assigned participants, adverse events were reported to clinicians at study sites during research visits and compared descriptively between the groups.

All statistical tests were two-sided (significance threshold p=0·05). R (version 4.1; survival, rpart, and caret packages) was used for data management and data analysis. The trial is registered with the International Standard Randomised Controlled Trial Number registry (ISRCTN51712593) and is no longer recruiting.

	EOT (n=170)	Early patching (n=164)
Age, years	5·2 (4·2–5·7)	5·4 (4·7–5·9)
Sex		
Female	69 (41%)	77 (47%)
Male	101 (59%)	87 (53%)
Not recorded	1 (1%)	1 (1%)
Type of amblyopia		
Anisometropic	115 (68%)	116 (71%)
Mixed	41 (24%)	34 (21%)
Strabismic	14 (8%)	14 (9%)
Spherical equivalent, dioptres		
Amblyopic eye	4·00 (2·50–5·00)	3·88 (2·75–5·25)
Contralateral (unaffected) eye	1·00 (0·25–2·25)	1·25 (0·38–2·25)
Baseline BCVA, logMAR		
Amblyopic eye	0·675 (0·500–0·800)	0·663 (0·550–0·800)
Contralateral (unaffected) eye	0·100 (0·050–0·180)	0·100 (0·025–0·175)
Baseline interocular visual acuity difference	0·525 (0·400–0·681)	0·550 (0·425–0·700)
Amblyopia severity		
Mild to moderate	66 (39%)	54 (33%)
Severe	104 (61%)	110 (67%)
Ethnicity		
White British	120 (71%)	122 (74%)
White Irish	8 (5%)	3 (2%)
White, other	14 (8%)	5 (3%)
Asian	16 (9%)	17 (10%)
Chinese	0	1 (1%)
Black or Black British	4 (2%)	6 (4%)
Mixed	6 (4%)*	7 (4%)†
Other	1 (1%)‡	1 (1%)§
Not recorded	1 (1%)	2 (1%)
Index of Multiple Deprivation (UK participants only)		
Mean (SD)	5·8 (3·0)	5·8 (2·9)

Data are median (IQR) or n (%), unless otherwise specified. Ethnicity based on parental report. BCVA=best corrected visual acuity. EOT=extended optical treatment. logMAR=logarithm of the minimum angle of resolution. *White and Black African (n=2), Mixed not further specified (n=2), White and Black Caribbean (n=1), and White and Thai (n=1). †White and Asian (n=2), White and Black African (n=1), White and mixed Black Caribbean and Indian (n=1), Arab (n=1), Romany (n=1), and Mixed not further specified (n=1). ‡Iraqi. §Irish Traveller. ¶135 participants in the EOT group and 135 participants in the early patching group were recruited from the UK.

Table: **Baseline characteristics**

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between June 20, 2013, and March 12, 2020, after an initial eligibility assessment by the local centre, 342 participants were recruited and randomly assigned (173 to the EOT group and 169 to the early patching group; figure 2). Recruitment was interrupted by the start of restrictions due to the COVID-19 pandemic and therefore ended with five participants short of the target. One participant was incorrectly assigned to both groups and was excluded from the modified ITT analysis without imputation due to missing data, but included with imputation in the early patching group. Detailed screening assessment performed at the baseline visit identified six participants as ineligible. One further participant withdrew consent. Consequently, 334 participants were eligible, resulting in the allocation of 170 participants to the EOT group and 164 to the early patching group. Four participants were subsequently excluded because data could not be collected (two in the EOT group due to COVID-19 restrictions, one in the early patching group was later discovered as not having amblyopia, and one in the early patching group could not reliably perform the logMAR Crowded test). A further 14 participants dropped out of the EOT group and three dropped out of the early patching group during the glasses use period.

Consequently, 154 participants in the EOT group wore glasses for at least 18 weeks and 159 participants in the early patching group wore glasses for at least 3 weeks. Eight participants wore glasses for longer than defined in the protocol (four in the EOT group for 23–36 weeks and four in the early patching group for 7–11 weeks, mainly due to missed and late appointments). All participants with protocol deviations were included in the mITT analysis.

