Interventions for strabismic amblyopia (Review)

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[Intervention Review]

Interventions for strabismic amblyopia

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ABSTRACT

Background

Amblyopia is reduced visual acuity in one or both eyes in the absence of any demonstrable abnormality of the visual pathway. It is not immediately resolved by the correction of refractive error. Strabismus develops in approximately 5% to 8% of the general population. The aim of treatment for amblyopia is to obtain the best possible level of vision in the amblyopic eye. Different treatment options were examined within the review.

Objectives

By reviewing the available evidence we wanted to establish the most effective treatment for strabismic amblyopia. In particular this review aimed to examine the impact of conventional occlusion therapy for strabismic amblyopia and to analyse the role of partial occlusion and optical penalisation for strabismic amblyopia.

Search methods

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2013, Issue 12), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to January 2014), EMBASE (January 1980 to January 2014), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to January 2014), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials. We last searched the electronic databases on 30 January 2014.

Selection criteria

We included randomised controlled trials (RCTs) for the treatment of strabismic amblyopia including participants of any age.

Data collection and analysis

Two authors working independently extracted and entered data into Review Manager 5 and then independently checked the data for errors.

Main results

We included three RCTs in this review. The studies reported mean logMAR visual acuity achieved. Mean difference in visual acuity was calculated. When comparing conventional part-time occlusion (with any necessary glasses), PEDIG 2006 reported that this treatment was more beneficial than glasses alone for strabismic amblyopia; the mean difference between groups was -0.18 LogMAR (statistically significant 95% confidence interval (CI) -0.32 to -0.04). Supplementing occlusion therapy with near activities may produce a better visual outcome compared to non-near activities after four weeks of treatment (PEDIG 2005). The results of the pilot study showed mean difference between groups was -0.17 LogMAR (95% CI -0.53 to 0.19). Results from a larger RCT (PEDIG 2008) are now available, showing that supplementing occlusion therapy with near activities may produce a better visual outcome after eight weeks of treatment; the mean difference between groups was -0.02 LogMAR (95% CI -0.10 to 0.06). One further article ia awaiting assessment as in its current format there is insufficient information to include (Alotaibi 2012).

Authors' conclusions

Occlusion, whilst wearing necessary refractive correction, appears to be more effective than refractive correction alone in the treatment of strabismic amblyopia. The benefit of combining near activities with occlusion is unproven. No RCTs were found that assessed the role of either partial occlusion or optical penalisation to refractive correction for strabismic amblyopia.

PLAIN LANGUAGE SUMMARY

Treatment of amblyopia (lazy eye) caused by strabismus (squint) with patching or optical treatment (glasses or penalisation) or both

Review question: Treatment of amblyopia (lazy eye) caused by strabismus (squint) with patching or optical treatment (glasses or penalisation) or both.

Background: Amblyopia is a common childhood condition which causes a reduction in vision of one or both eyes which is not caused by any eye disease. Amblyopia can be caused by the presence of a squint (misalignment of the eyes where one eye may turn inwards, outwards, upwards or downwards). This review aims to look at the treatment of reduced vision caused by the presence of a squint, not the treatment of the squint itself.

Search date: Searches were last run 30 January 2014.

Study characteristics: Three randomised controlled trials (RCTs) conducted in the United States were included in this review.

Key results: The results of one of these trials indicate that patching therapy combined with any necessary glasses is more effective than glasses alone in the treatment of this condition. Two of the trials analysed the role of adding near activities to supplement patching therapy. These trials suggest there may be benefit to adding near activities to prescribed occlusion regime. No trial examining the role of optical penalisation (altering glasses strength) or using partial occlusion (frosted lens opposed to a patch) was found. The effectiveness of optical penalisation and partial occlusion for the treatment of strabismic amblyopia is unknown.

Quality of the evidence: The quality of the available evidence is high.

BACKGROUND

Description of the condition

Amblyopia (lazy eye) is reduced visual acuity in one or both eyes in the absence of a demonstrable abnormality of the visual pathway. It is not immediately resolved by the correction of any refractive error.

Amblyopia develops only during the critical period when the visual system is vulnerable to amblyogenic factors such as strabismus (Ansons 2001). It is most marked in children under the age of two years (Awaya 1987). Treatment is thought to be effective only during this critical period which varies for different types of amblyopia.

There are five types of amblyopia, which are classified by causative factors:

- Strabismic (caused by misalignment of the eyes);
- Stimulus deprivation (reduced vision occurring secondary to an obstacle in the anterior visual pathway);
- Anisometropic (a difference in the refractive (focusing) error of both eyes);
- Ametropic (significant refractive error of both eyes);
- Meridional (astigmatism of both eyes).

Strabismus (squint) is a misalignment of the eyes in which the visual axes deviate from bifoveal fixation, that is, one eye will look straight ahead whilst the other turns inwards, outwards, up or down. Strabismus may be constant or intermittent (RCOphth 2002).

Any of the other types of amblyopia may co-exist with strabismic amblyopia. Each type of amblyopia is the subject of a Cochrane review (Antonio-Santos 2014; Li 2009; Taylor 2012).

This review will concentrate on strabismic amblyopia in isolation to prevent overlap with existing reviews.

Epidemiology

Strabismus develops in approximately 5% to 8% of the general population (Rowe 2004). If either parent has strabismus the risk of the child being affected is four times greater than that of a child of parents without strabismus. It has been found that 65% of affected children have a close relative with a strabismus (Ansons 2001).

Presentation and diagnosis

The majority of children present with strabismic amblyopia when a parent or a health professional becomes concerned about the appearance of the strabismus. The degree of strabismus may range from very small, for example, microtropia (five degrees or less) with useful binocular single vision (BSV), to more marked, cosmetically obtrusive misalignment.

There are five main stages in the diagnosis of strabismic amblyopia.

1. The visual acuity of each eye is tested using an age and ability-appropriate test.
2. Strabismus is detected by performing a cover test. This is an objective dissociative test in which the examiner observes the child's eyes whilst fixation is maintained and each eye is in turn covered and uncovered (Rowe 2004). Amblyopia is unlikely to be present if there is free alternation of the strabismus from one eye to the other.
3. External examination to identify any pathology, for example, ptosis (drooping of the eyelid).
4. Refraction (test for glasses), fundus and media check. Cycloplegic eye drops that temporarily paralyse the focusing muscle within the eye and dilate the pupil need to be used for these examinations. Glasses will be prescribed if necessary. A fundus and media check will determine whether there is any ocular pathology.
5. Re-testing the visual acuity with any refractive correction in place. It is likely that there will be some improvement if glasses have been worn as instructed. Stewart 2004 emphasised the importance of refractive adaptation, that is, allowing a child to 'settle' into his or her glasses prior to beginning occlusion or penalisation therapy to avoid unnecessary occlusion. Refractive adaptation is now seen as a distinct component of amblyopia treatment.

