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Cochrane Database of Systematic Reviews 2013, Issue 8. Art. No.: CD000122.

DOI: [10.1002/14651858.CD000122.pub2](https://doi.org/10.1002/14651858.CD000122.pub2).

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Early light reduction for preventing retinopathy of prematurity in very low birth weight infants (Review)

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[Intervention Review]

Early light reduction for preventing retinopathy of prematurity in very low birth weight infants

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Editorial group: Cochrane Neonatal Group

Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 8, 2013.

Citation: Jorge EC, Jorge EN, El Dib RP. Early light reduction for preventing retinopathy of prematurity in very low birth weight infants. *Cochrane Database of Systematic Reviews* 2013, Issue 8. Art. No.: CD000122. DOI: [10.1002/14651858.CD000122.pub2](https://doi.org/10.1002/14651858.CD000122.pub2).

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ABSTRACT

Background

Retinopathy of prematurity (ROP) is a complex condition of the developing retinal blood vessels and is one of the leading causes of preventable childhood blindness. Several risk factors for ROP have been studied over the past 50 years. Among them, general immaturity (low birth weight and low gestational age) and prolonged oxygen therapy have been consistently related to disease onset. However, it is understood that the progression of the disease is multifactorial and may be associated with others risk factors, such as multiple gestation, apnoea, intracranial haemorrhage, anaemia, sepsis, prolonged mechanical ventilation, multiple transfusions and light exposure. Furthermore, the precise role of these individual factors in the development of the disease has not yet been well established.

Objectives

To determine whether the reduction of early environmental light exposure reduces the incidence of retinopathy of prematurity (ROP) or poor ROP outcomes among very low birth weight infants.

Search methods

We searched the following databases: the Cochrane Neonatal Group Specialised Register, CENTRAL (*The Cochrane Library*), MEDLINE, EMBASE, CINAHL, HealthSTAR, Science Citation Index Database, CANCERLIT, the Oxford Database of Perinatal Trials and www.clinicaltrials.gov. We also searched previous reviews including cross-references, abstracts, conference and symposia proceedings, and contacted expert informants. This search was updated in October 2012.

Selection criteria

Randomised or quasi-randomised controlled trials that reduced light exposure to premature infants within the first seven days following birth were considered for this review. We also considered cluster-randomised controlled trials.

Data collection and analysis

Data on clinical outcomes including any acute ROP and poor ROP outcome were extracted by both review authors independently and consensus reached. We conducted data analysis according to the standards of the Cochrane Neonatal Review Group.

Main results

Data from four randomised trials with a total of 897 participants failed to show any reduction in acute ROP or poor ROP outcome with the reduction of ambient light to premature infants' retinas. The overall methodological quality of the included studies was about evenly split

between those in which the classification was unclear and those in which the studies were categorised as low risk of bias. There was no report on the secondary outcomes considered in this review: quality of life measures; and time of exposure to oxygen.

Authors' conclusions

The evidence shows that bright light is not the cause of retinopathy of prematurity and that the reduction of exposure of the retinas of premature infants to light has no effect on the incidence of the disease.

PLAIN LANGUAGE SUMMARY

Early light reduction for preventing retinopathy of prematurity in very low birth weight infants

Retinopathy of prematurity (a common retinal neovascular disorder of premature infants) is a leading cause of childhood blindness worldwide. The cause of advanced retinopathy of prematurity and the way the disease develops are not fully understood. In the past many factors, such as the use of supplemental oxygen, excessive light exposure and hypoxia (lack of oxygen), have been suggested as possible causes. Light exposure has been investigated because experimental studies have demonstrated that intensive lighting can result in irreversible damage to the retina. However, the clinical studies conducted to date have shown conflicting results in terms of the effects of light in the development of the disease. Furthermore, studies have concluded that reduction of light exposure does not reduce the progression of retinopathy of prematurity.

This systematic review aimed to evaluate the efficacy of early light reduction to prevent retinopathy of prematurity in very low birth weight infants. We selected randomised controlled trials (a specific type of scientific experiment to test the efficacy and/or effectiveness of various types of medical intervention within a patient population). Four studies (seven publications) with a reasonable methodological quality were included with a total of 897 participants. The evidence shows that bright light is not the cause of retinopathy of prematurity and that the reduction of exposure of the retinas of premature infants to light has no effect on the incidence of the disease. This evidence is up to October 2012.

BACKGROUND

Description of the condition

Retinopathy of prematurity (ROP) is a common retinal neovascular disorder of premature infants ([Palmer 1991](#)). It is of variable severity and usually heals with mild or no sequelae, but may progress in some infants to partial vision loss or blindness from retinal detachments or severe retinal scar formation. The disease is described clinically by the International Classification of ROP which uses the location in the retina (zones), extent of disease (clock hours of disease), severity of the neovascularisation (stages) and the presence or absence of 'plus' disease to describe categories of the disorder ([ICROP 1984](#)). Categories of 'pre-threshold' and 'threshold' are summary descriptions of ROP disease severity with prognostic significance developed by the Cryotherapy for ROP Co-operative Group, where eyes that developed threshold ROP had an observed rate of 47% progression to retinal detachment ([CRYO-ROP 1990](#)).

The incidence of both any acute ROP and of the more severe stages varies inversely with gestational age at birth. ROP is unusual (except in the mildest forms) in infants of more than 31 weeks gestation, and severe complications such as retinal detachment occur in less than one-half of one per cent of infants of more than 31 weeks gestation ([Palmer 1991](#)). However, 84% of infants of less than 28 weeks gestation develop some ROP and close to 11% develop 'threshold ROP' and undergo ablative surgery (cryotherapy or laser photocoagulation) to the peripheral avascular retina to reduce the risk of disease progression to retinal detachment ([CRYO-ROP 1990](#)).

In more than half a century of intense clinical and laboratory research, great advancements have been made in elucidating the pathogenesis of retinopathy of prematurity. Currently, it is known that ROP is a two-phase disease. Phase 1 begins when retinal vascular growth ceases after premature birth (roughly 22 to 30 weeks' postmenstrual age). For a period of time, the vessel formation is halted at the interface between the vascular and avascular retina. It is now understood that phase 1 involves relative hyperoxia and a decrease in vascular endothelial growth factor (VEGF) levels. Phase 2 (from roughly 31 to 44 weeks' postmenstrual age) is triggered by an increase in VEGF concentrations, in an attempt to compensate for the hypoxic retina ([Hellstrom 2001](#); [Smith 2003](#); [Mintz-Hittner 2011](#)).

