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D-Penicillamine for preventing retinopathy of prematurity in preterm infants (Review)

Qureshi MJ, Kumar M

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[Intervention Review]

D-Penicillamine for preventing retinopathy of prematurity in preterm infants

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ABSTRACT

Background

The rate of retinopathy of prematurity (ROP) in moderately premature infants has decreased dramatically with improved care in the neonatal intensive care unit. A low rate of this disorder was unexpectedly observed among infants treated with intravenous D-penicillamine to prevent hyperbilirubinaemia. This observation led to the investigation of its use, both enterally as well as intravenously, to prevent ROP.

Objectives

To determine the effect of prophylactic administration of D-penicillamine on the incidence of acute ROP or severe ROP and other morbidities in preterm infants.

Search methods

We used the Cochrane Neonatal Review Group search strategy. Two review authors independently searched multiple electronic databases, previous reviews including cross references, abstracts, conference/symposia proceedings, and expert informants. We updated the search on November 27, 2012.

Selection criteria

We included randomised or quasi-randomised controlled trials if they administered D-penicillamine and compared it with no treatment or placebo to premature infants and reported on the outcome of ROP.

Data collection and analysis

We used the criteria and standard methods of the Cochrane Neonatal Review Group to assess the methodological quality of the included trials. One review author examined trials for validity. A second review author checked validity and they reached consensus on the final data before entry into this review. We used the standards of the Neonatal Cochrane Review Group to analyse data.

Main results

Three randomised trials met the inclusion criteria. The meta-analysis showed no significant differences in the risk of any stage ROP (typical risk ratio (RR) 0.32, 95% confidence interval (CI) 0.03 to 3.70), severe ROP (typical RR 0.38, 95% CI 0.03 to 4.26) or death (typical RR 0.95, 95% CI 0.68 to 1.32) in all treated infants. When the subgroup of infants under 1500 g birth weight was examined, the results were similar. No side effects were reported, and follow-up at one year revealed no significant differences in spasticity or developmental delay.

Authors' conclusions

Administration of prophylactic D-penicillamine in preterm infants does not prevent acute or severe ROP, death or neurodevelopmental delay. D-penicillamine cannot be recommended for the prevention of ROP based on the available evidence.

PLAIN LANGUAGE SUMMARY

D-Penicillamine for preventing retinopathy of prematurity in preterm infants

Retinopathy of prematurity (ROP) is an eye disease of premature infants that continues to be a serious problem. The drug D-penicillamine, given by mouth, is commonly used to treat poisoning by iron or copper or other heavy metals. In research studies of D-penicillamine used for another problem that premature infants have (high bilirubin), it was observed that the treated infants had less ROP. However, this systematic review did not show any significant benefits of this drug for the outcomes of ROP, death or development of nerves. Thus, the use of this drug cannot be recommended for the prevention of ROP based on available evidence.

BACKGROUND

Description of the condition

Retinopathy of prematurity (ROP) is a common disorder of retinal neovascularization in premature infants (Palmer 1991). It is of variable severity, 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 neovascularization (stages) and the presence or absence of 'plus' disease to describe categories of the disorder (ICROP 1984). Categories of 'prethreshold' and 'threshold' are summary descriptions of ROP disease severity with prognostic significance developed by the Cryotherapy for ROP Cooperative Group, where eyes that developed threshold ROP had an observed rate of 47% progression to retinal detachment or macular fold (CRYO-ROP 1990).

The incidence of both 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 greater than 31 weeks' gestation (Palmer 1991). However, majority of infants less than 28 weeks' gestation develop early stages of acute ROP, and close to 11% develop 'threshold ROP' requiring ablative surgery (cryotherapy or laser photocoagulation) to the peripheral avascular retina to reduce the risk of disease progression to retinal detachment (CRYO-ROP 1990).

The pathophysiology is understood to start with injury to the incomplete developing retinal capillaries. This could potentially occur before or during birth, but is thought to primarily occur in the days following delivery. Once the developing vessels have been damaged, it is hypothesized that the retina responds with the production of vascular growth factors stimulating neovascularization (which is the observable retinopathy), which may successfully revascularize the retina (regression of the ROP), or progress to neovascular membranes in the vitreous and subsequent scarring (cicatrix) and retinal detachment. Research suggests that vascular endothelial growth factor (VEGF) is one of the more important growth factors involved in this process (Aiello 1996; Aiello 1997). 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, preventive efforts are directed at reducing stressors that may lead to injury of the developing retinal capillaries. To date (November 2012), investigations have focused on the antioxidants vitamin E or D-penicillamine, reduction of light exposure (Phelps 1997),

and control of exogenous oxygen delivery (Flynn 1987; Kinsey 1956; STOP-ROP 2000). Animal models and clinical data have suggested that each of these mechanisms may cause retinal vascular injury. For 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 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 neovascularization (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 neovascularization and ablating retina that would need new vessels.

Description of the intervention

D-penicillamine is a chelating agent used in a diverse number of disorders including Wilson's disease, cystinuria and scleroderma. Previously, it has been used as a treatment for arsenic poisoning.

How the intervention might work

Oxygen free radicals are candidates for causing the injury to developing retinal capillaries in the premature infant. As a chelator of pro-oxidant heavy metals, D-penicillamine has the potential to reduce the amount of free radical activity in the tissues of the premature infant when given soon after birth. In addition to its oxygen radical scavenger properties, D-penicillamine is also known to alter the biological profile of native peptides by acting on disulphide bonds. Since most of the vascular growth factors depend on disulphide linkages, it could also act through reducing the bioavailability of the growth factors VEGF, endothelin-1, etc. (Hunt 1993; Matsubara 1989; McBrien 1994; Pietraforte 1995; Siemeister 1996; Yoshida 1995).