The primary outcome analysis, after 12 weeks of prescribed patching, included 158 participants from the EOT group and 159 from the early patching group, of

which 136 participants (86%) from the EOT group and 151 participants (95%) from the early patching group provided BCVA measurements; 22 participants (14%) from the EOT group and eight participants (5%) from the early patching group were lost to follow-up. Treatment success or failure could not be accurately assessed in ten participants (6%) from the EOT group and three participants (2%) from the early patching group because they missed the primary outcome visit and so these participants were excluded from the main primary analysis but were included in the imputation analysis.

The baseline characteristics of allocated participants are shown in the table. Median follow-up was 42 weeks (IQR 42–42) in the EOT group and 27 weeks (27–27) in the early patching group.

For the primary outcome, a significantly larger proportion of children had a successful treatment (ie, ≤0·20 logMAR interocular difference in BCVA) in the early patching group (107 [67%; 95% CI 60–75] of 159) than in the EOT group (86 [54%; 46–62] of 158) after 12 weeks of prescribed patching (13% difference; p=0·019). Similar patterns were observed with the imputation of missing values (appendix p 6). A breakdown of children reaching thresholds from 0·00 to 0·50 logMAR interocular difference in BCVA in 0·1 increments, including for different types of amblyopia, after 12 weeks and 24 weeks of patching is shown in figure 3. Results at baseline and at each visit spanning the patching period, without and with imputation of missing values, are available in the appendix (pp 5–6). The time course of improvement in mean interocular difference in BCVA across the study without imputation of missing data is shown in figure 4; equivalent data with missing data imputed are also shown in the appendix (p 7). The improvement in interocular difference in BCVA during EOT, with glasses use only, occurred mostly during the first 6 weeks, with the mean change of 0·127 logMAR (SD of