Description of the intervention

Efforts to reduce morbidity from ROP can be grouped into preventive and interdictive categories. While prevention would be best aimed at preventing premature birth, once that birth is inevitable such efforts are directed at reducing the stresses that may lead to injury of the developing retinal capillaries. To date, these have focused on antioxidants, reduction of light exposure and control of exogenous oxygen delivery. Animal models or clinical data have suggested that each of these are candidates for causing retinal injury. For the purposes of determining what preventive treatments to consider using, it is important to remember that preventive interventions must be applied to all premature infants, not just those infants who develop ROP, and that therefore potential side effects should be minimal.

Interdictive approaches target just those eyes that already have ROP of a defined severity. The goal is to control or arrest the

progression of the neovascularisation (even at the sacrifice of some of the retina) in order to preserve central vision. Cryosurgical or laser ablation of the peripheral avascular retina destroys the cells that are the putative source of the neovascular growth factors, thus allowing regression of the neovascularisation. Anti-VEGF drugs are an alternative treatment for poor ROP.

How the intervention might work

Exogenous light exposure

It is hypothesised that oxygen free radicals are one cause of injury to developing retinal capillaries in the premature infant ([Hepner 1949](#); [Locke 1952](#); [Riley 1969](#)). Energy from light striking the retina may induce, or increase, the number of oxygen free radicals in the retina, particularly in the face of high levels of tissue oxygen. Numerous animal studies have demonstrated retinal injury from light, but these injuries have been to other parts of the retina than the blood vessels, namely the photoreceptors, cornea or lens, depending on the amount and wavelengths of the light used ([Lawwill 1982](#); [Ricci 1990](#); [Penn 1992](#); [Wesolowski 1994](#)).

Why it is important to do this review

Many years ago, light was seen as a risk factor for the development of ROP in very low birth weight infants. There is still some controversy about whether reduced light could have significant protection in the development of ROP. This systematic review aims to update the knowledge in this field.

Previous overviews of light exposure

A search of MEDLINE, EMBASE and bibliographic references of published research on light exposure and personal discussion with investigators involved in ROP research uncovered only one systematic review, published in the book 'Effective Care of the Newborn Infant' (New Reference). No meta-analysis was attempted in that review due to methodological difficulties with the reported studies. New data had been published since that review ([Seiberth 1994](#); [Braz 2006](#)) and, therefore, the first Cochrane review was carried out and published in February 1997. Subsequent new research led to updates of that review in July 1997 (adding [Kennedy 1997](#)) and August 1998 (adding [Reynolds 1998](#)). This is a second update of the review with new authorship for this update.

OBJECTIVES

The objective of this review is to determine whether the reduction of early environmental light exposure reduces the incidence of retinopathy of prematurity (ROP) or poor ROP outcomes among very low birth weight infants.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) and quasi-RCTs (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) as well as cluster-randomised controlled trials were to be included in this systematic review.

Types of participants

All premature human infants.

Types of interventions

Intervention of interest: beginning within the first week after birth, covering of the infant's eyes, or reduction of light falling on the infant's face, in a controlled manner.

We considered trials where comparisons have been made between the intervention of interest and no intervention. We also considered studies which evaluate different interventions against each other.

Types of outcome measures

Primary outcomes

1. Acute ROP: any stage of ROP during the weeks after birth, observed by direct or indirect ophthalmoscope (ICROP 2005).
2. Poor ROP outcome: in either the acute period, or in follow-up, the ROP observed advanced to Stage 4b (partial retinal detachment involving the macula), extensive cicatrix obscuring the visual axis, or stage 5 ROP (total retinal detachment), or the ROP advanced to the point where cryotherapy or laser treatment was used for threshold ROP.

A special note regarding data from eyes (two) versus infant (one) is warranted. In ROP, outcomes between eyes are strongly correlated, but not perfectly so. Therefore, it is important in each study to carefully consider whether outcomes in eyes or outcomes in infants are being reported, and if by infant whether the worst stage in the worst eye is used (usually the case), or some sort of average.

Secondary outcomes

1. Quality of life measures: any validated measurement scale which aims to measure the impact of visual function loss on the quality of life of participants.
2. Time of exposure to oxygen.

Search methods for identification of studies

We conducted systematic searches for randomised or quasi-randomised controlled trials. We also considered cluster-randomised controlled trials. We did not use any language, publication year or publication status restrictions. The date of the last search was 23 October 2012.

Electronic searches

We obtained randomised controlled trials from the following sources: the Cochrane Neonatal Group's Specialised Register of Controlled Trials, the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*), MEDLINE (1966 to October 2012), EMBASE (1980 to October 2012), CINAHL (through October 2012), HealthSTAR (to August 1996), Science Citation Index (Current Contents) Database (1984 to October 2012), CANCERLIT, www.clinicaltrials.gov and the Oxford Database of Perinatal Trials using the search strategy for clinical situation and intervention in [Appendix 1](#). Because so few citations were expected, the search was not limited by type of methodology used.

Searching other resources

We obtained further reports from cross-referencing the bibliographies of retrieved articles and interviews with expert informants.

Data collection and analysis

We used the standard methods of the Cochrane Neonatal Review Group and The Cochrane Collaboration for conducting this systematic review.

Selection of studies

Two authors (ECJ and RED) independently screened the trials identified by the literature search. We resolved disagreements by discussion for quality assurance of the processes.

Data extraction and management

Two authors (ECJ and RED) independently extracted data. We resolved any discrepancies by discussion. We used a standard data extraction form to extract the following information: characteristics of the study (design, methods of randomisation); participants; interventions; outcomes (types of outcome measures, adverse events). We then checked for errors before entering the data into RevMan 5 ([Review Manager 2011](#)).

Assessment of risk of bias in included studies

For the assessment of study quality, we used the new 'Risk of bias' approach for Cochrane reviews ([Higgins 2011](#)). We used the following five separate criteria.

1. Random sequence generation: was the allocation sequence adequately generated, for example with random number tables or computer-generated random numbers? We recorded this as 'low risk of bias' (the method used is either adequate or unlikely to introduce confounding), 'uncertain risk of bias' (there is insufficient information to assess whether the method used is likely to introduce confounding), or 'high risk of bias' (the method used (e.g. quasi-randomised trials) is improper and likely to introduce confounding).
2. Allocation concealment: was allocation adequately concealed in a way that would not allow either the investigators or the participants to know or influence allocation to an intervention group before an eligible participant was entered into the study (for example, using central randomisation or sequentially numbered, opaque, sealed envelopes held by a third party)? We recorded this as 'low risk of bias' (the method used (e.g. central allocation) is unlikely to induce bias in the final observed effect), 'uncertain risk of bias' (there is insufficient information to assess whether the method used is likely to induce bias in the estimate of effect), or 'high risk of bias' (the method used (e.g. open random allocation schedule) is likely to induce bias in the final observed effect).
3. Masking: were the study outcome assessors masked from knowledge of which intervention a participant received? We recorded this as 'low risk of bias' (the outcome measurement is not likely to be influenced by lack of masking), 'uncertain risk of bias' (there is insufficient information to assess whether the type of masking used is likely to induce bias in the estimate of effect), or 'high risk of bias' (the outcome or the outcome measurement is likely to be influenced by lack of masking).