There is a lack of clarity as to what constitutes a significant interocular difference in visual acuity and there is little evidence as to what is 'normal' on many of the commonly used visual acuity tests at different ages. We decided to define amblyopia as the best-corrected visual acuity (BCVA) of worse than 6/9 on a Snellen based test, or 0.2 on a LogMAR based test (or equivalent) of the amblyopic eye. The fellow, non-amblyopic eye will have a best-corrected visual acuity of 6/9 Snellen or 0.2 LogMAR or better. This review included both LogMAR and Snellen-based optotype-based measures of visual acuity.

Description of the intervention

The methods of treatment for amblyopia are based on correcting any refractive error and then preventing use of the better eye in order to promote use of the amblyopic eye. This can be done in the following ways:

- Total occlusion: total to form and light (usually using conventional patching or less frequently the use of an occlusive contact lens).
- Partial occlusion, including optical penalisation: reduction in form vision. Frosting the lens or altering the spectacle lens to blur the image in front of the non-amblyopic eye can achieve this.
- Pharmacological: cycloplegic drugs are used to temporarily blur the vision of the good eye.
- A combination of these options.

Total occlusion of the non-amblyopic eye remains the mainstay of treatment for strabismic amblyopia. The effectiveness of this form

of treatment has been questioned because of a lack of randomised controlled trials (RCTs) (Cleary 2000).
All pharmacological interventions are excluded from this review as they are part of a separate Cochrane review (Li 2009).

How the intervention might work

Occlusion, either partial or total, works by degrading the quality of the image seen by the non-amblyopic eye. Total occlusion removes all light and form seen by the non-amblyopic eye whilst partial occlusion still allows light to enter the eye.

Factors affecting outcome

The aim of treatment for amblyopia is to obtain the best possible level of vision in the amblyopic eye. Factors thought to influence the treatment outcome include age at onset of amblyopia, age when treatment commenced, type of amblyopia and presenting level of visual acuity, with more severely reduced acuity possibly having a poorer prognosis. Epelbaum 1993 reported a maximum improvement in strabismic amblyopia if treatment was started before three years of age, but it has also been suggested that improvement is possible in older children (Mintz-Hittner 2000; Mohan 2004).
Non-compliance with treatment also influences the success of treatment. Newsham 2000 found that poor parental knowledge regarding the critical period and correct implementation of the treatment regimen led to non-concordance and therefore poorer treatment outcomes.
In certain circumstances it is not possible to achieve equal vision. Co-existence of strabismus and anisometropia is known to constitute a barrier to the achievement of 'normal' visual acuity and therefore increase the likelihood of a poor vision outcome (Cleary 2000). However, it is not always known why visual acuity does not respond to treatment.

Why it is important to do this review

The rationale for treatment of unilateral amblyopia is that an individual with poor visual acuity due to untreated amblyopia may be disadvantaged should they lose the vision in their better eye. The projected lifetime risk of this occurring is approximately 3% (Rahi 2002). Poor vision, even in one eye, may also be a barrier to certain careers (Taylor 1995). Good bilateral and binocular vision is a requirement for some employment such as the armed forces, some police work and driving heavy goods vehicles.
There is a lack of standardisation as to the type and amount of occlusion given for any type of amblyopia, including strabismic (Cleary 2000; Tan 2003). Occlusion may range from full-time (all waking hours) to just one hour per day depending upon the management regime followed. Therefore this review aims to investigate the effectiveness of treatment for strabismic amblyopia. The results of this review will be relevant to eye professionals, affected children and their parents.

OBJECTIVES

By reviewing the available evidence we wanted to establish the most effective treatment for strabismic amblyopia. In particular, this review aimed to:

1. Examine the impact of conventional occlusion therapy on the outcome of treatment of strabismic amblyopia; and

2. Analyse the roles of partial occlusion and optical penalisation for strabismic amblyopia.

METHODS

Criteria for considering studies for this review

Types of studies

This review included RCTs of treatment for strabismic amblyopia. We imposed no language or date restrictions on the trials included.

Types of participants

We included trials with participants of any age, diagnosed with strabismic amblyopia.
The criteria for diagnosis was:
1. Presence of a manifest strabismus diagnosed by cover test (with any necessary refractive correction in place);
2. Corrected visual acuity in the amblyopic eye of worse than 6/9 (Snellen) or 0.2 (LogMAR) or equivalent, measured on an age-appropriate test;
3. Corrected visual acuity in the non-amblyopic eye of 6/9 (Snellen) or 0.2 (LogMAR) or better measured on an age-appropriate test.
All participants had undergone cycloplegic refraction and had corrected visual acuity assessed using an age-appropriate test prior to diagnosis. All participants were allowed a period of refractive adaptation as defined by each study to settle into glasses prescribed prior to being enrolled into a study. The results of all trials were analysed with the refractive adaptation time period in mind and results discussed in this context.

Types of interventions

We considered trials that included the use of the following as primary interventions:
1. Full-time total occlusion (more than six hours per day);
2. Part-time total occlusion (six hours or less per day);
3. Partial occlusion (any regime);
4. Optical penalisation (alteration of glasses lens in front of the better seeing eye in order to blur vision).
All topical pharmacological interventions were excluded as they are the subject of a separate Cochrane review (Li 2009).
The comparisons examined within this review were:
1. Conventional full-time total occlusion versus glasses alone/observation;
2. Conventional part-time total occlusion versus glasses alone/observation;
3. Partial occlusion versus glasses alone/observation;
4. Optical penalisation versus glasses alone/observation;
5. Occlusion with prescribed near activities versus occlusion without near activities/distance activities.
The 'observation' group included participants wearing any refractive correction but not any of the above treatments.

Types of outcome measures

Primary outcomes

The primary outcome for this review was change in BCVA of the amblyopic eye on an age specific test at 12 months from cessation of treatment.
As LogMAR data was available from start to finish of treatment we analysed the degree of change in visual acuity. This produced continuous data, hence analysis of the weighted mean difference was carried out to summarise the result.

Secondary outcomes

The secondary outcome for this review was best-corrected final visual acuity at any time point during or after cessation of treatment.

Adverse effects

Information reported in studies regarding adverse events was divided into mild or severe:
Mild

- Psychological effects which do not require treatment.
- Allergies, for example skin irritations to patch.
- Disorientation if visual acuity is very poor in the amblyopic eye.