Over an eight-year period (1974 to 1982), while studying the administration of intravenous D-penicillamine to prevent or treat hyperbilirubinaemia, Lakatos and colleagues noted a low incidence of ROP among the treated infants with few, if any, side effects (Lakatos 1986).

Side effects of oral D-penicillamine therapy when used for rheumatoid arthritis, Wilson's disease and cystinuria, have been reported in literature, and could be fatal. These include pruritus, membranous glomerulonephritis, lupus erythematosus (or similar skin eruptions), Goodpasture's syndrome, drug fever, myasthenia gravis, polymyositis, aplastic anaemia, thrombocytopenia and agranulocytosis (Drosos 1997). Infants born following in-utero exposure have been reported with connective tissue disruption, poor wound healing or cutis laxa, although most infants exposed to D-penicillamine in utero have been normal (Pinter 2004).

However, short courses of oral D-penicillamine therapy used in children or adults for acute heavy metal overdose have not been associated with such side effects. Among earlier studies enrolling both term and preterm newborns for the treatment of hyperbilirubinaemia, only three infants were found to have side effects; two had mild erythematous rashes that quickly resolved with antihistamines, and one had vomiting that resolved when the drug was stopped (Koranyi 1978; Lakatos 1976; Lakatos 1976a). Specific testing of renal and hepatic function were within normal limits on a few selected infants, and growth was not affected.

Why it is important to do this review

This review updates previous version of the Cochrane review on this intervention (Cochrane 2001).

OBJECTIVES

To determine if early administration of D-penicillamine reduces the incidence of acute or severe ROP in preterm infants compared with placebo or no treatment.

METHODS

Criteria for considering studies for this review

Types of studies

Clinical trials with random or quasi-random assignment of the participants to the study groups.

Types of participants

Premature human infants at risk for development of retinopathy.

Types of interventions

Intravenous or oral administration of D-penicillamine initiated within first two weeks of life compared with no treatment or placebo.

Types of outcome measures

Primary outcomes

- ROP: any stage of ROP observed by direct or indirect ophthalmoscopy.
- Severe ROP: any ROP with extraretinal fibrovascular proliferation or stage 3 and above as per the International Classification of ROP (ICROP 2005), or meeting criteria for laser or cryotherapy.

Secondary outcomes

- Death from any cause prior to discharge to home.
- Abnormal neurodevelopment defined as abnormal neurological examination, epilepsy, cerebral palsy or developmental quotient (DQ) less than 70 diagnosed at one year of corrected age or older.
- Any other drug-related side effects reported.

Search methods for identification of studies

We used the search strategy for the Cochrane Neonatal Review Group (CNRG 2011).

Electronic searches

Multiple sources (listed below) were searched with the strategy of the following used as MeSH headings (MEDLINE) or keywords: [retrolental fibroplasia or retinopathy of prematurity] and [penicillamine/ad,pd,tu], or both MeSH heading and keywords.
Databases searched included: the Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 1, 2013), MEDLINE (1946 to November Week 3, 2012), Scopus (1999 to November 2012), CINAHL (July 1996 to November 2012), EMBASE (1974 to 2012 week 47), HealthSTAR (1966 to October 2012) and International Pharmaceutical Abstracts (1970 to October 2012).

Searching other resources

We retrieved additional references from the bibliography of the selected articles if they appeared to answer the research question. We did not apply any language restrictions.

Data collection and analysis

We used the standard methods of the Cochrane Neonatal Review Group, as documented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Selection of studies

Both review authors independently reviewed the methods section of each relevant trial to determine if the study met the eligibility criteria for inclusion in this review. Studies were included in the review if they met the following criteria: random or quasi-random allocation of participants among the study groups, compared D-penicillamine initiated within first two weeks of life compared with no treatment or placebo in preterm infants; and, measured any stage ROP or severe ROP (as defined in Primary outcomes).

Data extraction and management

One review author (MQ) assessed validity of trials and the second review author (MK) double-checked validity before we extracted data. We reached consensus by discussion.

Assessment of risk of bias in included studies

We used the standardized review methods of the Cochrane Neonatal Review Group to assess the methodological quality of included studies. We assessed each identified trial for methodological quality: a) allocation concealment, b) blinding of the intervention, c) completeness of follow-up and d) blinding of outcome ascertainment.
In addition, review authors independently assessed study quality and risk of bias using the following criteria documented in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

- Sequence generation: was the allocation sequence adequately generated?
- Allocation concealment: was allocation adequately concealed?
- Blinding of participants, personnel and outcome assessors for each main outcome or class of outcomes: was knowledge of the allocated intervention adequately prevented during the study?
- Incomplete outcome data for each main outcome or class of outcomes: were incomplete data adequately addressed?
- Selective outcome reporting: were reports of the study free of suggestion of selective outcome reporting?
- Other sources of bias: was the study apparently free of other problems that could put it at a high risk of bias? We will give particular attention to baseline imbalance in factors and to the length of follow-up studies to identify whether any benefits claimed were robust.

We intended to request additional information and clarification of published data from the authors of individual trials. We assessed each trial for risk of bias based on the criteria listed above and marked as: 'low' risk of bias, 'unclear' risk of bias, and 'high' risk of bias.

Measures of treatment effect

We analysed the results of the studies using Review Manager 5 software (RevMan 2011). We summarized data in a meta-analysis if they were sufficiently homogeneous, both clinically and statistically.

Dichotomous data: for dichotomous data, we presented results as risk ratios (RR) with 95% confidence intervals (CI). If there was a statistically significant reduction, we intended to report risk differences (RDs) and calculate the number needed to treat for additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH), and associated 95% CIs.

Continuous data: for continuous data, we used the mean difference (MD) if outcomes were measured in the same way between trials. We used the standardized mean difference (SMD) to combine trials that measured the same outcome, but use different methods.

Unit of analysis issues

The unit of randomisation and the unit of analysis was the individual infants.