4. Incomplete outcome data: were incomplete outcome data adequately addressed? Incomplete outcome data essentially include: attrition, exclusions and missing data. If any withdrawals occurred, were they described and reported by treatment group with reasons given? We recorded whether or not there were clear explanations for withdrawals and dropouts in the treatment groups. An example of an adequate method to address incomplete outcome data is the use of an intention to-treat analysis (ITT). We recorded this item as 'low risk of bias' (the underlying reasons for missingness are unlikely to make treatment effects depart from plausible values, or proper methods have been employed to handle missing data), 'uncertain risk of bias' (there is insufficient information to assess whether the missing data mechanism in combination with the method used to handle missing data is likely to induce bias in the estimate of effect), or 'high risk of bias' (the crude estimate of effects (e.g. complete case estimate) will clearly be biased due to the underlying reasons for missingness, and the methods used to handle missing data are unsatisfactory).
5. Selective reporting: are reports of the study free from any suggestion of selective outcome reporting? This was interpreted as no evidence that statistically non-significant results might have been selectively withheld from publication, for example selective under-reporting of data or selective reporting of a subset of data. We recorded this as 'low risk of bias' (the trial protocol is available and all of the trials prespecified outcomes that are of interest in the review have been reported or similar), 'uncertain risk of bias' (there is insufficient information to assess whether the magnitude and direction of the observed effect is related to selective outcome reporting), or 'high risk of bias' (not all of the trials prespecified primary outcomes have been reported or similar).

Information relevant for making a judgement on a criterion were copied from the original publication into an assessment table. When additional information was available from study authors, this was also entered in the table along with an indication that this was unpublished information. Two review authors (ECJ and RED) independently made a judgement as to whether the risk of bias for each criterion was considered to be 'low', 'uncertain' or 'high'. We resolved disagreements by discussion.

We considered trials which were classified as low risk of bias for sequence generation, allocation concealment, blinding, incomplete data and selective outcome reporting as low risk of bias trials.

We recorded this information for each included trial in 'Risk of bias' tables in RevMan 5 (Review Manager 2011) and summarised the risk of bias for each study in a summary 'Risk of bias' figure and graph.

Measures of treatment effect

Binary outcomes

We used the risk ratio (RR) as the effect measure with 95% confidence intervals (CI) for dichotomous data.

Continuous outcomes

We planned to present the results as mean differences (MD) with 95% confidence intervals (CI) for continuous data. When pooling data across studies we planned to estimate the mean difference if the outcome was measured in the same way between trials. We

planned to use the standardised mean difference (SMD) to combine trials that measured the same outcome but used different methods.

Unit of analysis issues

The unit of analysis was the eye of individual participants. However, for quality of life the unit of analysis was the patient.

Dealing with missing data

An intention-to-treat analysis (ITT) is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether they received the intervention or not. We assumed that participants who dropped out are non-respondents. For each trial we reported whether or not the investigators stated if the analysis was performed according to the ITT principle. If participants were excluded after allocation, we reported any details provided in full.

Furthermore, we planned to perform an intention-to-treat analysis (Newell 1992) whenever possible. Otherwise, we adopted the 'available case analysis' (i.e. per protocol analysis).

Assessment of heterogeneity

We looked for clinical heterogeneity by examining the study details then testing for statistical heterogeneity between trial results using the Chi² test and the I² statistic (Deeks 2008). We classified heterogeneity using the following I² values:

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Assessment of reporting biases

Apart from assessing the risk of selective outcome reporting, considered under assessment of risk of bias in included studies, we planned to assess the likelihood of potential publication bias using funnel plots, provided there were at least eight trials. If small studies in a meta-analysis tended to show larger treatment effects, we planned to consider other causes including selection biases, poor methodological quality, heterogeneity, artefact and chance.

Data synthesis

We used the fixed-effect model to analyse data. If significant heterogeneity (e.g. I² higher than 50%) was identified, we computed pooled estimates of the treatment effect for each outcome under a random-effects model (with two or more studies).

Subgroup analysis and investigation of heterogeneity

We planned to use subgroup analysis to pool the results in the case of excessive clinical heterogeneity (I² > 50%). Subgroup analyses are secondary analyses in which the participants are divided into groups according to shared characteristics and outcome analyses are conducted to determine if any significant treatment effect occurs according to that characteristic. When data permitted, we planned to carry out the following subgroup analyses:

- infants of less than 1000 g birth weight and those 1000 to 2000 g birth weight (i.e. smaller versus larger premature infants).

Sensitivity analysis

We planned to perform a sensitivity analysis to explore causes of heterogeneity and the robustness of the results when there was an adequate number of studies. We planned to include the following factors in the sensitivity analysis, separating studies according to:

- low risk of bias versus high risk of bias;
- rates of withdrawal for each outcome (less than 20% versus 20% or more).

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

For the original review in 1997, one review author scanned all citations (title and abstract if listed) retrieved with the search strategy (over 90) and determined 24 to be possibly relevant (human premature infants, light reduced in the first week and ROP outcome data reported). An independent review author made the same determination on a subset of 20 of these citations and selected all of the same top-ranked 18 citations that appeared in that subset, plus four others. However, upon review of photocopies of those additional four full citations, none proved to be relevant and the decisions of the first review author were accepted on the remainder for identifying all the possibly relevant articles. During the search process, two sets of unpublished data (part of the 24), two abstracts and one ongoing trial were identified.

Photocopies of the 24 possibly relevant articles were provided to two independent review authors to determine the true relevance of the article and the methodology used in the study. Thirteen relevant studies contained in 12 citations were identified (one citation contained two studies). Twelve other citations proved to be editorials, letters, duplicate abstracts or subsequent publications based on the data from one of the 10 studies. The two citations of unpublished data sets were also evaluated by the review authors: one was technical pilot data without a control group and the other involved a problematic comparison group.

Photocopies of the 12 relevant citations were provided to two review authors to independently determine the methodology used. Methods were evaluated for masking of randomisation, masking of intervention, completeness of follow-up and masking of outcome measurement. Five randomised or quasi-randomised trials were identified. Five cohort studies comparing a period of reduced light to a non-randomised control cohort were identified, and two studies had no controls.

For the first update of this review in 2000, no new trials were identified.