Severe

- Psychological effects which require further investigation or treatment.
- Intractable diplopia (double vision): diplopia which is caused by the loss of suppression through occlusion therapy where binocular single vision cannot be achieved with prisms and the patient cannot re-suppress. This leads to permanent double vision.
- Occlusion amblyopia: reduction in visual acuity of the non-amblyopic eye, increase in size of strabismus or dissociation of strabismus.

Quality of life measures

- We reported any quality of life measures associated with having residual amblyopia.
- We described any quality of life measures relating to the treatment of amblyopia.

Economic data

Any data reporting the cost of treating amblyopia were included.
Follow up
The follow-up period for all included trials was likely to vary. The results were reported in the context of the actual follow-up period.

Search methods for identification of studies

Electronic searches

We searched CENTRAL (which contains the Cochrane Eyes and Vision Group Trials Register) (2013, Issue 12), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to January 2014), EMBASE (January 1980 to January 2014), Latin American and Caribbean Health Sciences Literature Database (LILACS) (January 1982 to January 2014), the *meta*Register of Controlled Trials (*m*RCT) (www.controlled-trials.com), ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp/search/en). We did not use any date or language restrictions in the electronic searches for trials.We last searched the electronic databases on 30 January 2014.
See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4), *m*RCT (Appendix 5), ClinicalTrials.gov (Appendix 6), and the ICTRP (Appendix 7).

Searching other resources

We manually searched the reference lists of the trials included in the review for additional trials. We did not handsearch journals or conference proceedings specifically for this review.

Data collection and analysis

Selection of studies

Both review authors undertook independent assessment of abstracts to ascertain which studies met the inclusion criteria for the review. Abstracts were labelled as included, unclear or excluded. Full copies of all included and unclear studies were obtained and the two review authors once again worked independently to determine which studies met the inclusion criteria.

Data extraction and management

Two authors working independently extracted data from included trials using a data collection form. Where possible, data were collected directly from the published paper but in some cases extra data were provided by trial co-ordinators (PEDIG 2005; PEDIG 2006; PEDIG 2008). For PEDIG 2005 and PEDIG 2006, data were entered into Revman using the double data entry facility to check for errors. This facility was not available in RevMan 5 (RevMan 2011). For PEDIG 2008 data were extracted by the authors independently and results compared. Data were then entered into RevMan by one author (KS) and checked by the other (SE).

Assessment of risk of bias in included studies

Once studies had been identified as meeting the inclusion criteria the two authors assessed them for methodological quality according to Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

The following parameters were considered: generation of the random sequence, masking (blinding) of examiners, allocation concealment and completeness of follow up. In addition the authors considered whether there appeared to be any evidence of selective reporting of results or other sources of bias.

We graded each parameter of trial quality as 'low risk of bias', 'high risk of bias' or 'unclear'. Where any parameter was graded as unclear we contacted trial authors for clarification.

Data synthesis

Data analysis followed the guidelines in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011). For continuous outcomes, we calculated the weighted mean difference. Meta-analysis was not performed as insufficient data was present for each comparison. If in future updates it is possible to carry out a meta-analysis, we will use a fixed-effect model where the number of trials is less than three.

Sensitivity analysis

Sensitivity analysis was planned to assess how robust our review results are. In updates of the review we will continue to:

1. Exclude studies of lower methodological quality;
2. Exclude unpublished studies.

RESULTS

Description of studies

Results of the search

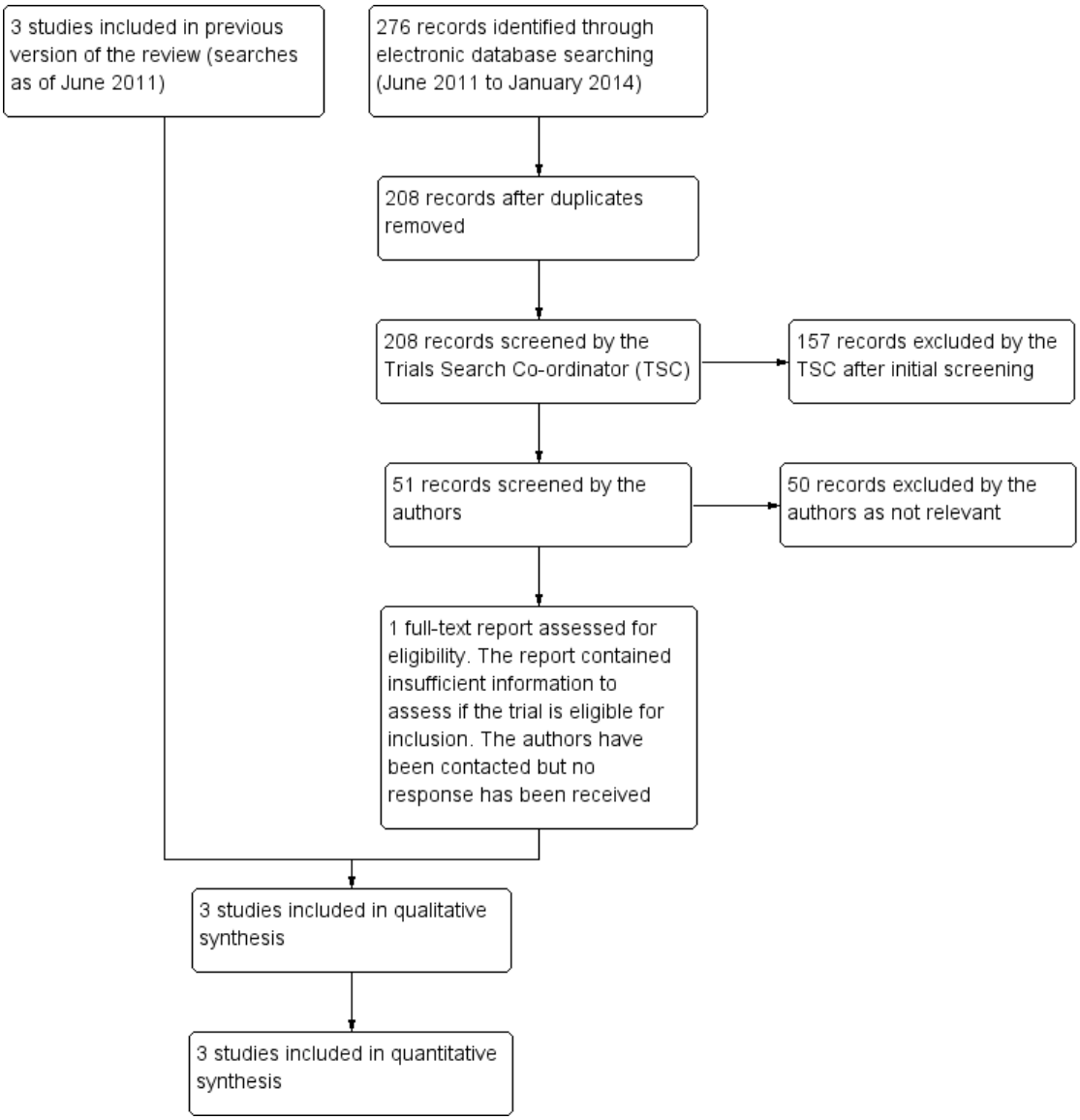
The electronic searches found 771 titles and abstracts. We screened the titles and abstracts according to the criteria outlined above and identified 16 potential trial reports. After discussion, we decided to obtain the full-text of eight trials.