Dealing with missing data

We intended to contact the authors of all published studies if clarifications were required, or to provide additional information. In the case of missing data, we described the number of participants with missing data in the Results section and the Characteristics of included studies table. We only present results for the available participants.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we had found substantial heterogeneity, we planned to explore it by prespecified subgroup analysis and sensitivity analysis. We intended to grade the degree of heterogeneity as: 0% to 30% (might not be important); 31% to 50% (moderate heterogeneity); 51% to 75% (substantial heterogeneity); and 76% to 100% (considerable heterogeneity).

Data synthesis

We conducted our statistical analysis using Review Manager 5 software (RevMan 2011). We used a fixed-effect Mantel-Haenszel method meta-analysis for combining data where trials were examining the same intervention, and if we judged the trial's population and methods to be similar.

Subgroup analysis and investigation of heterogeneity

If sufficient data were available, we planned to explore potential sources of clinical heterogeneity through a priori subgroup analyses.

Potential subgroups for analysis included: gestational age less than 30 weeks and methodological quality of included trials.

Sensitivity analysis

If sufficient data were available, we planned to explore methodological heterogeneity through the use of sensitivity analyses. We planned to perform these through including trials of higher quality, based on the presence of any of the following: adequate sequence generation, allocation concealment, and less than 10% loss to follow-up.

RESULTS

Description of studies

Results of the search

The original search strategy retrieved 77 unique citations of which we excluded 60 based upon title and abstract screening. We identified three randomised controlled trials of D-penicillamine in preterm infants for inclusion that reported on ROP outcomes involving 369 infants, along with an additional publication reporting one-year outcomes of one of the included trials.

Included studies

A brief description of the included studies is as follows:

1. Lakatos 1986: randomised controlled trial of intravenous D-penicillamine given to 204 outborn infants of 750 to 2000 g birth weight between 1 January 1983 and 6 March 1984. Randomization after informed consent occurred in birth weight strata using sealed envelopes. D-penicillamine was started within 12 hours after birth, and given intravenously at 300 mg/kg/day (divided into three doses) for three days, then at 50 mg/kg/day (in a single dose) up to two weeks if the birth weight was less than 1500 g. Between 1500 g and 2000 g, drug was continued beyond three days only if the infant continued on oxygen. No placebo was used because of the characteristic odour of the drug. Starting at six weeks, infants were examined for ROP with an indirect ophthalmoscope without scleral depression. The ophthalmologist did not know which infants had earlier received D-penicillamine. Because scleral depression was not used, mild stages of ROP in zone 3 may have been missed in this study. However, since both groups were examined

with the same technique, the rates of diagnoses in the two groups could be compared. The international classification of ROP was used to record the findings.

If acute ROP was diagnosed at any stage, children in the control group were then given D-penicillamine 50 mg/kg daily for three weeks. Therefore, the diagnosis of progression to severe ROP in this analysis, as well as other longer-term morbidities occurred following administration of active drug to some of the infants in the control group after six weeks of age. Most neonatal deaths occurred in the first week following birth, thus the outcome of death is unlikely to have been affected by administration of active drug to control infants who developed ROP. However, this study design feature contaminates to some degree other long-term outcomes such as growth and neurodevelopmental follow-up.

Deaths before discharge occurred at similar rates (29/100 in the treated infants, 34/104 in the controls), and ROP was diagnosed in none of the 71 treated survivors, and in six of the 70 control survivors. Two of the infants with ROP progressed to cicatricial stages; but neither of those cases progressed to blindness. No acute toxicity was reported in either group during hospitalisation, but there was no prospective, systematic collection of potential side effects either.

1a. Vekerdy-Lakatos 1987 (follow-up of infants in Lakatos 1986): at one year of age, the infants from the study reported above were evaluated in follow-up. There were three deaths after discharge so that 69 treated (69%) and 69 control infants (66%) survived to one year of age. Of these, 87% in each group returned for evaluation. Spasticity or seizures occurred in three (5%) of the treated infants and five (8%) of the children originally randomised to the control group. There were no significant differences in developmental quotients or growth parameters, but re hospitalizations occurred more frequently in control infants (59 times in 28 children) than in the treated infants (23 times in 15 children).

2. Lakatos 1987 (2nd trial data): the results of this trial were reported by the authors in combination with the results of Lakatos 1986 trial. Therefore, the results from this separate randomised controlled trial have been extracted from the data provided in these two publications. Seventy-seven infants of birth weights 751 to 1500 g were randomised to receive D-penicillamine or be controls between 1 July 1984 and 1 March 1985. Randomization was designed to be weighted 2:1 (treated:control) and the study was to end if three or more infants in the control group developed ROP. The dose was 300 mg/kg/day (divided into three doses) for three days, then 50 mg/kg/day (single dose) through to two weeks of age. Infants in the control group who later developed acute ROP were then given active drug, D-penicillamine, for three weeks (50 mg/kg/day intravenously) starting at the time of diagnosis of the ROP.

While a 2:1 randomisation ratio was intended through sealed envelopes, when the study was terminated after three infants developed ROP in the control group, the actual ratio of treated versus no treated infants was 1.4:1. Eighteen of 45 infants treated with D-penicillamine died compared to 10/32 control infants. Acute ROP occurred in 0/27 D-penicillamine survivors and in 3/22 control survivors.