For the second update of the review in 2013, only 82 references were identified by the searches. We then selected three references for careful reading. Following assessment of the full articles, we considered two further publications for inclusion in this review: [Braz 2006](#) and [Reynolds 1998](#) met the minimal methodological requirements to be included in this review.

Included studies

Four studies (seven publications) were included in this review ([Seiberth 1994](#); [Kennedy 1997](#); [Reynolds 1998](#); [Braz 2006](#)), with a total of 897 participants.

It is important in each study to carefully consider whether outcomes in eyes or outcomes in infants are being reported. In the Locke study, the intervention (patching) was applied to one eye with the opposite eye serving as control, and thus each infant contributed two outcomes; one for the treated group and one for the control. In [Seiberth 1994](#); [Kennedy 1997](#); [Reynolds 1998](#) and [Braz 2006](#) both eyes of each infant were treated in the same way. Therefore, each infant could contribute only once to the outcomes and was reported/recorded as the worst stage of ROP observed (presumably in either eye).

Additionally, because light hypothetically might be expected to affect acute ROP differently than severe ROP (poor ROP outcome), we also extracted data in categories of ROP severity, if possible. 'Poor ROP outcome' was defined as retinal detachments, partial or complete (stages 4b or 5 in the International Classification of ROP detachments, [ICROP II 1987](#)), or ROP of threshold severity requiring cryo/laser surgery. Original authors kindly confirmed data extraction and responded to questions that were unclear from their publications ([Seiberth 1994](#); [Braz 2006](#)).

1. [Seiberth 1994](#): 169 infants of less than 1501 g birth weight from one nursery were enrolled and then randomised (by a phone call to the randomisation centre - personal communication from authors) to no patching or patching of both eyes from the day of birth until 35 weeks postmenstrual age. Parents, nurses and paediatricians could observe the treatment assignment, but ophthalmologists determining outcomes were masked to the study group. Three families in the patched group withdrew after randomisation. Eye examinations were standardised and a calculated sample size and a priori hypotheses stated. A similar number of infants in each group were lost to follow-up due to transfers (16%) or death (six patched and eight controls). Outcomes were based on the worst stage of ROP reached in each infant and no significant differences were found.
2. [Braz 2006](#) (further two publications as abstracts: [Lopes 1997](#); [Braz 1996](#)): a randomised controlled trial enrolling 226 infants of less than 1600 g birth weight or < 32 weeks gestation. In the experimental group, patching of both eyes began on the day of birth and continued until 35 weeks postmenstrual age. Because a paired randomisation within birth weight groups (two per block) was used, the investigator obtaining consent was sometimes aware of what the next randomisation assignment would be. Indirect ophthalmoscopy was performed every two weeks and recorded according to the International Classification of ROP. To date, results in 74 control and 75 experimental group survivors are reported. In both groups, 37% of surviving infants developed some degree of ROP. Two control and no experimental infants were treated with cryotherapy (presumed to have threshold ROP). It is unclear whether this study is ongoing. (Authors kindly provided additional information in addition to that in published abstracts.)
3. [Kennedy 1997](#): a randomised controlled trial randomising infants weighing 1250 g or less, or of gestational age 32 weeks or less, at 0 to 6 hours after birth with consent subsequently obtained to continue the study. Goggles were worn until 31

weeks and the primary outcome was electroretinograms at 35 weeks postmenstrual age. Seventy-one of 135 infants born at less than 1251 g during the study period were randomised and 10 families subsequently refused consent to continue in the study (six control and four goggles). Of the 61 infants in the study, 11 had no outcomes due to death (six control, three goggles), or protocol violation (one goggle) or per study criteria of second surviving twin (one control). ROP was a secondary outcome, determined by residents or attendings who were masked to study assignment, and reported only as present or as reaching pre-threshold stage according to the CRYO-ROP study definitions. Therefore, only acute ROP can be reported. Acute ROP rates were similar in both groups: 29% goggles, 31% controls. While the loss to follow-up by this unusual randomisation method raises some concern, similar numbers from each group withdrew at the point of consent.

4. **Reynolds 1998:** infants of less than 31 weeks gestation and less than 1251 g birth weight were randomised after informed consent through a central registry to wearing goggles or control. The goggles were placed on the infant within 24 hours of birth, reducing light by 97% (100% of ultraviolet) and were continued until the infant was 31 weeks postmenstrual age or four weeks chronological age, whichever occurred later. Oxygen exposure and use was not reported. Certified study ophthalmologists masked to group assignment examined all infants starting at 32 weeks postmenstrual age and classified ROP according to the International Classification of ROP. Confirmed ROP was required for the study outcome and consisted of at least three clock hours of ROP in any zone observed on at least two examinations. However, 'any ROP' was also reported in the tables permitting direct comparison of results with previous studies. Of the 409 infants randomised, 46 died before the ROP outcome could be determined and two were lost to follow-up (distribution of these 48 infants between the 17 missing goggled infants (8.3%) and 31 missing controls (15%) is not described but has to approximate mortality in the two groups since only two infants were not lost because of death). The comparable numbers for 'any ROP' were 130 (69%) in the goggled group and 121 (70%) in the controls, and these numbers are the ones used in this review. For pre-threshold ROP it was 19/188 (10%) goggled versus 15/173 (9%) controls, and for threshold ROP it was 9/188 (4.8%) goggled versus 9/173 (5.2%) controls. For the subgroup analysis (< 1 kg and > 1 kg) only 'confirmed ROP' was reported and therefore was used in the data tables in this review. There were no significant differences between the two groups. Examination of the baseline characteristics revealed only minimal differences between the groups and these were associated with a slightly higher predicted risk of ROP in the control group and therefore do not affect the conclusions. Poor ROP outcome as vision loss was not reported, however, threshold ROP was used for the 'poor outcome' variable. Oxygen exposure, oxygen use and vitamin E use were not reported, and the statistical section did not address sample size or power.

Excluded studies

Six studies were excluded and are described in the table [Characteristics of excluded studies](#).

1. **Locke 1952:** in this study, conducted before knowledge of the oxygen link to ROP, one eye of each of 22 infants (less than 2001 g birth weight) was patched from within 24 hours after birth through

discharge. Non-survivors are not mentioned. Although selection of which eye was to be patched is not described, there is no biological rationale to expect one eye to be more likely to develop ROP than another. Control eyes were examined weekly with a direct ophthalmoscope, and patched eyes only at the time of discharge. If mild, transient ROP were an outcome, this would be problematic; however, the type and severity of ROP that could be detected with the direct ophthalmoscope would have been the same in both groups given the timing of examinations. Outcomes are based on eyes, rather than infants since each eye received different treatment. The first author performed all eye examinations and was not masked as to study group. No differences were observed.