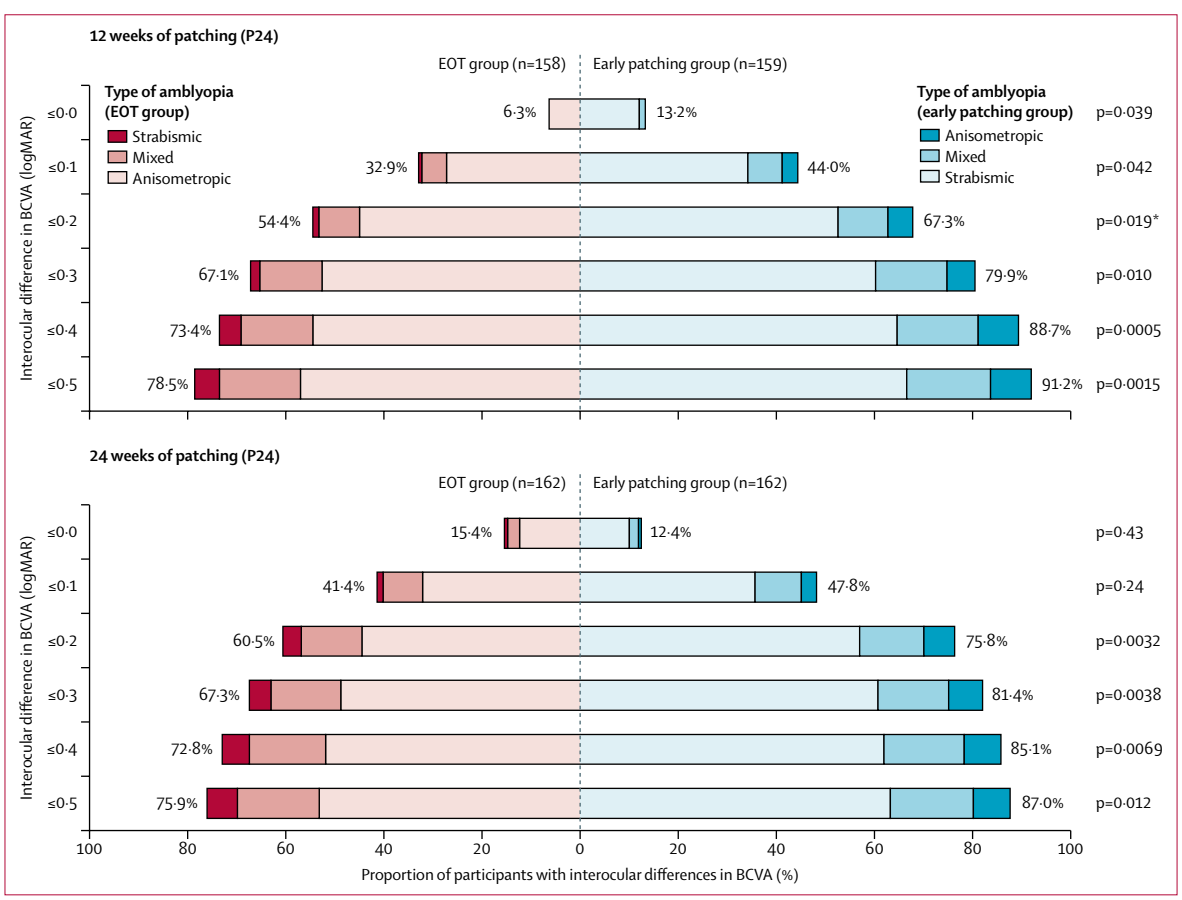


Figure 3: **Proportion of participants reaching interocular differences in visual acuity at the primary outcome and end of study (without imputation of missing values)**

Different shades of colour show the breakdown by type of amblyopia (anisometropic, mixed, strabismic) for the primary outcome (12 weeks of patching) and the final outcome (24 weeks of patching). Statistical comparisons between the EOT group and the early patching group were done with χ^2 tests. The two panels represent the timepoints indicated by P12 and P24 on figure 1. For each panel, the proportions of participants reaching the thresholds of improvement indicated on the y axis are provided for the EOT group (red) and for the early patching group (blue). The percentage values provided are for all participants in each group. *EOT=extended optical treatment. logMAR=logarithm of the minimum angle of resolution. The primary outcome (ie, ≤0·20 logMAR interocular difference at 12 weeks). BCVA=best corrected visual acuity.

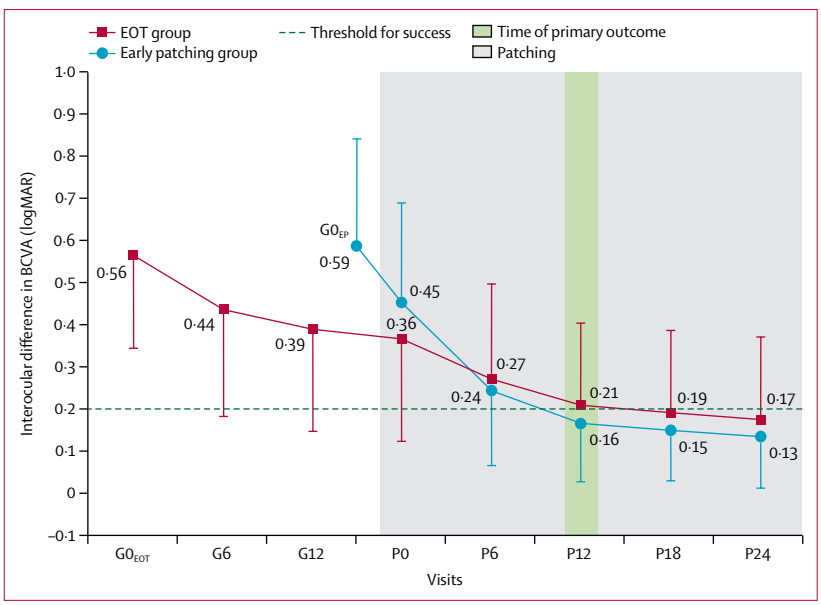


Figure 4: **Time course of changes in interocular differences in BCVA throughout the study, without imputation of missing values and excluding study dropouts**