An update search was done in November 2009 which yielded a further 138 references. The Trials Search Co-ordinator (TSC) scanned the search results and removed any references which were not relevant to the scope of the review. A total of 44 references were screened against the inclusion criteria for the review and we obtained the full-text of one report of a trial (PEDIG 2008).

Updated searches were run in June 2011. The electronic searches yielded a total of 184 titles and abstracts. After deduplication the TSC scanned 130 records and discarded 75 records as they were not relevant to the scope of the review. Both authors independently screened the title and abstracts of the remaining 55 references and it was deemed no new trials met the inclusion criteria of the review. We excluded one trial (PEDIG 2010).

An update search run in January 2014 identified a further 276 references (Figure 1). The Trials Search Co-ordinator removed 68 duplicates and screened the remaining 208 references, of which 157 were not relevant to the scope of the review. We reviewed the remaining 51 references and discarded 50 reports as not relevant. We obtained one full-text report for potential inclusion in the review (Alotaibi 2012) however insufficient information was available in the published article to assess if the trial was eligible for inclusion. We contacted the authors of the manuscript but to date no reply has been received. The article has therefore been classified as 'awaiting assessment'. Should further information become available then the article will be reassessed.

Figure 1. Results from searching for studies for inclusion in the review



Included studies

We included three studies in this review. See the 'Characteristics of included studies' table for more information on each study.

PEDIG 2005

This pilot study (leading to the full study reported in PEDIG 2008) included 64 participants aged between three and seven years of age. All children had been diagnosed with anisometropic, strabismic or mixed amblyopia. The authors were able to provide data on the 20 participants diagnosed with strabismic amblyopia as defined within this review. All study participants with vision ranging from 0.300 to 1.300 LogMAR were randomised to receive two hours of daily occlusion with near or distance activities. Data on the 20 participants with strabismic amblyopia was extracted as a subgroup of the total randomised population and therefore may not represent a truly randomised comparison. Compliance to prescribed treatment was assessed via parental diaries and weekly telephone calls. Visual acuity in the amblyopic eye was reported after four weeks of treatment.

PEDIG 2006

This trial randomised 180 participants to either two hours of daily occlusion with glasses or to a glasses only treatment group. All participants had been diagnosed with moderate (0.300 to 0.600 LogMAR) or severe (0.700 to 1.300 LogMAR) amblyopia and were aged between three and seven years. The main outcome measure of the trial was best-corrected vision in the amblyopic eye after five weeks of treatment.

Participants who required refractive correction entered a spectacle run-in phase of the trial prior to treatment. Optimal refractive correction was prescribed and worn full-time until vision in the amblyopic eye stabilised. Participants were then randomised into a glasses only group or occlusion group. The trial was designed to assess whether the visual acuity of the amblyopic eye would improve more in the occlusion group compared to the glasses only group.

Of the 180 participants included within the study, 39 had strabismic amblyopia as defined within this review. Data on these 39 participants with strabismic amblyopia was extracted as a subgroup of the total randomised population and therefore may not represent a truly randomised comparison. The authors were able to provide visual acuity outcomes for these participants at the five-week examination point.

PEDIG 2008

This trial included 425 participants aged between three and seven years of age, diagnosed with amblyopia (0.300 to 1.300 LogMAR) caused by anisometropia, strabismus or both. Participants were randomised to receive two hours of daily occlusion with near activities or two hours of daily occlusion with distance activities. The main outcome of this trial was visual acuity in the amblyopic eye after eight weeks of treatment. Participants who required any refractive correction were prescribed glasses. Correction was worn for a minimum of 16 weeks or until no documented improvement in visual acuity of the amblyopic eye was reported for two consecutive visits. Compliance to treatment was documented via parental diaries used to document the numbers of hours patched per day and the activities carried out whilst occluded.

Of the included participants, 130 were defined as having strabismic amblyopia and eligible for inclusion within this review. Data on these participants was extracted as a subgroup of the total randomised population. The authors were able to provide data for these participants.

Excluded studies

Seven trials (Awan 2005; PEDIG 2003a; PEDIG 2003b; PEDIG 2005b; PEDIG 2007; PEDIG 2010; Stewart 2007) have been excluded from the review and reasons for exclusion are documented in the 'Characteristics of excluded studies' table.

Risk of bias in included studies

For full methodological quality and assessment on risk of bias please see Figure 2 and Figure 3.

Figure 2. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.