(Used for discussion). In Locke's second study, 33 premature infants in one nursery had both eyes patched from within 24 hours of birth until discharge, and were compared to 33 premature infants of matched birth weights from the immediately preceding time period in the same nursery. Determinations of eye outcomes were with direct ophthalmoscopes as noted in study A from the same citation. These historical controls were close in time and from the same nursery, but leave reason to be concerned about the results because of potential changes in practice even over this time period. No significant differences were observed.

2. **Hommura 1988:** (used for discussion). Control infants included all 21 survivors of less than 1501 g birth weight born in one hospital in 1983 to 1984. Treated infants were all 16 survivors of less than 1501 g birth weight born in 1985 to 1986. Treated infants had both eyes patched from the day of birth until discharge home. Examinations were conducted weekly by one ophthalmologist not masked to study group. There were fewer cases of acute ROP in the patched infants. The results, when reported as eyes rather than as infants, are statistically significant, but not so if reported as infants. This is concerning because left and right eyes are closely correlated in this disease and therefore not independent events. For this discussion, eye outcomes were converted to infant outcomes based on the worst eye from each infant. The authors provided supplemental information to Professor Ogawa who assisted in translation.

3. **Glass 1985:** (used for discussion). This study was designed to have an immediately preceding control cohort because the authors believed that concurrent controls were not possible. They felt that personnel accustomed to shielded incubators would insist on shielding all infants once the intervention had been taught. Premature infants from two nurseries had light reduction via shields placed over the incubators. The time from birth to placement in incubators that were then shielded was not controlled. This creates a potential bias against finding an effect of shielding because the sickest infants, and therefore the ones most likely to get ROP, could be more likely to stay in the radiant warmers longer and therefore could have had later shielding from light than more healthy infants.

Eye examinations were conducted by experienced ophthalmologists according to usual practice and they were unaware of group assignment, which could have meant that they were unaware of the research project, particularly during the control period. No mention of specific research data forms is made in the report. This is problematic because the manner in which ophthalmologists viewed ROP and its staging and medical record notes were undergoing significant changes during just this period of time. The first meeting to talk about a new international classification for ROP occurred in 1981 at the Ross Conference

on ROP held in Washington DC. The second meeting which resulted in a draft classification which was to be taken home and tried out for a year occurred in Calgary, Canada in 1982. The third meeting was held at the NIH in 1983, and led to the final International Classification of ROP published in 1984. This evolution of the classification was happening during this study which recruited controls mostly in 1982 and shielded infants mostly in 1983. Therefore, these data raise concerns around the definitions of diagnoses changing with time as the study moved from enrolling controls to enrolling treated infants, as well as the non-random allocation. Statistically significantly lower rates of ROP were observed in the shielded infants. The results are used for discussion.

4. [Ackerman 1989](#): (used for discussion). This study compared historical controls from an immediately preceding period to similar infants after instituting shielding of incubators. In this manner, most of the problems from the Glass study are replicated, except that the possible changing of the ROP classification is less of a problem. The time from birth until shielding is not well described, with the same bias against finding an effect as in the Glass study. Some infants may have been in open warmers for more than a week after birth before being shielded. Ophthalmologists determining outcomes were unaware of shielding status and no differences between the two cohorts was observed. There are significant chances for bias and therefore these data are used only for discussion.

5. [Hepner 1949](#): five premature infants had both eyes covered by 30 hours after birth and the patching was continued until near discharge when the first eye examination was performed. There were no controls or mention of baseline or historical rates of ROP in the paper. Four of the five infants developed severe ROP in both eyes. Ironically, the generous use of oxygen is well documented in each of these careful case histories. The authors accepted these findings as having ruled out the possibility that ambient light caused ROP. Without controls, the data cannot contribute to a meta-analysis.

6. [Repka 1996](#) (unpublished): these data are unpublished and found only as a personal communication in a Manual of Procedures for a current ongoing study. The data were discussed with the author (MXR) and describe the incidence of ROP in two different nurseries with different ambient levels of light by actual measurement. All infants were less than 1000 g birth weight and the brighter nursery had a higher incidence of ROP. However, the nurseries have very different populations (race, illness rates, insurance, etc.) and different physicians and policies involved in their care. Therefore, it is not appropriate to compare these outcomes directly and the investigators have decided not to submit the outcomes for publication.

Risk of bias in included studies

Please see [Figure 1](#) and [Figure 2](#).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Braz 2006	?	?	+	?	?	+	+
Kennedy 1997	-	+	+	+	-	+	+
Reynolds 1998	+	+	+	+	+	+	+
Seiberth 1994	?	?	+	+	-	+	+

Allocation

[Braz 2006](#) and [Seiberth 1994](#) did not report how the allocation generation and concealment was achieved.

[Kennedy 1997](#) randomised the patients using sequential, sealed, opaque cards, while [Reynolds 1998](#) used a computer-assisted randomisation protocol for each centre by a third party. Therefore, we classified both studies as low risk of bias.

Blinding

Not applicable for participants and personnel.

With regard to blinding of outcome assessors in [Seiberth 1994](#), [Kennedy 1997](#) and [Reynolds 1998](#), the ophthalmologists were masked to group when determining outcome, except for [Braz 2006](#) in which blinding of outcome assessors was not reported.

Incomplete outcome data

In [Braz 2006](#) the authors lost 16.81% from the total randomised patients (less than 20%), therefore the study could be rated as low risk of bias. In the [Reynolds 1998](#) study, the authors lost less than 20% per group (8.2% and 15.2% in the goggle and control groups, respectively), therefore we classified the study as low risk of bias.

[Kennedy 1997](#) presented a high risk of bias as they lost 11.5% and 4.1% of patients from the goggle and control groups, respectively, for electroretinogram (ERG) analysis. For the visual acuity exam, 46.1% and 50% of the patients were lost to follow-up from the goggle and control groups, respectively. We also classified [Seiberth 1994](#) as high risk of bias as there was a loss of 27% and 22.6% for the patched and non-patched groups, respectively, in the final analysis.

Selective reporting

There was no evidence of selective reporting in any of the included studies (Seiberth 1994; Kennedy 1997; Reynolds 1998; Braz 2006).

Other potential sources of bias

None known.

Effects of interventions

Reduced light versus controls

All studies tested the effect of covering the eyes and none observed a significant difference in the incidence of any acute retinopathy of prematurity (ROP), or of poor ROP outcomes, either in all infants (all studies), or those of less than 1000 g or 1000 to 2000 g birth weight (Seiberth 1994; Reynolds 1998). Meta-analysis of the results gave the same answer. The summary risk ratios (RR) for the infants with their eyes covered, compared to controls, were 1.00 (95% confidence interval (CI) 0.89 to 1.13) (Analysis 1.1) for acute ROP and 1.13 (95% CI 0.49 to 2.61) (Analysis 1.4) for poor ROP outcome.