Means and SDs of interocular differences in BCVA are shown, with the EOT group data shown in red squares and the early patching group data shown in blue circles. G0, G6, and G12 indicate weeks of glasses use; P0, P6, P12, P18, and P24 indicate weeks of patching. The threshold for successful treatment is indicated by the dashed line. BCVA=best corrected visual acuity. EOT=extended optical treatment. $G0_{EP}$=week 0 of glasses use in the early patching group. logMAR=logarithm of the minimum angle of resolution.

differences 0·161) from 0 weeks to 6 weeks being almost twice as large as that occurring between 6 weeks and 18 weeks (mean change 0·061 logMAR [0·120]). The change of 0·127 logMAR (0·161) in the EOT group from 0 weeks to 6 weeks was similar to that occurring in an even shorter period from 0 weeks to 3 weeks in the early patching group (mean change 0·133 logMAR [0·170]). For the participants who reached a 0·10 logMAR difference in BCVA or less after EOT, 14 participants were prescribed 0 h/day of patching, eight were prescribed 2–4 h/day of patching, and two were prescribed 10 h/day of patching for the initial 6 weeks of patching. Neither of the two participants who were prescribed 10 h of patching showed reverse amblyopia; one of these participants improved in stereoacuity by two octaves and the other remained stable.

During 18 weeks of EOT, the mean improvement was 0·190 logMAR (SD of differences 0·183; effect size 1·035 [95% CI 0·835–1·232]) for the interocular difference in BCVA, and 0·255 logMAR (0·191; 1·337 [1·116–1·557]) for BCVA in amblyopic eyes. When patching commenced, the mean interocular difference in BCVA was better in the EOT group than in the early patching group, but accelerated improvement in the early patching group resulted in better interocular difference in BCVA after 12 weeks of prescribed patching, which continued to the end of the trial. After 12 weeks of prescribed patching, the mean interocular difference in BCVA was worse in the EOT group (0·209 logMAR [SD 0·195]) than in the early patching group (0·162 logMAR [0·157]; p=0·026).

For secondary outcomes without imputation of missing data, significantly more children had treatment success in the early patching group than in the EOT group after 18 weeks and 24 weeks of prescribed patching (figure 3; appendix p 8). Similar patterns were observed with imputation of missing values (appendix pp 6, 8). Statistically significant differences between groups were also apparent in the proportion of children having successfully reached 0·30 logMAR interocular difference in BCVA or better (except after 24 weeks of patching with imputation of missing values; appendix p 8). For the proportion of children having successfully reached 0·10 logMAR interocular difference in BCVA or better, significant differences between the groups were only observed after 12 weeks of patching without imputation of missing values and after 18 weeks of patching with imputation of missing values.

In the time-to-event analysis, the Kaplan–Meier estimate (n=255) of the median time from start of patching to treatment success was 12 weeks (95% CI 6–12) in the early patching group and 18 weeks (12–not calculable) in the EOT group (p=0·0001; appendix p 9). Children in the early patching group had a 67% (95% CI 60–73) higher probability of treatment success after commencing patching compared with the EOT group. The multivariable Cox proportional hazards regression model found that older age and higher amblyopic eye BCVA at baseline were significantly associated with a longer time to success (appendix p 10).

In the EOT group (without imputation of missing values), 44 (27%) of 163 children had treatment success (ie, ≤0·20 logMAR interocular difference in BCVA) after 18 weeks of glasses use before commencement of patching (appendix p 8). Age, amblyopic eye BCVA at baseline, and interocular difference in spherical equivalent (but not type of amblyopia) were identified as the most important variables by the partitioning model to assess success of EOT before patching (appendix p 11). A decision tree showing probabilities of success, including these variables, is given in figure 5. The decision tree had 83% (95% CI 76–88) internal accuracy, 68% (52–81) sensitivity, and 88% (81–94) specificity. External validations of the decision tree were assessed in 326 participants from the US PEDIG collaborative[10,15] (of which 103 met our inclusion criteria [appendix p 4]), 223 participants from the UK MOTAS and ROTAS collaborative[14,27,28] (of which 18 met our inclusion criteria), and 40 participants from the Ulverscroft Eye Unit group in Leicester, UK[22] (of which 32 met our inclusion criteria). The UK data, which used similar visual acuity tests to the current study, generated a higher accuracy score (90% [95% CI 78–97]; sensitivity 67% [38–88]; specificity 100% [90–100]) compared with the US data (62% [52–72]; sensitivity 52% [37–67]; specificity 70% [57–82]).