3. Tandon 2010: randomised, double-blind, single-centre, placebo-controlled trial in which oral D-penicillamine was given to 88 inborn neonates with birth weight 750 to 1500 g, gestation 32 weeks or less, age 5 days or less. Subjects were stratified for birth weight (less than 1250 g and 1250 g or greater). Block randomisation with randomly varying block sizes was carried out. The random sequence was generated online from a website by an investigator who was not involved in recruiting subjects. Between 1 January 2007 and 31 December 2007, enrolled subjects were randomly allocated to receive oral D-penicillamine suspension at 100 mg/ kg/dose every eight hours for three days, followed by 50 mg/kg/day for another 11 days or placebo. The primary outcome was 'any ROP or death'. Secondary outcomes included any ROP, treatable ROP, adverse effects and feeding intolerance. Retinal examination was performed by an ophthalmologist with expertise in ROP screening at four to six weeks after birth or at a postmenstrual age of 31 to 33 weeks, whichever was earlier. ROP screening was repeated depending on the status of the retina.

Subjects were followed up until death, treatment of ROP or until the last retinal examination was performed and the baby was declared to have no ROP. A total of 88 infants were enrolled. The D-penicillamine and placebo groups comprised 44 infants each. No subject was lost to follow-up. Ten of 44 infants (22.7%) in each group either died or had ROP. Seven of 44 infants (15.9%) from the D-penicillamine group and 4/44 from the control group developed ROP. One baby in the D-penicillamine group had ROP and subsequently died. The other deaths took place before the first ROP screen. Three subjects from the D-penicillamine group and one from the placebo group required treatment.

Excluded studies

We excluded 10 studies (Christensen 2006; Christensen 2007; Lakatos 1980; Lakatos 1982a; Lakatos 1982b; Lakatos 1982c; Lakatos 1982d; Lakatos 1985; Lakatos 1988; Lakatos 1989). See Characteristics of excluded studies table for details.

Risk of bias in included studies

Allocation

Random sequence generation: all three included studies described a random component in the sequence generation process. However, only the Tandon 2010 trial provided a satisfactory description sequence generation.

Allocation concealment: all three included studies used sealed envelopes to conceal allocation of treatments.

Blinding

Blinding of participants and personnel (performance bias and detection bias): the study participants and personnel were blinded to study interventions in the Tandon 2010 trial through use of a placebo. There was no blinding involved in the other two trials.
Blinding of outcome assessment: all three studies reported that the ophthalmologist was blinded to the outcome assessment. However, group assignment was not concealed from paediatricians in Lakatos 1986 and Lakatos 1987 (2nd trial data). The one-year longitudinal follow-up study, Vekerdy-Lakatos 1987 reported blinding of follow-up staff to allocated interventions.

Incomplete outcome data

The length of participant follow-up varied in the included studies, with ROP outcomes reported on majority of infants enrolled in all studies. The Lakatos 1986 study reported follow-up data on 87.5% of survivors at one year of age.

Selective reporting

It was unclear whether the authors had resorted to selective reporting of their trial data, as none of the included studies had protocols available online for reference.

Effects of interventions

Outcome of any retinopathy of prematurity and severe retinopathy of prematurity (outcomes 1.1, 1.2, 2.1 and 2.2)

All three included studies reported on any ROP and severe ROP. ROP of some degree was observed in 13/180 (7.2%) of all control infants reported. The RR of developing any ROP in the D-penicillamine group was 0.32 (95% CI 0.03 to 3.70) and that of severe ROP was 0.38 (95% CI 0.03 to 4.26). For infants under 1500 g birth weight, the RR of developing any ROP in the D-penicillamine group was 0.32 (95% CIs 0.03 to 3.70), and that of severe ROP was 0.69 (95% CI 0.11 to 4.22) (Analysis 1.1; Analysis 1.2; Analysis 2.1; Analysis 2.2; Figure 1; Figure 2; Figure 3; Figure 4).

Figure 1. Forest plot: D-Penicillamine versus controls, Outcome: Any retinopathy of prematurity.

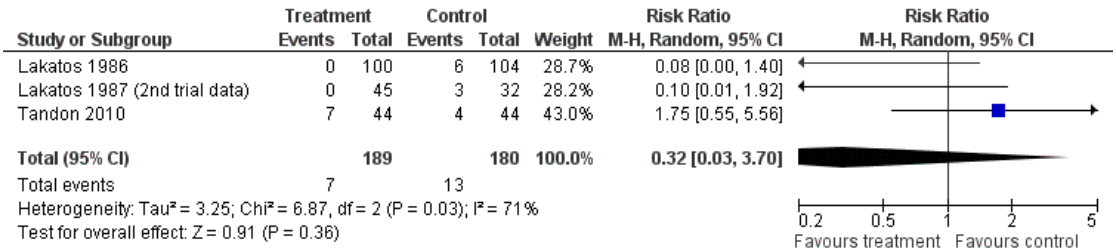


Figure 2. Forest plot: D-Penicillamine versus controls, Outcome: Severe retinopathy of prematurity

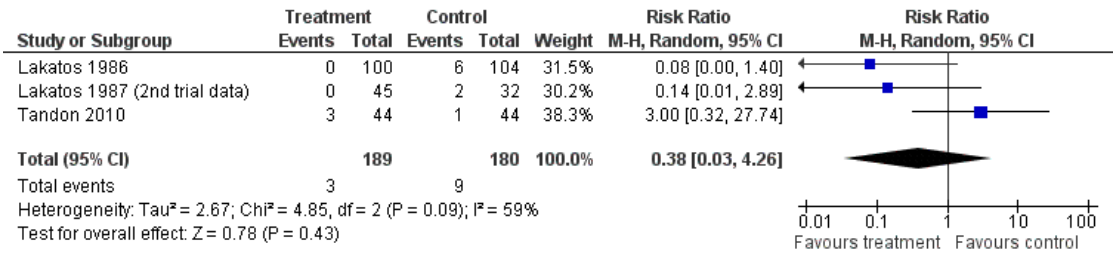


Figure 3. Forest plot: D-Penicillamine versus controls, < 1500 g birth weight, Outcome: Any retinopathy of prematurity.