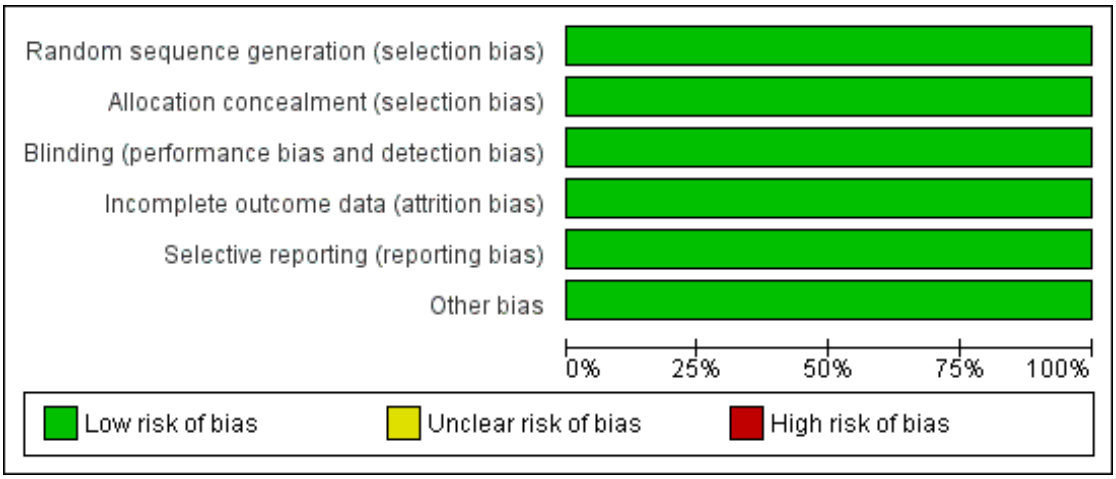
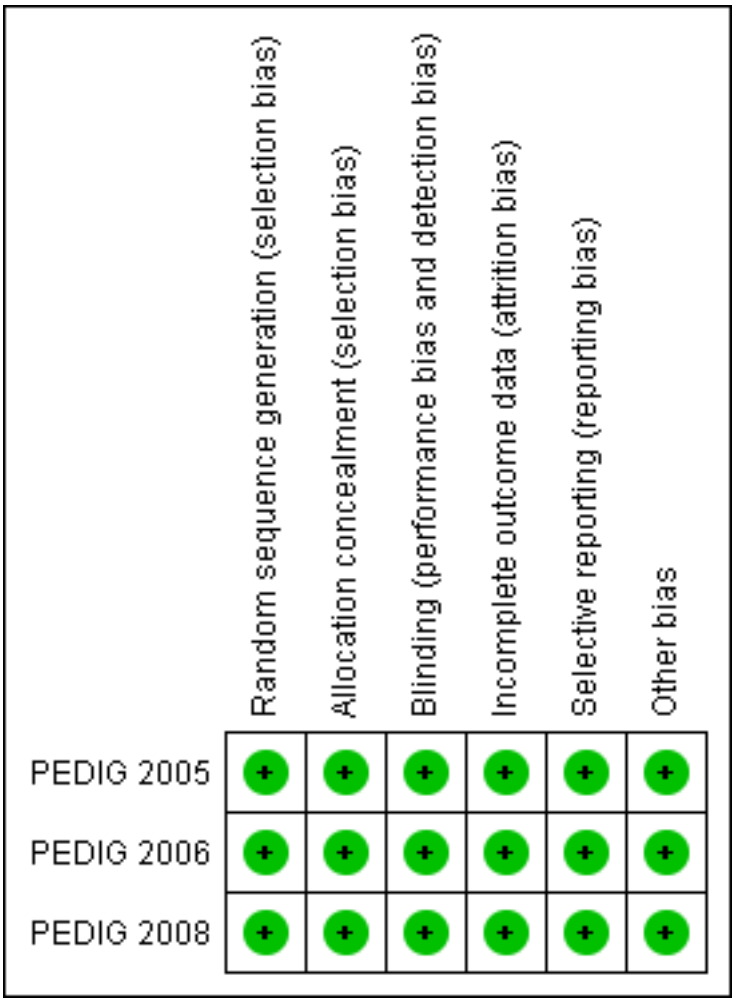


Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



Effects of interventions

The three included trials provided data for two separate comparisons within the review. The results for each comparison are summarised below.

1. Occlusion with prescribed near activities versus occlusion with non-near activities

Two studies (PEDIG 2005; PEDIG 2008) were included for this comparison (*see* Analysis 1.1). PEDIG 2005 is a pilot study comparing prescribed near and non-near activities whilst carrying out occlusion therapy and PEDIG 2008 is the follow-on trial.

PEDIG 2005 included 64 children aged between three to seven years, however, only 20 participants were diagnosed with strabismic amblyopia as defined within the review. As randomisation was not stratified according to the type of amblyopia, these participants represent a subgroup within the trial. The authors were contacted and the information regarding these 20 participants was analysed. All participants in the trials were asked to carry out two hours of daily occlusion. Participants were then randomised into carrying out near or non-near (distance) activities for a period of four weeks. Both a telephone interview and a daily diary assessed compliance to treatment. At the 4 week outcome assessment, the near activities group (n = 12) recorded a mean visual acuity of 0.38 LogMAR (0.17 standard deviation (SD)) and the non-near group (n = 8) recorded a mean visual acuity of 0.55 LogMAR (0.50 SD) at the masked examination. The mean difference is therefore -0.17 LogMAR (95% confidence interval (CI) -0.53 to 0.19). Overall

(for all included participants), the results of this pilot trial suggested that there may be some benefit from supplementing occlusion with near activities and so a full trial was conducted.

PEDIG 2008 included 425 participants in total of which 130 were diagnosed with strabismic amblyopia as defined in this review. These participants represent a subgroup of the total of the randomised population. Glasses were prescribed for full-time wear until vision stabilised or 16 weeks. Participants were then prescribed two hours daily occlusion randomised to be supplemented with either near activities or distance activities. Examples of near activities included homework, arts and crafts, computer games and writing and reading. Examples of distance activities included playing with remote control toys, television and general playing. Compliance to treatment was assessed via parental diaries and weekly telephone calls. Occlusion therapy with near activities or with distance activities was prescribed for 17 weeks. The primary outcome for the review was visual acuity at the eight week exam. It is possible that some participants may have continued to have a change in their visual acuity after the eight week outcome assessment. The near activities group (n = 65) recorded a mean visual acuity of 0.331 LogMAR (0.23 SD) at outcome and the distance group (n = 65) recorded a mean visual acuity of 0.350 LogMAR (0.243 SD). The mean difference was calculated to be -0.02 LogMAR (95% CI -0.10 to 0.06), showing no statistical significance between the two treatments for participants with strabismic amblyopia. This is consistent with the findings of the trial when examining all types and severity of amblyopia.

2. Conventional part-time occlusion versus glasses

One study (PEDIG 2006) was included for this comparison (*see* Analysis 2.1). This trial compared two hours of daily occlusion to a control group. The control group were wearing any refractive correction necessary but undergoing no other treatment.

This prospective trial included 180 children aged between three to seven years diagnosed with amblyopia. Thirty-nine participants were diagnosed with strabismic amblyopia and were eligible for inclusion in this review. As for the previous trials, randomisation was not stratified according to the type of amblyopia, therefore these patients also represent a subgroup within the RCT.

All children included were prescribed the necessary refractive correction for a minimum of 16 weeks before being enrolled within the randomised phase of the trial.