There were no significant differences between groups in stereoacuity improvement from baseline to 12 weeks

(p=0·34; appendix p 12), 18 weeks (p=0·11), or 24 weeks (p=0·11) of patching.

The median hours of prescribed patching dropped from the first 0–6 weeks of the patching period to the final 18–24 weeks in both groups (appendix p 13). However, possibly because of a higher rate of improvement in the early patching group, the reduction in prescribed patching hours was more pronounced in the early patching group than in the EOT group (interaction between group and time p=0·0063).

Electronic dose monitor measurements were unavailable for 749 (45%) of 1664 recordings (appendix pp 13–14). Median electronically recorded adherence to glasses use was above 70% of waking hours during both the 18 weeks of glasses use only in the EOT group and 3 weeks of glasses use only in the early patching group, and during the patching phase of the trial (appendix p 14). Median electronically recorded adherence to patching was above 70% of that prescribed and similar between the groups. There were no significant between-group differences in electronically monitored glasses use or patching for any trial phase (data not shown). There were also no significant differences in interocular difference in BCVA after 12 weeks, 18 weeks, or 24 weeks of patching between participants allocated to electronic dose monitors compared with those not allocated (data not shown).

We observed broadly positive attitudes to glasses use overall for children (ie, happy when wearing glasses) and parents (ie, perceiving glasses use not to be particularly burdensome). The proportion of positive responses was 80% or higher for both adults and children at 12 weeks and 24 weeks of patching, with no significant differences between groups (appendix p 15). In adults, attitudes towards patching were significantly more positive in the early patching group than in the EOT group (p=0·0007 for the difference in the proportion of responses after 12 and 24 weeks of patching). Children's attitudes towards wearing patches were less positive compared with adults (66 [38%] of 175 children had a positive response at 12 weeks of patching and 72 [38%] of 188 had a positive response at 24 weeks *vs* 175 [83%] of 211 adults at 12 weeks and 171 [82%] of 209 adults at 24 weeks), with no significant difference between children in the two groups (appendix p 15).

No serious adverse events related to the interventions in either treatment group were reported by parents or guardians. Two serious adverse events unrelated to treatment—a broken arm (EOT group) and a tonsillectomy (early patching group)—occurred during the trial and were reported to the study sponsor (University of Leicester, Leicester, UK).

Discussion

This study is the first prospective randomised controlled trial to directly compare EOT before patching and patching without EOT in children with amblyopia. EOT is currently the mainstay treatment for amblyopia included in clinical guidelines in numerous countries.[29,30] We conclude that early patching, with only 3 weeks of glasses use before patching, resulted in a significantly higher rate of treatment success after 12 weeks of patching than EOT, which required 18 weeks of glasses use before patching (treatment success 67% [95% CI 60–75] in the early patching group *vs* 54% [46–62] in the EOT group). Similar outcomes were also observed with definitions of treatment success beyond that of the primary endpoint, other timepoints, and with imputation of missing values. Vision improvement was faster in the early patching group, with a median time to successful treatment of 12 weeks (95% CI 6–12) of patching in the early patching group and 18 weeks (12–not calculable) of patching in the EOT group. Attitudes of parents or guardians were more positive towards patching in the early patching group than in the EOT group. The rate at which patching was reduced in the early patching group was also faster than in the EOT group. Children younger