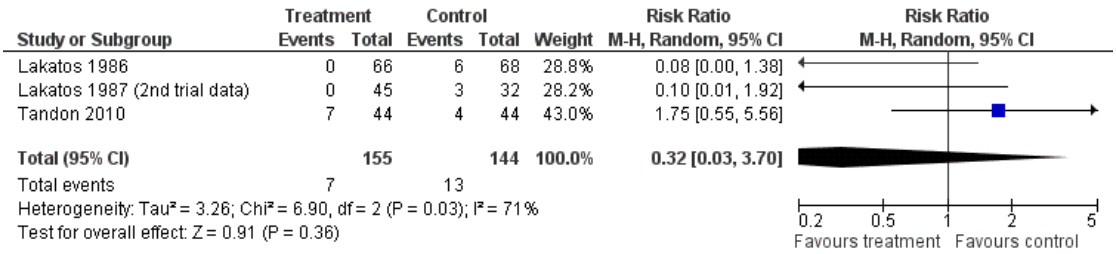
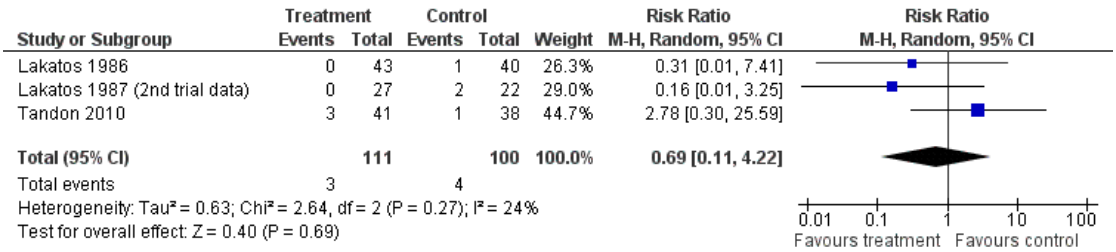


Figure 4. Forest plot: D-Penicillamine versus controls, < 1500 g birth weight, Outcome: Severe retinopathy of prematurity.



Death (outcomes 1.3 and 2.3)

All three included studies reported death and found no difference between the groups (RR 0.95, 95% CI 0.68 to 1.32). For infants less than 1500 g birth weight, the RR for death was 0.93 (95% CI 0.65 to 1.32) (Analysis 1.3; Analysis 2.3; Figure 5; Figure 6).

Figure 5. Forest plot: D-Penicillamine versus controls, Outcome: Death.

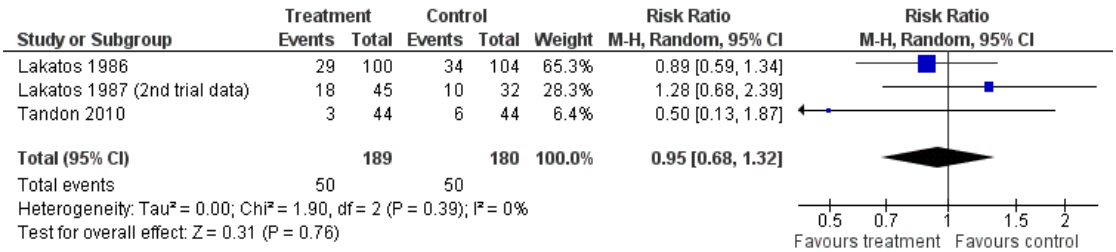
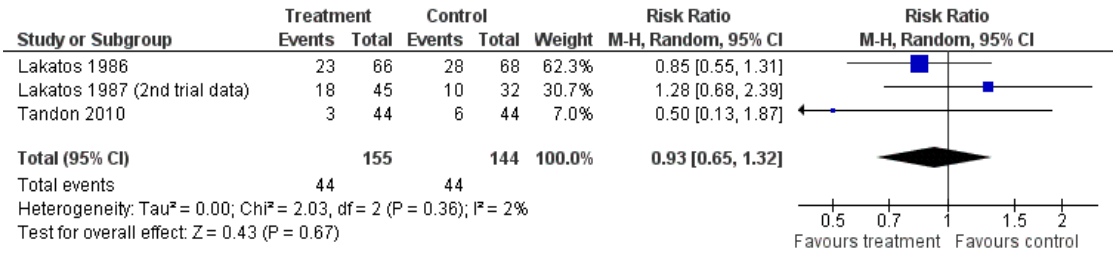


Figure 6. Forest plot: D-Penicillamine versus controls, < 1500 g birth weight, Outcome: Death.



Abnormal neurodevelopment (outcomes 1.4 and 2.4)

Only one study, reported data on abnormal neurodevelopment with long-term follow-up completed in 87.5% of the one-year survivors (Vekerdy-Lakatos 1987). There were no significant differences between the intervention groups in terms of developmental quotients, spasticity or survival. This study also did not find any differences for measures of physical growth (weight, length or head circumference) (Analysis 1.4; Analysis 2.4; Figure 7; Figure 8).

Figure 7. Forest plot: D-Penicillamine versus controls, Outcome: Abnormal neurodevelopment in survivors.