The primary outcome for this trial was vision in the amblyopic eye at the five week masked examination. This examination was carried out for 98% of the participants in the patching group and 95% of the participants in the control group. At this masked examination, the mean visual acuity for the treatment group (n = 19) was recorded as 0.33 LogMAR (0.15 SD) and for the control group (n = 20), 0.51 LogMAR (0.29 SD). The mean difference was therefore calculated as -0.18 LogMAR (95% CI -0.32 to -0.04), which is statistically significant.

Analysis 2.1 shows that for the participants in this trial, two hours daily occlusion combined with necessary refractive correction is more beneficial than refractive correction alone for strabismic amblyopia. All levels of amblyopia from 20/400 (6/120) to 20/40 (6/12) were included in this trial.

DISCUSSION

Occlusion therapy for amblyopia is prescribed in order to reverse amblyopia in young children, however, the number of hours prescribed varies widely from practitioner to practitioner and country to country (Mazow 2000; Tan 2003). Data from the three studies included in this review provide some evidence of the effectiveness of treatments for strabismic amblyopia but this evidence is currently limited and there remains a need for more robust data on optimal treatment for this condition. It should also be noted that for all included trials within this review only a subgroup of the participants were eligible for inclusion and therefore there may not be sufficient power to show an effect.

Occlusion versus glasses

One trial was included for this comparison. PEDIG 2006 concluded that occlusion with necessary refractive correction was more effective than glasses alone for the treatment of strabismic amblyopia. It is important to remember that the results of this trial are reported after five weeks of treatment and this has important implications for the interpretation of the results. Reported acuities are unlikely to reflect optimal treatment effect but rather show the difference between the two treatments at the five-week outcome. In addition, there are no long-term data available to assess if the treatment effect is sustained once treatment ceases.

Prescribed near versus non-near activities to supplement occlusion

Two RCTs were found that assessed the role of near activities as a supplement to occlusion therapy. PEDIG 2005 showed that for children undergoing two hours daily occlusion for unilateral strabismic amblyopia the vision outcome appeared better, on average (although not statistically significant), in those who were instructed to carry out near activities. This pilot trial included participants with all levels of amblyopia from 20/400 (60/120) to 20/40 (6/12) treated for four weeks. Only part of the data set of the full trial is included within the review as not all participants met the inclusion criteria. PEDIG 2008 also compared near activities to distance activities with two hours daily prescribed occlusion. The trial included participants with all types and levels of amblyopia. Data provided by the trial organisers on a subgroup of participants diagnosed with strabismic amblyopia showed a minimal

improvement compared to vision in the near activities group after eight weeks of treatment.

Partial occlusion and optical penalisation

No RCTs were found that assessed the role of either partial occlusion or optical penalisation to glasses alone for strabismic amblyopia. In order to assess their effectiveness a RCT needs to be carried out. One trial comparing partial occlusion (Bangerter filters) to conventional occlusion has been excluded from this review (PEDIG 2010). This trial included 186 children aged between three and seven years with moderate amblyopia (0.300 to 0.600) of all types. The trial concluded that similar results were produced by both treatment however as this trial did not compare visual acuity outcomes to glasses wear alone it did not meet the inclusion criteria of this review.

Factors thought to affect outcomes

- Age at onset: All studies within this review included children aged between three to seven years. Treatment is deemed to be more effective during the sensitive period. Currently no RCT is available examining the role of occlusion treatment in those over the age of seven years with strabismic amblyopia.
- Age at commencement of treatment: All three studies in this review included children between the ages of three to seven years. Several case reports comment on the treatment of strabismic amblyopia in older children. Park 2004 described two children aged 10 and 12 years that underwent a regime of full-time occlusion followed by part-time occlusion for several months. Both children improved to a satisfactory level of vision. Mintz-Hittner 2000 reported a series of nine strabismic amblyopia patients that underwent a variety of treatments from occlusion to the use of an occlusive contact lens. All patients in the series showed an improved level of vision, however, there was no control treatment or randomisation in these studies.
- Type of amblyopia: All trial participants included within this review were diagnosed with strabismic amblyopia as defined previously within this review. Separate Cochrane reviews are available that assess the treatment options for stimulus deprivation amblyopia and refractive amblyopia.
- Presenting visual acuity: All participants included within the review had a starting acuity in the amblyopic eye of 20/40 to 20/400 (6/12 to 6/120, 0.300 to 1.000). This is a wide range of acuities from mild amblyopia to severe amblyopia. PEDIG 2006 and PEDIG 2008 carried out a subgroup analysis to analyse moderate and severe amblyopia separately. The authors reported no difference in the level of improvement in visual acuity. PEDIG 2005 carried out subgroup analyses for moderate and severe amblyopia; this showed that participants (all types of amblyopia) with the worse starting acuity (20/100, 6/30, 0.700 or worse) improved more with the near activities compared to the non-near activities.
- Compliance: PEDIG 2006 assessed compliance to the prescribed treatment via a parental calendar to document the number of hours of treatment. Compliance was assessed as excellent (76% to 100%) in 68% of all participants. PEDIG 2005 assessed compliance with calendars completed weekly by the parents and by a weekly telephone call. Based on the calendars, the children randomised to receive near activities whilst undergoing occlusion spent on average 1.6 hours daily carrying out near tasks. PEDIG 2008 also assessed compliance via parental diaries and phone calls. Of the two hours daily patching prescribed to both groups, the mean duration of occlusion was 1.9 $\pm$ 0.2 hours per day in the distance activities group and 1.9 $\pm$ 0.3 hours in the near activities group with 1.5 $\pm$ 0.4 hours spent carrying out near activities.

No studies were found that investigated the cost-effectiveness of treatment or looked at the factors that affected the quality of life of the participants.

AUTHORS' CONCLUSIONS

Implications for practice

The lack of multiple RCTs for the treatment of strabismic amblyopia makes it difficult to evaluate many areas of treatment. The data included in this review demonstrates that occlusion with necessary refractive correction is more effective than glasses alone for the treatment of strabismic amblyopia. The additional benefit of carrying out near activities whilst undergoing occlusion therapy is unconvincing and it is possible that the same results may be achieved by a concentrated visual effort regardless of the distance.

For clinicians, patients and care-givers, it would be of benefit to have a more comprehensive, evidence-based, management regime for optimal treatment outcomes for strabismic amblyopia, but at present the evidence to support such a framework does not exist.

Implications for research

There is a need for good quality trials to be conducted in this area to improve the evidence base for the management of strabismic amblyopia. Areas specifically that require more study include:

1. Identification of factors affecting success of occlusion treatment, such as:

a. Age of onset of strabismus;

b. Age of commencement of treatment;

c. Starting visual acuity;

d. Compliance with treatment.