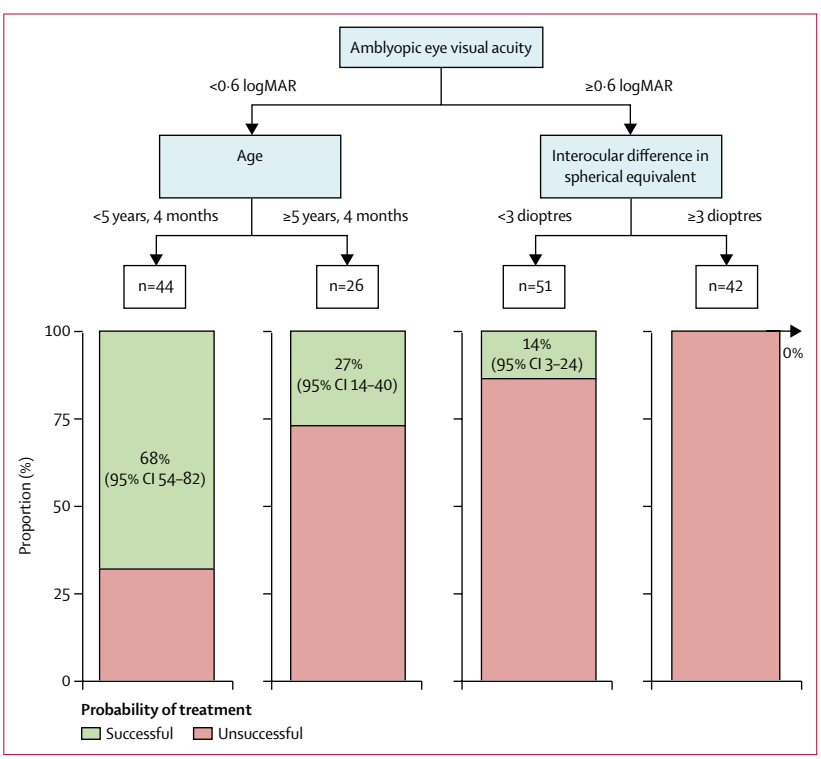


Figure 5: **Decision tree for probability of treatment success with EOT**
To assist in future clinical decision making, this decision tree shows the probability of successful treatment (with 95% CIs) with EOT only (before patching) on the basis of study participants' demographic and clinical characteristics. We included 163 children in the EOT group and used the recursive partitioning method. The sample of 163 participants included 149 children who had BCVA measurements available after 18 weeks of glasses use (including two participants who continued to wear glasses for 23 weeks and 24 weeks and were excluded from the primary outcome analysis after 12 weeks of patching) and 14 children who had dropped out before measurements were obtained at 18 weeks of glasses use. Using recursive partitioning, we identified the optimal split of predictor variables that would partition the data into outcome groups (successful treatment *vs* unsuccessful treatment). Finally, sensitivity and specificity of the decision tree for predicting successful treatment during the EOT period was calculated. Age, amblyopic eye BCVA at baseline, and interocular difference in spherical equivalent remained in the model. BCVA=best corrected visual acuity. EOT=extended optical treatment. logMAR=logarithm of the minimum angle of resolution.

than 5 years and 4 months with less severe amblyopia (BCVA <0·60 logMAR) were more likely to respond to EOT than older children and those with more severe amblyopia (≥0·60 logMAR). Older children with more severe amblyopia and larger interocular differences in spherical equivalent benefitted more from initiating patching without undergoing EOT than younger children with less refractive error. These findings are useful for the optimisation of treatment strategies and support the design of interventions tailored to the needs of children with different characteristics.

Numerous studies have measured the improvement in BCVA during optical treatment without including a suitable control group with no optical treatment. The improvement of 0·248 logMAR we observed for BCVA in amblyopic eyes over 18 weeks of EOT was similar to that of previous reports.[15,28] Higher rates of resolution (ie, reaching ≤0·1 logMAR interocular difference) than those seen in our study have been reported in previous studies during EOT, which could be explained by a difference in age, type of amblyopia, and severity of amblyopia and refractive error in participants in those studies compared with our own.[10,28] In particular, it has been reported that only 5·6% of children with anisometropia who have severe amblyopia[3] have resolution of symptoms after 18 weeks of EOT.[11] Previous EOT studies have been collated in a meta-analysis[9] in which the combined effect size of improvement in amblyopic eye BCVA was estimated to be 1·07 (95% CI 0·58–1·55). The effect size in our EOT cohort was better at 1·308 (95% CI 1·101–1·513), indicating a relatively effective treatment regimen for EOT.