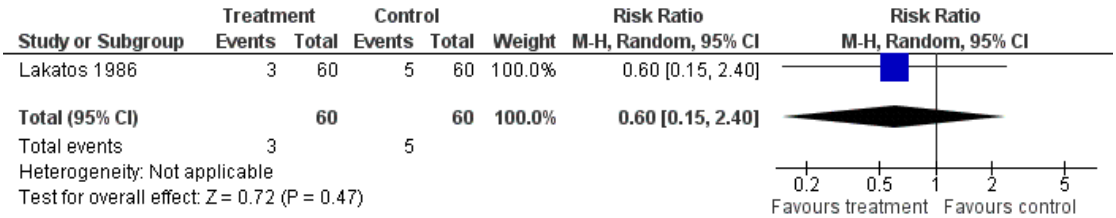
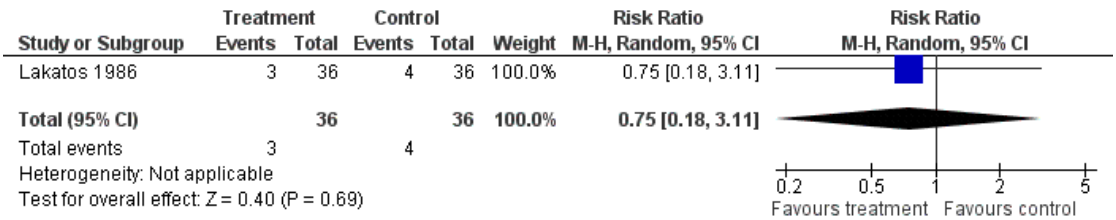


Figure 8. Forest plot: D-Penicillamine versus controls, < 1500 g birth weight, Outcome: Abnormal neurodevelopment in survivors.



The combined outcome of death or abnormal neurodevelopment was also not different between the groups (RR0.85, 95% CI 0.58 to 1.25 (Analysis 1.5;Figure 9). For infants less than 1500 g birth weight, the RR for death or abnormal neurodevelopmental outcome was 0.85 (95% CI 0.59 to 1.23) (Analysis 2.5;Figure 10).

Figure 9. Forest plot: D-Penicillamine versus controls, Outcome: Death or abnormal neurodevelopmental outcome.

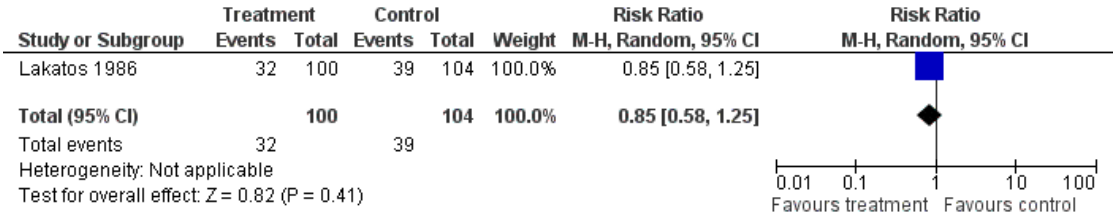
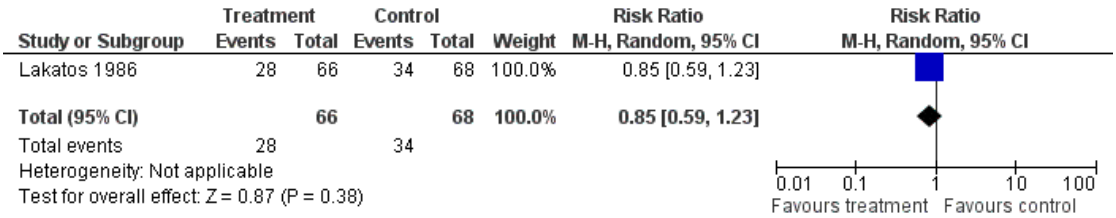


Figure 10. Forest plot: D-Penicillamine versus controls, < 1500 g birth weight, Outcome: Death or abnormal Neurodevelopmental outcome.



Both the trials by Lakatos and colleagues (Lakatos 1986; Lakatos 1987 (2nd trial data)), did not report any side effects from the intravenous use of D-penicillamine in neonates. In the study by Tandon 2010, four infants in the D-penicillamine group and two in the placebo group had feeding intolerance. Tandon 2010 also systematically monitored for haematological and renal parameters, showing no difference between the groups.

DISCUSSION

The primary goal of this updated review was to determine the effect of prophylactic administration of D-penicillamine on the incidence of acute ROP, severe ROP, death and neurodevelopmental outcome. We identified three primary trials and the results of our review showed no significant difference for any of these outcomes. While the Lakatos 1986 and Lakatos 1987 (2nd trial data) trials used intravenous D-penicillamine, the more recent study by Tandon 2010 used oral D-penicillamine.

The studies included in our review investigated a small number of preterm infants (369 total, or 269 survivors). The trials by Lakatos 1986 and Lakatos 1987 (2nd trial data) were not placebo controlled and there was no concealment of allocation and allowed cross-over. Although they showed significant risk reduction in the incidence of ROP, it is not clear whether the lack of placebo resulted in bias.

In Tandon 2010, D-penicillamine was administered orally and at a lower dose. The absolute bioavailability of oral D-penicillamine is 50% to 70% (Kukovetz 1983). It is unclear whether the lack of any treatment benefit noted in this trial was due to these reasons.

Current treatment for severe ROP focuses on laser therapy and visual rehabilitation, and potential new treatment strategies include targets within oxidative pathways, erythropoietin, and anti-VEGF agents (Hartnett 2012). Although laser treatment of infants at risk for severe ROP decreases retinal detachment and reduces blindness by 25% (Good 2004), non-blinding ocular morbidity is not reduced by treatment and makes preventive efforts desirable (Chen 2010).

The effectiveness of anti-VEGF treatment has been demonstrated (Mintz-Hittner 2011; Spandau 2012), but there remain concerns and limitations about its systemic safety. The anti-VEGF agent persists in the blood long after the initial intravitreal injection (Lee 2011; Matsuyama 2010; Sato 2012). To date, very little is known about the possible anti-VEGF effects in the brain and the lungs. Another antioxidant that has been studied for the prevention of ROP, vitamin E, has had less impact than hoped for on the incidence of ROP, but may reduce severe stages of ROP with an RR of at least 50% and also warrants further study (Raju 1997).