2. Investigation into the effectiveness of partial occlusion and optical penalisation.

3. Establishing overall impact of treatment:

a. Effect on psycho-social and emotional well-being of the child;

b. Non-concordance with therapy - causes, effects, measures to reduce.

c. Cost-effectiveness of treatment.

4. Long-term follow-up data assessing reoccurrence rates and sustainability of vision following treatment for amblyopia.

Varying outcome measures and review time scales make the review of trials in this area of clinical practice problematic. Trials report varying follow up times from immediately post-treatment to several months afterwards. Treatment duration also often varies. By assessing outcomes immediately post-treatment, treatment gains can be measured to show how effective a particular treatment is. By assessing outcomes one year post-treatment, recurrence rates can be established as well as the long-term visual stability of treated amblyopia. This information would be very useful for clinicians treating strabismic amblyopia.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

PEDIG 2005

Methods	Randomised into treatment or control group via study website. Treatment outcome masked. No participant was excluded after randomisation. Only 3 participants were lost to follow-up
Participants	All participants were enrolled within the United States. All participants aged between 3 and 7 years. The inclusion criteria were presence of manifest squint and VA in the amblyopic eye of 20/40 to 20/400 (6/12 to 6/120, 0.300 to 1.00). All participants were to undergo 2 hours daily occlusion. Participants were excluded if they had undergone any amblyopia treatment in the month previous to the trial
Interventions	Treatment group: 2 hours daily occlusion with near activities. Control group: 2 hours daily occlusion with non-near activities
Outcomes	Visual acuity in amblyopic eye at 4 week assessment.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequence was computer generated using a permuted block design
Allocation concealment (selection bias)	Low risk	Allocation via study website after recruitment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Masked examiners carried out vision testing. No documented reports of masking being breached
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar rates of follow-up in both treatment groups. Main outcome measure was completed by 94% in treatment group and 88% in control group
Selective reporting (reporting bias)	Low risk	Study protocol is published and outcomes are reported as pre-specified
Other bias	Low risk	No other sources of bias were detected or suspected.

PEDIG 2006

Methods	Randomised into treatment or control group via study website. Outcome of treatment analysed masked. No participant was excluded after randomisation. Only 3 participants were lost to follow-up
Participants	All participants were enrolled within the United States. All participants aged between 3 and 7 years. The inclusion criteria were presence of manifest squint and visual acuity in the amblyopic eye of 20/40 to 20/400 (6/12 to 6/120, 0.300 to 1.000). Participants were excluded if they had undergone any amblyopia treatment in the month prior to the trial
Interventions	Treatment group: 2 hours daily occlusion Control group: observation
Outcomes	Visual acuity in amblyopic eye at end of trial.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence was computer generated using a permuted block design
Allocation concealment (selection bias)	Low risk	Allocation via study website after recruitment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Masked examiners carried out vision testing. Percentage of occasions when the masking was breached is published; 5% in the patching group, 1% in the control group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar rates of follow-up in both treatment groups. Main outcome measure was completed by 98% in treatment group and 95% in control group
Selective reporting (reporting bias)	Low risk	Study protocol is published and outcomes are reported as pre-specified
Other bias	Low risk	No other sources of bias were detected or suspected.

PEDIG 2008

Methods	Randomised into treatment or control group via study website. Treatment outcome masked. No participant was excluded after randomisation. 27 participants were lost to follow-up
Participants	All participants were enrolled within the United States. All participants aged between 3 and 7 years. The inclusion criteria were presence of manifest squint and VA in the amblyopic eye of 20/40 to 20/400 (6/12 to 6/120, 0.300 to 1.00). All participants were to undergo 2 hours daily occlusion. Participants were excluded if they had undergone any amblyopia treatment in the 6 months prior to the trial
Interventions	Treatment group: 2 hours daily occlusion with near activities. Control group: 2 hours daily occlusion with distance activities
Outcomes	Visual acuity in the amblyopic eye at 8 week masked visit.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sequence was computer generated using a permuted block design
Allocation concealment (selection bias)	Low risk	Allocation via study website after recruitment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Masked examiners carried out vision testing. Percentage of occasions when the masking was breached is published; 3% in the patching group, 3% in the control group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar rates of follow-up in both treatment groups. Main outcome measure was completed by 92% in treatment group and 95% in control group
Selective reporting (reporting bias)	Low risk	Study protocol is published and outcomes are reported as pre-specified
Other bias	Low risk	No other sources of bias were detected or suspected.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Awan 2005	This randomised trial investigates compliance.
PEDIG 2003a	This randomised trial reviews 2 hours versus 6 hours occlusion for moderate amblyopia. The role of this review is not to establish the most effective part-time occlusion regime
PEDIG 2003b	This randomised trial reviews 6 hours daily occlusion to 12 hours daily occlusion for severe amblyopia. It is not the role of this review to compare occlusion regimes
PEDIG 2005b	This randomised trial compares occlusion therapies, including a pharmacological intervention, in older children. All pharmacological treatments will be covered in a separate Cochrane review
PEDIG 2007	The paper presents case reports of the treatment of strabismic amblyopia and is not a randomised trial
PEDIG 2010	This trial compares two treatment regimes; Bangerter filters and occlusion. It is not within the scope of this review to compare these two interventions to one another
Stewart 2007	This randomised trial compares 6 hours daily occlusion to 12 hours daily occlusion. The aim of this review is not to compare occlusion regimes

Characteristics of studies awaiting assessment *[ordered by study ID]*

Alotaibi 2012

Methods	Part-time occlusion carried out by all trial participants. One group recommended to undertake 3 hours of near activities whilst wearing occlusion (such as reading), the other group advised not to do any near tasks
Participants	The study was carried out in the Pediatric Ophthalmology and Orthoptics Clinics of King Abdul-Aziz University Hospital, Riyadh, Saudi Arabia for the period from January to November 2010. One hundred and thirty participants were followed-up for a 12-week period
Interventions	Treatment group: 3 hours daily occlusion with near activities. Control group: 3 hours daily occlusion with non-near activities
Outcomes	Main outcome measures were best-corrected visual acuity for both groups and line improvement
Notes	Unclear method of group selection/randomisation. Authors contacted March 2014 for further details. No response received as yet. Details will be updated should more information become available

DATA AND ANALYSES

Comparison 1. Occlusion with near activities versus occlusion with non-near activities

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean visual acuity at cessation of treatment	2	150	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.11, 0.05]

Comparison 2. Conventional part-time occlusion versus observation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean visual acuity at cessation of treatment	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only

Analysis 1.1. Comparison 1 Occlusion with near activities versus occlusion with non-near activities, Outcome 1 Mean visual acuity at cessation of treatment.