Most of the improvement in vision occurred in the first 3–6 weeks of glasses use (0·133 logMAR improvement in the interocular difference in BCVA in the early patching group after 3 weeks and 0·127 logMAR improvement in the EOT group after 6 weeks) with only a 0·061 logMAR improvement occurring between weeks 6 and 18 in the EOT group (figure 4; appendix p 7).

Binocular outcomes are also an important consideration, especially given that EOT engages binocular mechanisms in contrast to patching. Wang and colleagues[31] have shown, in a small sample of 14 people with anisometropia, who were on average older than our cohort, that EOT benefits binocular perception. In our trial, there was no difference in the change of stereoacuity between EOT and early patching at either primary or secondary outcome timepoints.

During the patching phase, an accelerated improvement in interocular difference in BCVA occurred in the early patching group compared with the EOT group, with better vision in the early patching group compared with the EOT group from 12 weeks of patching onwards. Visual improvement during the 12-week patching period in both groups was similar to that reported in previous studies that used similarly intense patching regimens.[22,28,32] Based on the time course (figure 4; appendix p 7), it is possible that the EOT group continued to improve after the end of the trial.

An argument in favour of EOT assumes that fewer hours of prescribed patching are required to achieve good visual outcomes than with any early patching regimen, meaning that children are potentially exposed to less stigma and bullying and making treatment easier for children as well as for parents and guardians. The amount of prescribed and electronically monitored patching was not significantly different between the two groups, although a wide variation was observed (appendix pp 13–14). Electronic dose monitor measurements were not available for 45% of recordings. Improvements could be made to electronic monitors by increasing reliability, improving the appearance, or incorporating monitors into glasses or patches.

Attitudes of parents or guardians were significantly more favourable towards patching in the early patching group than in the EOT group. The prescribed number of patching hours over the trial decreased significantly faster in the early patching group, which might, along with the accelerated improvement in vision, have generated a more positive view that patching was working. Intense patching (ie, 10 h/day), including the use of an educational intervention, was recommended as the starting dose in this study with the aim of keeping the whole treatment period as short as possible. This dose was based on the results of our previous study, in which this approach was found to be an effective way to improve adherence to patching.[20] The ongoing PEDIG study (NCT04378790) will establish whether similar results apply to lower dosages of patching. The adherence to patching recorded in this study was higher than previously reported,[19,20,28] which is possibly due to an over-representation of more highly motivated participants who continued using the monitors, influenced by the extended duration of the study.

Age, amblyopic eye BCVA at baseline, and interocular difference in spherical equivalent were identified as key factors affecting success of treatment with glasses at the end of the EOT period. The decision tree (figure 5) indicates that children with less severe amblyopia (amblyopic eye BCVA <0·60 logMAR at baseline) and children younger than 5 years, 4 months are the most likely to respond to EOT. By contrast, children with severe amblyopia (BCVA ≥0·60 logMAR at baseline) and substantial anisometropia (interocular difference of ≥3 dioptres spherical equivalent) show a very low likelihood of responding to EOT. These findings can contribute to better discussions with families of the advantages and disadvantages of each approach to treating amblyopia—a step towards personalised treatment strategies, which is still an unmet clinical need for this condition.