The summary risk ratios for the infants with their eyes covered, compared to controls, for acute ROP were as follows.

Acute ROP, all infants less than 2001 g birth weight (Outcome 1.1):

Four studies enrolling 726 infants reported on this outcome. No reduction in the risk of any acute ROP was seen with light reduction as there was no statistically significant difference (typical RR 1.00, 95% CI 0.89 to 1.13; typical RD 0.00, 95% CI -0.07 to 0.07) (Analysis 1.1).

Acute ROP, infants less than 1000 g birth weight (Outcome 1.2):

Two studies enrolling 270 infants reported on this outcome. No reduction in the risk of any acute ROP was seen with light reduction as there was no statistically significant difference (RR 0.96, 95% CI 0.82 to 1.13; RD -0.03, 95% CI -0.14 to 0.08) (Analysis 1.2).

Acute ROP, infants 1000 to 2000 g birth weight (Outcome 1.3):

Two studies enrolling 218 infants reported on this outcome. No reduction in the risk of any acute ROP was seen with light reduction as there was no statistically significant difference (RR 1.00, 95% CI 0.68 to 1.49; RD 0.00, 95% CI -0.12 to 0.12) (Analysis 1.3).

Poor ROP outcome, all infants less than 2001 g birth weight (Outcome 1.4):

Two studies enrolling 488 infants reported on this outcome. No reduction in the risk of any acute ROP was seen with light reduction as there was no statistically significant difference (RR 1.13, 95% CI 0.49 to 2.61; RD 0.01, 95% CI -0.03 to 0.04) (Analysis 1.4).

Poor ROP outcome, infants less than 1000 g birth weight (Outcome 1.5):

One study enrolling 62 infants reported on this outcome. No reduction in the risk of any acute ROP was seen with light reduction as there was no statistically significant difference (RR 10.24, 95% CI 0.51 to 203.83; RD 0.10, 95% CI -0.04 to 0.24) (Analysis 1.5).

Poor ROP outcome, infants 1000 to 2000 g birth weight (Outcome 1.6):

One study enrolling 81 infants reported on this outcome. The RR was not estimable (RR 0.00, 95% CI -0.05 to 0.05) (Analysis 1.6).

To consider the question at a less rigorous level, we incorporated the data from the five observational cohort studies by repeating the analysis with all 10 studies (data not shown in graphs). The pooled results also indicate that reducing light exposure produced no effect on the incidence of acute ROP, or poor ROP outcomes, in all premature infants, those under 1000 g birth weight or those of 1001 to 2000 g birth weight (where data were available). The 95% CI intervals for the risk ratios all encompassed 1.0, even with these larger aggregate sample sizes.

Quality of life measures

No included study reported on this outcome.

Time of exposure to oxygen

No included study reported on this outcome.

DISCUSSION

Data available from valid studies in the published literature provide strong evidence that a reduction in light will not reduce the overall incidence of acute retinopathy of prematurity (ROP). The data are less conclusive about reduction of poor ROP outcomes because of sample size and the low rates of these severe stages. Additional reports using non-randomised controls do not provide data that are sufficiently free of potential bias to include in the meta-analysis, but in aggregate they also show no reduction in ROP.

If such a relatively simple, inexpensive intervention as reducing light could reduce poor visual outcomes it would be extremely valuable and it has been important to settle the question. The addition of the LIGHT-ROP study (Reynolds 1998) strengthens the conclusion that light reduction is not the solution to preventing ROP vision loss. Critics of this study state that the goggles should have been placed on the infants sooner than within the first 24 hours, but subgroup analysis of the 15% who were goggled within six hours of birth also showed no difference (similarly for the Kennedy 1997 study where infants were also goggled within six hours of birth.)

The confidence intervals around these conclusions are fairly narrow for reducing ROP overall so that a true absolute difference in the incidence rates would be no more than 7%, and the risk ratio is contained within the interval of 0.88 to 1.14. However, the 95% confidence interval for the relative risk difference in poor retinal outcomes is larger because the rates are so low. With the current aggregate sample sizes, the risk ratio could fall between 0.52 and 2.38, although the absolute risk reduction would fall between a 3.1% reduction to a 4.1% increase in absolute rates of poor retinal outcomes.

The question for investigators and funding agencies now is whether to commit further resources to conducting even larger studies of light reduction. The chance that a true effect of light reduction has been missed is now small. Complicating this decision are the other reasons for reducing light exposure in the neonatal intensive care unit, along with noise reduction and other noxious stimuli related to better rest and recovery and growth. These are the subjects

of other studies and will complicate future efforts to examine, in isolation, the effects of light reduction.

The number of infants studied to date allows 95% confidence that if there were a true difference being missed, it would be smaller than seven percentage points on a background of 54% of all infants under 2 kg developing ROP based on risk difference.

Future research is unlikely to change the conclusion reached in this analysis: that light reduction to the retina of premature infants does not significantly reduce the incidence or severity of ROP.

Summary of main results

This review examined the efficacy of light reduction for preventing retinopathy of prematurity in very low birth weight infants. Four studies were included with a total of 897 infants. We included three randomised and one quasi-randomised controlled trial. Although the quality of included studies was reasonable, it was not possible to use analytical methods such as subgroup analysis of weight gain or duration of supplemental oxygen therapy, or to explore heterogeneity.

Overall completeness and applicability of evidence

Because of our comprehensive search strategy and contact with experts in the field, we are confident that we have mapped all clinical trials comparing any intervention aiming to cover the infant's eyes or to decrease of light falling on the infant's face. Although the evidence on the use of goggles for preventing retinopathy of prematurity in very low birth weight infants came from only four small trials, the included studies seem to confirm that bright light is not the cause of retinopathy of prematurity.

Quality of the evidence

The overall methodological quality of the included studies was about evenly split between those in which the classification was unclear ([Seiberth 1994](#); [Braz 2006](#)) and those in which the studies were categorised as low risk of bias ([Kennedy 1997](#); [Reynolds 1998](#)).

Potential biases in the review process

We applied a very comprehensive search strategy to identify all potential studies and their reports. Although we have sent an email

to [Braz 2006](#) to request clarification of methodological issues and further information on the study, we await their response (with the exception that the participants from the Lopes 1997 study are the same as those from the most recent study ([Braz 2006](#))). All relevant outcome data prespecified in our protocol were reported.