Review: Interventions for strabismic amblyopia

Comparison: 1 Occlusion with near activities versus occlusion with non-near activities

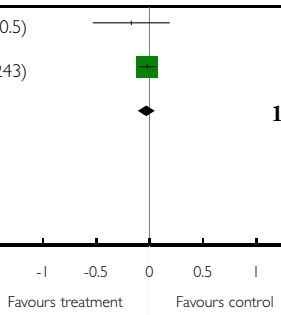
Outcome: 1 Mean visual acuity at cessation of treatment

Study or subgroup	Treatment (near) N	Mean(SD)	Control (non-near) N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
PEDIG 2005	12	0.38 (0.17)	8	0.55 (0.5)		4.9 %	-0.17 [-0.53, 0.19]
PEDIG 2008	65	0.331 (0.23)	65	0.35 (0.243)		95.1 %	-0.02 [-0.10, 0.06]
Total (95% CI)	**77**		**73**			**100.0 %**	**-0.03 [-0.11, 0.05]**

Heterogeneity: Chi² = 0.64, df = 1 (P = 0.42); I² =0.0%

Test for overall effect: Z = 0.65 (P = 0.52)

Test for subgroup differences: Not applicable



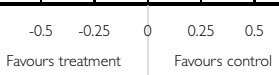
Analysis 2.1. Comparison 2 Conventional part-time occlusion versus observation, Outcome 1 Mean visual acuity at cessation of treatment.

Review: Interventions for strabismic amblyopia

Comparison: 2 Conventional part-time occlusion versus observation

Outcome: 1 Mean visual acuity at cessation of treatment

Study or subgroup	Treatment (2 hrs) N	Mean(SD)	Control (gls) N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
PEDIG 2006	19	0.33 (0.15)	20	0.51 (0.29)			-0.18 [-0.32, -0.04]
Subtotal (95% CI)	**0**		**0**				**0.0 [0.0, 0.0]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P < 0.00001)							
Test for subgroup differences: Not applicable							



APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor Strabismus
#2 strabism*
#3 squint*
#4 (#1 OR #2 OR #3)
#5 MeSH descriptor Amblyopia
#6 amblyop*
#7 (#5 OR #6)
#8 (#4 AND #7)

Appendix 2. MEDLINE (OvidSP) search strategy

1 randomised controlled trial.pt.
2 (randomised or randomised).ab,ti.
3 placebo.ab,ti.
4 dt.fs.
5 randomly.ab,ti.
6 trial.ab,ti.
7 groups.ab,ti.
8 or/1-7
9 exp animals/

10 exp humans/
11 9 not (9 and 10)
12 8 not 11
13 exp strabismus/
14 strabism$.tw.
15 squint$.tw.
16 or/13-15
17 exp amblyopia/
18 amblyop$.tw.
19 or/17-18
20 16 and 19
21 12 and 20

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville (Glanville 2006).

Appendix 3. EMBASE (OvidSP) search strategy

1 exp randomised controlled trial/
2 exp randomisation/
3 exp double blind procedure/
4 exp single blind procedure/
5 random$.tw.
6 or/1-5
7 (animal or animal experiment).sh.
8 human.sh.
9 7 and 8
10 7 not 9
11 6 not 10
12 exp clinical trial/
13 (clin$ adj3 trial$).tw.
14 ((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).tw.
15 exp placebo/
16 placebo$.tw.
17 random$.tw.
18 exp experimental design/
19 exp crossover procedure/
20 exp control group/
21 exp latin square design/
22 or/12-21
23 22 not 10
24 23 not 11
25 exp comparative study/
26 exp evaluation/
27 exp prospective study/
28 (control$ or prospectiv$ or volunteer$).tw.
29 or/25-28
30 29 not 10
31 30 not (11 or 23)
32 11 or 24 or 31
33 exp strabismus/
34 strabism$.tw.
35 squint$.tw.
36 or/33-35

37 exp amblyopia/
38 amblyop$.tw.
39 or/37-38
40 36 and 39
41 32 and 40

Appendix 4. LILACS search strategy

strabism$ or squint$ and amblyop$

Appendix 5. *meta*Register of Controlled Trials search strategy

strabismus and amblyopia

Appendix 6. ClinicalTrials.gov search strategy

Strabismus AND Amblyopia

Appendix 7. ICTRP search strategy

Strabismus AND Amblyopia

WHAT'S NEW

Last assessed as up-to-date: 30 January 2014.

Date	Event	Description
18 July 2014	New citation required but conclusions have not changed	Issue 7, 2014: One potential study identified (Alotaibi 2012) but awaiting further information before including it in the review
18 July 2014	New search has been performed	Issue 7, 2014: Electronic searches updated.

HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 2, 2008

Date	Event	Description
29 June 2011	New citation required but conclusions have not changed	Lead author's surname has changed.
27 June 2011	New search has been performed	Issue 8 2011: Updated searches yielded no new trials.
12 June 2009	New search has been performed	Issue 1, 2010: Updated searches yielded one new trial for inclusion in the review (PEDIG 2008).
18 October 2008	Amended	Converted to new review format.
12 February 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Conceiving the review: KS, CB

Designing the review: KS, SE

Co-ordinating the review: KS

Data collection for the review

- Designing search strategies: Cochrane Eyes and Vision Group

- Undertaking searches: KS, SE

- Screening search results: KS, SE

- Organising retrieval of papers: KS, SE

- Screening retrieved papers against inclusion criteria: KS, SE

- Appraising quality of papers: KS, SE

- Extracting data from papers: KS, SE

- Writing to authors of papers for additional information: KS

- Providing additional data about papers: SE

- Obtaining and screening data on unpublished studies: KS, SE

Data management for the review

- Entering data into RevMan: KS, SE

Analysis of data: KS, SE

Interpretation of data

- Providing a methodological perspective: KS, SE

- Providing a clinical perspective: KS, SE

- Providing a policy perspective: KS, SE

- Obtaining a consumer perspective: KS, SE

Writing the review: KS, SE

Providing general advice on the review: KS, SE

Updating the review: KS, SE

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Institute of Health Research (NIHR), UK.

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INDEX TERMS

Medical Subject Headings (MeSH)

Amblyopia [etiology; *therapy]; Eyeglasses; Randomized Controlled Trials as Topic; Sensory Deprivation; Strabismus [complications; *therapy]; Visual Acuity

MeSH check words

Child; Child, Preschool; Humans