A different loss to follow-up between groups is a known source of bias in clinical trials. The attrition rate in the study was relatively low at 9% overall (30 of 330; 13% [22 of 168] in the EOT group and 5% [eight of 162] in

the early patching group). This anticipated problem was built into the study design with an mITT approach in which all participants lost to follow-up and those who deviated from the protocol were included in the analysis. Although a full ITT analysis was not possible in this study, we believe that the results and conclusion of the study were unlikely to have been affected by the small number of randomised participants who were not analysed (11 [3%] of 341). Methodological limitations in ITT estimates, including non-compliance, differential measurement error, and heterogeneous treatment effects, can introduce biases and distort the estimates. Additionally, selection bias from non-random missing outcome data can bias findings if dropout reasons are linked to successful or unsuccessful treatment. Although these biases cannot be fully eliminated, we observed similar effects in the analyses of non-imputed and imputed data.

In addition to this difference in the dropout rates between treatment groups (figure 2), which was not unexpected given that one group underwent treatment for longer, the study weaknesses also included an absence of many electronic dose monitor readings because of poor tolerance or technical issues. Another limitation caused by the built-in selection bias is the limitation of our period-specific hazard ratio.[33] As a result, our hazard ratio estimates and, consequently, the probability of success driven by the hazard ratio estimate should be interpreted cautiously. Given that examiners were not masked and clinical decisions on prescribed patching were taken at the clinician's discretion, a bias cannot be excluded. However, examiner bias is unlikely to have substantially affected our findings because EOT is recommended in current clinical guidelines. The strengths of this study include the large sample size; the participation of clinical settings across several European centres; a stratified randomisation design; comparison of alternative approaches to dealing with missing data; and adherence to CONSORT standards.

In conclusion, our data indicate that high-intensity early patching is a more effective treatment for amblyopia than is EOT before patching, and that younger children with less severe amblyopia are the most likely to successfully respond to EOT. The results of our study contribute to further personalisation of therapeutic approaches to amblyopia.

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Contributors

FAP, AD-N, and IG contributed to the study conception and design. FAP, AD-N, and IG were responsible for the funding acquisition. FAP, MH, GM, EP, and IG developed the study protocol including modification of the questionnaire. The EUPATCH study investigator group was responsible for the recruitment of participants, assessment of eligibility, and collection of clinical data including visual acuity assessments under the supervision of FAP, MH, GM, EP, and IG. FAP, MH, GM, EP, AD-N, PK, JS, CB, and IG were responsible for the project administration. FAP, MH, GM, AM, and IG contributed to data curation. FAP, MH, AM, and IG planned, undertook, and interpreted the statistical analysis of the data. FAP, MH, AM, and IG accessed, verified, and validated the data. FAP, MH, AM, and IG were responsible for visualisation of data and writing of the original draft. FAP, MH, GM, EP, AM, AD-N, PK, JS, CB, and IG contributed to manuscript revisions. All authors had full access to all the data in the study and had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

FAP, A-DN, and IG were awarded grants from Action Medical Research and the Ulverscroft Foundation for this study. FAP reports travel funding from the main grant body, Action Medical Research, to attend the 2023 Annual Research in Vision and Ophthalmology meeting 2023, New Orleans, LA, USA, to present the findings for the study; and is a consultant for Leica Microsystems. MH and GM were funded through Action Medical Research, the NIHR Clinical Research Network and the Ulverscroft Foundation. AM reports funding from Action Medical Research to provide statistical support. A-DN is the local principal investigator for commercially sponsored randomised controlled trials (through Moorfields Eye Hospital, London, UK) for MyopiaX, Nevakar/Vyluma, Ocumension/Ora Health, and the UK National Institute for Health and Care Research (NIHR); and reports honoraria for educational activities from Santen, Novartis, Zeiss, and CooperVision, and for participation on advisory boards from Santen, SightGlassVision, Thea, and CooperVision. EP, PK, JS, and CB declare no competing interests.

Data sharing

Due to ethical considerations, data underpinning this publication cannot be made openly available. However, anonymised data can be made available upon request to FAP (fap1@leicester.ac.uk) to interested researchers after approval of a detailed proposal on the use of data through a data access agreement with the University of Leicester (Leicester, UK). These data will be available from the date of publication for at least 10 years. Further information about the data and conditions for access are available from the University of Leicester Institutional Repository.

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