Agreements and disagreements with other studies or reviews

Our findings are consistent with all the included studies ([Seiberth 1994](#); [Kennedy 1997](#); [Reynolds 1998](#); [Braz 2006](#))

AUTHORS' CONCLUSIONS

Implications for practice

The evidence shows that bright light is not the cause of retinopathy of prematurity and that the reduction of exposure of the retinas of premature infants to light has no effect on the incidence of the disease.

Implications for research

Additional, very large controlled trials of light reduction would be needed to further limit the possibility of having missed a small true difference in the rates of severe ROP among light-restricted and control premature infants. However, the data to this point show that no significant benefit is to be expected.

ACKNOWLEDGEMENTS

Original review:

Dr. John C. Sinclair for support, encouragement and editorial assistance.

Dr. Catherine Clase for providing independent reviewing.

Professor Yunosuke Ogawa and Ben Miura for assistance in translation.

Review update 2011:

We would like to thank the Cochrane Neonatal Group, mainly Diane Houghton and Yolanda Brosseau, the Managing Editors, for their support.

We would also like to thank Dr. Dale Phelps for her authorship of the original review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Braz 2006

Methods	Design: randomised clinical trial Multicentre (2 neonatal intensive care units) Period: June 1995 to November 1996
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Braz 2006 (Continued)

Sample size: not reported
Follow-up: not reported

Participants	N = 226 randomised; 188 evaluated (control n = 93; trial n = 95) Sex: control 61 male; trial 48 male Age (mean): control 29.7; trial 30.2 Setting: neonatal intensive care Inclusion criteria: infants < 1600 g birth weight or < 32 weeks gestation Exclusion criteria: not reported
Interventions	Patching of both eyes from birth to 35 weeks postmenstrual age
Outcomes	Incidence of retinopathy of prematurity
Notes	Abstracts also published at an earlier stage (Lopes 1997 and Braz 1996) We sent an email for the main author on 19 January 2012 asking about the generation of randomisation, allocation concealment, blinding of outcome assessment, exclusion criteria and sample size

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported, although the authors stratified the patients in pairs within birth weight groups, with the first of the pair randomised blindly (per authors)
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not applicable
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The authors lost 16.81% from the total randomised patients (less than 20%). Per-protocol analysis
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Kennedy 1997

Methods	Design: quasi-randomised clinical trial Single centre (Parkland Memorial Hospital Special Care Nursery) Period: August 1993 to June 1994 Sample size: alpha = 0.05, beta = 80%, log k of 0.15 log unit Follow-up: 4 to 6 months corrected age
Participants	N = 71 randomised; 61 completed randomisation and 50 evaluated (24 goggles, 26 controls) Sex: goggles 11 male; controls 12 male

Kennedy 1997 (Continued)

Age (mean): goggles 27.8; controls 28.2

Setting: Parkland Memorial Hospital Special Care Nursery, USA

Inclusion criteria: infants < 1251 g birth weight or < 33 weeks

Exclusion criteria: congenital abnormalities of one or both eyes, lethal or irreparable congenital anomalies noted at birth and unlikely viability (infants not receiving full intensive care support)

Interventions	Goggles on both eyes within 6 hours of birth and continued until 31 weeks postmenstrual age or 4 weeks chronological age, whichever was later
Outcomes	Electroretinograms (ERG) showed no differences Acute ROP any stage was reported in 7/24 (29%) goggled infants and in 8/26 (31%) controls, and pre-threshold ROP occurred in one of each group
Notes	Primary outcome was electroretinogram; sample size was not determined to detect changes in ROP frequency

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	The patients were randomised by a sequential method
Allocation concealment (selection bias)	Low risk	Sealed opaque cards
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not applicable
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	11.5% and 4.1%, respectively, from the goggle and control groups were lost to follow-up for the ERG analysis For the visual acuity exam, 46.1% and 50%, respectively, for the goggle and control groups were lost to follow-up
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Reynolds 1998

Methods	Design: randomised clinical trial Multicentre (3 centres in USA) Period: July 1995 to March 1997
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Reynolds 1998 (Continued)

Sample size: incidence of any ROP, a detectable difference of at least 35%, a 2-sided alpha of 0.05, power of 80%, required 88 patients per group

Follow-up: 9 months after randomisation

Participants	<p>N = 410 randomised (LIGHT-ROP 1999); 409 enrolled; 361 evaluated (18 goggles, 204 controls)</p> <p>Sex: goggles 50.7% male; controls 56.4 male</p> <p>Age (mean): goggles 27.2; controls 27.0</p> <p>Setting: Buffalo, Dallas and San Antonio, USA</p> <p>Inclusion criteria: infants < 1251 g birth weight, < 31 weeks gestation and admission of outborn infants at participating neonatal intensive care units within 24 hours of birth</p> <p>Exclusion criteria: death before randomisation, lethal or irreparable congenital anomaly, major congenital abnormality of one or both eyes, non viability of infant, anticipated transfer of infant to non-participating unit prior to 40 weeks' postconceptional age and inability to begin goggle wear within 24 hours following birth</p>
Interventions	<p>100% ultraviolet light and 97% light-reducing goggles worn in the intervention group only from within 24 hours of birth to 31 weeks postmenstrual age or 4 weeks chronological age, whichever was longer</p> <p>The control group was exposed to the amount of light that was usual for the intensive care unit</p>
Outcomes	<p>409 randomised (205 goggles, 204 controls); 46 died and 2 were lost to follow-up (17 in goggles and 31 in controls)</p> <p>Among survivors evaluated 130/188 (69%) goggled infants developed any ROP and 121/173 (70%) of controls. Threshold ROP occurred in 4.7% of goggled vs 5.2% of controls (9 in each group). Poor visual outcome or need for cryo/laser treatment was not reported</p>
Notes	<p>No differences in ROP between groups</p> <p>Also no difference in the subgroup that was goggled within 6 hours of birth</p> <p>The difference in mortality between the 2 groups is not addressed by the authors and no apparent biological explanation is forthcoming</p> <p>Note: authors used 'confirmed ROP' as the primary outcome in their report, but 'any ROP' is used here in order to be consistent with other reports in the analysis</p>

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-assisted randomisation protocol for each centre (block 2:6)
Allocation concealment (selection bias)	Low risk	Third party (co-ordinating centre)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not applicable
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Examiners were masked to study group assignment

Reynolds 1998 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 20% per group: 8.2% and 15.2% in goggles and control groups, respectively
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