D-penicillamine is a powerful antioxidant and VEGF inhibitor (Sanderud 1995). Although our review did not show any significant benefit for any of the desired outcomes studied, the 95% CIs for many of our estimates are large, meaning that there continues to be uncertainly regarding the effects of this intervention. With point estimates of RRs well below unity for outcomes of any ROP and severe ROP, a clinical important effect cannot be ruled out in future from a randomised trial adequately powered to those outcomes. The most recent American Academy of Pediatrics guidelines proposed a birth weight of 400 g or gestational age of 23 weeks as appropriate thresholds for resuscitation (American Heart Association 2005). Since then there has been a trend to offer resuscitation to extremely premature babies. As none of the trials included in this review observed any serious adverse effects there is scope for conducting further trials with possibly more prolonged administration of the drug. Until then, the use of D-penicillamine cannot be recommended for the prevention of ROP based on the available evidence.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to recommend routine use of D-penicillamine to prevent retinopathy of prematurity (ROP) in premature infants.

Implications for research

Two of the actions of D-penicillamine provide a good biological basis for continuing investigations to test the likelihood of benefit from this drug, that is, 1) its ability to interrupt disulphide bonds and, therefore, reduce the bioavailability of vascular growth factors and impede in vivo neovascularization (Matsubara 1989), and 2) its function as a free radical oxygen scavenger (Saugstad 1984; Staite 1984). Safety data to date do not raise concerns with its short-term intravenous or oral use.

In addition to the larger placebo-control trials to test the efficacy of D-penicillamine in the prevention of ROP in preterm infants, future trials could also compare the efficacy of this drug against new treatments such as anti-vascular endothelial growth factor agents. Careful prospective determination of the safety of this drug in the premature birth population must be a part of any such trial.

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REFERENCES

References to studies included in this review

Lakatos 1986 *{published data only}*

* Lakatos L, Hatvani I, Oroszlan G, Balla G, Karmazsin L, Alaka O, et al. Controlled trial of D-penicillamine to prevent retinopathy of prematurity. *Acta Paediatrica Hungary* 1986;**27**(1):47–56.

* Vekerdy-Lakatos S, Lakatos L, Oroszlan G, Itzes B. One year longitudinal follow-up of premature infants treated with D-penicillamine in the neonatal period. *Acta Paediatrica Hungary* 1987;**28**(1):9–16.

Lakatos 1987 (2nd trial data) *{published data only}*

Lakatos L, Lakatos Z, Hatvani I, Oroszlan G. Controlled trial of use of D-penicillamine to prevent retinopathy of prematurity in very low-birth-weight infants. In: Stern L, Oh W, Friis-Hansen B editor(s). *Physiologic Foundations of Perinatal Care*. Vol. **2**, New York: Elsevier, 1987:9–23.

Tandon 2010 *{published data only}*

Tandon M, Dutta S, Dogra MR, Gupta A. Oral D-penicillamine for the prevention of retinopathy of prematurity in very low birth weight infants: a randomised, placebo-controlled trial. *Acta Paediatrica* 2010;**99**(9):1324–8. [DOI: 10.1111/j.1651-2227.2010.01837.x]

References to studies excluded from this review

Christensen 2006 *{published data only}*
Christensen RD, Alder SC, Richards SC, Horn JT, Lambert DK, Baer VL. A pilot trial testing the feasibility of administering D-penicillamine to extremely low birth weight neonates. *Journal of Perinatology* 2006;**26**(2):120–4. [DOI: 10.1038/sj.jp.7211440]

Christensen 2007 *{published data only}*
Christensen RD, Alder SC, Richards SC, Lambert DK, Schmutz N, Wiedmeier SE, et al. D-Penicillamine administration and the incidence of retinopathy of prematurity. *Journal of Perinatology* 2007;**27**(2):103–11. [DOI: 10.1038/sj.jp.7211653]

Lakatos 1980 *{published data only}*
Lakatos L, Hatvani I, Karmazsin L. Is the treatment of prematurely born infants with D-penicillamine decreasing the frequency of retrolental fibroplasia? [In Hungarian]. *Szemeszet Ophthalmologica Hungarica* 1980;**117**(1):9–12.

Lakatos 1982a *{published data only}*
Lakatos L. Antioxidant effects of d-penicillamine in the neonatal period. *Magyar Pediater* 1982;**16**:355–62.
* Lakatos L, Hatvani I, Karmazsin L, Oroszlan G. Prevention of retrolental fibroplasia in very low birth weight infants by D penicillamine. *European Journal of Pediatrics* 1982;**138**(2):199–200.
Lakatos L, Hatvani I, Oroszlan GY, Karmazsin L, Matkovics B. Prevention of retrolental fibroplasia with D-penicillamine [In Hungarian]. *Gyermekgyogyaszat* 1981;**32**:525–30.

Lakatos 1982b *{published data only}*
Oroszlán G, Lakatos L, Karmazsin L. Neonatal oxygen toxicity and its prevention: D-penicillamine offers benefits without harmful side-effects. *Acta Paediatrica Academiae Scientiarum Hungaricae* 1982;**23**(4):459–71.

Lakatos 1982c *{published data only}*
Lakatos L, Hatvani I, Oroszlan G, Karmazsin L, Matkovics B. D-penicillamine in the prevention of retrolental fibroplasia. *Acta Paediatrica Academiae Scientiarum Hungaricae* 1982;**23**(4):327–35.

Lakatos 1982d *{published data only}*
Lakatos L, Hatvani I. Penicillamine, vitreous proliferation, and retinopathy of prematurity. *American Journal Ophthalmology* 1982;**93**(5):662.

Lakatos 1985 *{published data only}*
Lakatos L, Hatvani I, Oroszlan GY, Vekerdy ZS. Clinical observations in the prevention of retrolental fibroplasia with D-penicillamine. In: Stern L, Xanthou M, Friis-Hansen B editor(s). *Physiologic Foundations of Perinatal Care*. New York: Praeger, 1985:293–305.