Seiberth 1994

Methods	Design: randomised clinical trial Single centre Period: January 1987 to July 1991 Sample size: decrease incidence of ROP from 40% to 20%, alpha of 10% and a power of 80%, needed 62 patients per group Follow-up: 6 months postpartum
Participants	N = 169 randomised (85 patched and 84 controls); 127 enrolled and evaluated (62 patched, 65 non patched) Sex: 23 male in the patched group; 35 male in the controls Age (mean): patched 29.3; controls 29.0 Setting: neonatal intensive care unit at the Women's Hospital of the University of Heidelberg, Germany Inclusion criteria: ≤ 1500 g birth weight and ≤ 32 weeks gestation Exclusion criteria: not reported
Interventions	Both eyes were patched from the day of birth until 35 weeks postmenstrual age (= gestational age at birth plus chronological age in weeks)
Outcomes	Death occurred in 6 patched and 8 controls, 3 infants from the patched group were withdrawn by parents and 25 were lost because of transfer before complete evaluation (14 patched and 11 controls) Similar numbers developed acute ROP: 26/62 patched and 25/65 controls 2 cases of poor ROP outcome causing blindness occurred, both in the patched group
Notes	Despite a predetermined sample size, this study was stopped early because of a trend favouring the controls at an interim analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported

Seiberth 1994 (Continued)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Not applicable
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Ophthalmologists masked to group when determining outcome
Incomplete outcome data (attrition bias) All outcomes	High risk	27% and 22.6%, respectively, for the patched and non-patched groups were lost to follow-up for the final analysis
Selective reporting (reporting bias)	Low risk	No evidence
Other bias	Low risk	No evidence

ERG: electroretinogram

ROP: retinopathy of prematurity

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ackerman 1989	The comparison cohort was not randomly allocated (from a preceding time period)
Glass 1985	Self controlled clinical trial
Hepner 1949	No control group was reported
Hommura 1988	The comparison group was a historical control cohort
Locke 1952	Self controlled trial and case series report
Repka 1996	Control cohort not randomly allocated; rates of ROP from 2 different nurseries with different ambient light levels

ROP: retinopathy of prematurity

DATA AND ANALYSES
Comparison 1. Reduced light versus controls

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Acute ROP, all infants < 2001 g birth weight	4	726	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.89, 1.13]
2 Acute ROP, infants < 1000 g birth weight	2	270	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.82, 1.13]

Early light reduction for preventing retinopathy of prematurity in very low birth weight infants (Review)

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Acute ROP, infants 1000 to 2000 g birth weight	2	218	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.68, 1.49]
4 Poor ROP outcome, all infants < 2001 g birth weight	2	488	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.49, 2.61]
5 Poor ROP outcome, infants < 1000 g birth weight	1	62	Risk Ratio (M-H, Fixed, 95% CI)	10.24 [0.51, 203.83]
6 Poor ROP outcome, infants 1000 to 2000 g birth weight	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Reduced light versus controls, Outcome 1 Acute ROP, all infants < 2001 g birth weight.

Analysis 1.2. Comparison 1 Reduced light versus controls, Outcome 2 Acute ROP, infants < 1000 g birth weight.

Analysis 1.3. Comparison 1 Reduced light versus controls, Outcome 3 Acute ROP, infants 1000 to 2000 g birth weight.

Analysis 1.4. Comparison 1 Reduced light versus controls, Outcome 4 Poor ROP outcome, all infants < 2001 g birth weight.

Analysis 1.5. Comparison 1 Reduced light versus controls, Outcome 5 Poor ROP outcome, infants < 1000 g birth weight.

Analysis 1.6. Comparison 1 Reduced light versus controls, Outcome 6 Poor ROP outcome, infants 1000 to 2000 g birth weight.

APPENDICES

Appendix 1. Search strategy for clinical situation and intervention

((retrolental fibroplasia) OR (retinopathy of prematurity)) AND (light OR light/ae OR lighting OR lighting/ae OR light/tu OR light/st)

WHAT'S NEW

Date	Event	Description
14 October 2012	New search has been performed	This updates the review 'Early light reduction for preventing retinopathy of prematurity in very low birth weight infants' (Phelps 2001). New authorship as of October 2012.
14 October 2012	New citation required but conclusions have not changed	Updated search in October 2012 identified further two studies, although both of them have been published in previous years and were mentioned in the original review (Phelps 2001). Methods, types of studies and types of intervention updated. 'Risk of Bias' table added.

HISTORY

Protocol first published: Issue 2, 1997

Review first published: Issue 2, 1997

Date	Event	Description
15 September 2008	Amended	Converted to new review format.
13 November 2000	New search has been performed	This review updates the existing review of 'Early light reduction for preventing retinopathy of prematurity in very low birth weight infants' which was published in <i>The Cochrane Library</i> Issue 2, 1997, and updated in <i>The Cochrane Library</i> Issue 4, 1998.

Date	Event	Description
		As of November 2000, no additional data were discovered to alter the findings or conclusions.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: Eliane Chaves Jorge (ECJ) and Edson Nacib Jorge (ENJ)

Co-ordinating the review: Regina El Dib (RED)

Undertaking manual searches: ECJ

Screening search results: ECJ

Organising retrieval of papers: ECJ

Screening retrieved papers against inclusion criteria: ECJ and RED

Appraising quality of papers: ECJ and RED

Abstracting data from papers: ECJ and ENJ

Writing to authors of papers for additional information: ECJ

Providing additional data about papers: ECJ and ENJ

Obtaining and screening data on unpublished studies: ECJ and ENJ

Data management for the review: ECJ and RED

Entering data into Review Manager (RevMan 5): ECJ and RED

RevMan statistical data: RED

Other statistical analysis not using RevMan: RED

Double entry of data: (data entered by person one: ECJ; data entered by person two: RED)

Interpretation of data: ECJ, ENJ and RED

Statistical inferences: ECJ, ENJ and RED

Writing the review: ECJ, ENJ and RED

Guarantor for the review (one author): ECJ

Person responsible for reading and checking review before submission: ECJ, ENJ and RED

DECLARATIONS OF INTEREST

The authors (ECJ, ENJ and RED) from the second update of this review declare no conflict of interest.

Dale Phelps served as a member of the Data Safety Monitoring Committee for the LIGHT-ROP study.

SOURCES OF SUPPORT

Internal sources

- University of Rochester, NY, USA.

External sources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA.

Editorial support of the Cochrane Neonatal Review Group has been funded with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN275201100016C.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The risk of bias (RoB) was updated according to [Higgins 2011](#) as well as it was added the RoB table. Furthermore, in the original review the authors have considered [Locke 1952](#) as an included study, however we have classified it as a self controlled trial and case series report therefore this study was moved to the excluded studies section.

INDEX TERMS

Medical Subject Headings (MeSH)

*Infant, Very Low Birth Weight; *Lighting [adverse effects]; Eye Protective Devices; Infant, Premature; Light [*adverse effects]; Randomized Controlled Trials as Topic; Retinopathy of Prematurity [etiology] [*prevention & control]

MeSH check words

Humans; Infant, Newborn