Lakatos 1988 *{published data only}*
Lakatos L. D-penicillamine and retinopathy of prematurity [letter]. *Pediatrics* 1988;**82**(6):951–2.

Lakatos 1989 *{published data only}*
Lakatos L, Oroszlan G, Lakatos Z. D-penicillamine in the neonatal period. In: Stern L, Orzalesi M, Friis-Hansen B editor(s). *Physiologic Foundations of Perinatal Care*. New York: Elsevier, 1989:188–97.

Additional references

Aiello 1996
Aiello LP. Vascular endothelial growth factor and the eye - past, present, and future. *Archives of Ophthalmology* 1996; **114**(10):1252–4.

Aiello 1997
Aiello LP. Vascular endothelial growth factor. 20th-century mechanisms, 21st-century therapies. *Investigative Ophthalmology & Visual Science* 1997;**38**(9):1647–52.

American Heart Association 2005
American Heart Association, American Academy of Pediatrics. 2005 American Heart Association (AHA) guidelines for cardiopulmonary resuscitation (CPR) and emergency cardiovascular care (ECC) of pediatric and neonatal patients: neonatal resuscitation guidelines. *Pediatrics* 2006;**117**(5):e1029–e1038.

Chen 2010
Chen ML, Guo L, Smith LE, Dammann CE, Dammann O. High or low oxygen saturation and severe retinopathy of prematurity: a meta-analysis. *Pediatrics* 2010;**125**(6): e1483–92. [DOI: 10.1542/peds.2009–2218]

CNRG 2011
Soll RF, Bracken MB, Horbar JD, Ohlsson A, Suresh G, Haughton DE. Cochrane Neonatal Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs). NEONATAL 2011, issue 3.

Cochrane 2001
Phelps DL, Lakatos L, Watts JL. D-Penicillamine for preventing retinopathy of prematurity in preterm infants. *Cochrane Database of Systematic Reviews* 2001, Issue 1. [DOI: 10.1002/14651858.CD001073]

CRYO-ROP 1990
Cryotherapy for Retinopathy of Prematurity Cooperative Group. Multicenter trial of cryotherapy for retinopathy of prematurity. One-year outcome - structure and function. *Archives of Ophthalmology* 1990;**108**(10):1408–16.

Drosos 1997
Drosos AA, Geogriou P, Politi EN, Voulgari PV. D-penicillamine in early rheumatoid arthritis. *Clinical and Experimental Rheumatology* 1997;**15**(5):580–1.

Flynn 1987
Flynn JT, Bancalari E, Bawol R, Goldberg R, Cassady J, Schiffman J, et al. Retinopathy of prematurity: a randomised, prospective trial of transcutaneous oxygen monitoring. *Ophthalmology* 1987;**94**(6):630–8.

Good 2004
Good WV. Early Treatment for Retinopathy of Prematurity Cooperative Group. Final results of the Early Treatment for Retinopathy of Prematurity (ETROP) randomised trial. *Transactions of the American Ophthalmological Society* 2004; **102**:233-8; discussion 248-50.

Hartnett 2012
Hartnett ME, Penn JS. Mechanisms and management of retinopathy of prematurity. *New England Journal*

of Medicine 2012;**367**(26):2515–26. [DOI: 10.1056/NEJMra1208129]

Higgins 2011
Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al, Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928. [DOI: 10.1136/bmj.d5928]

Hunt 1993
Hunt JT, Lee VG, Liu ECK, Moreland S, McMullen D, Webb ML, et al. Control of peptide disulfide regioisomer formation by mixed cysteine-penicillamine bridges. *International Journal of Peptide and Protein Research* 1993; **42**(3):249–58.

ICROP 1984
An International Committee for the Classification of Retinopathy of Prematurity. The Committee for the Classification of Retinopathy of Prematurity. *Archives of Ophthalmology* 1984;**102**(8):1130–4.

ICROP 2005
An International Committee for the Classification of Retinopathy of Prematurity. The International Classification of Retinopathy of Prematurity revisited. *Archives of Ophthalmology* 2005;**123**(7):991–9.

Kinsey 1956
Kinsey V. Retrolental fibroplasia: cooperative study of retrolental fibroplasia and the use of oxygen. *Archives of Ophthalmology* 1956;**56**(4):481–547.

Koranyi 1978
Koranyi G, Kovacs J, Voros I. D-Penicillamine treatment of hyperbilirubinaemia in preterm infants. *Acta Paediatrica Academiae Scientiarum Hungaricae* 1978;**19**(1):9–16.

Kukovetz 1983
Kukovetz WR, Beubler E, Kreuzig F, Moritz AJ, Nirnberger G, Werner-Breitenecker L. Bioavailability and pharmacokinetics of D-penicillamine. *Journal of Rheumatology* 1983;**10**(1):90–4.

Lakatos 1976
Lakatos L, Kover B, Vekerdy S, Dvoracsdk E. D-Penicillamine therapy in neonatal jaundice: comparison with phototherapy. *Acta Paediatrica Academiae Scientiarum Hungaricae* 1976;**17**(2):93–102.

Lakatos 1976a
Lakatos L, Kover B, Oroszlan G, Vekerdy Z. D-Penicillamine therapy in ABO haemolytic disease of the newborn infant. *European Journal of Pediatrics* 1976;**123** (2):133–7.

Lee 2011
Lee SJ, Kim SY, Yoo B, Kim H, Kim Y. Plasma level of vascular endothelial growth factor in retinopathy of prematurity after intravitreal injection of bevacizumab. *Investigative Ophthalmology & Visual Science* 2011;**52**: Abstract 3165.

Matsubara 1989
Matsubara T, Saura R, Hirohata K, Ziff M. Inhibition of human endothelial cell proliferation in vitro and neovascularization in vivo by D-penicillamine. *Journal of Clinical Investigation* 1989;**83**(1):158–67.

Matsuyama 2010
Matsuyama K, Ogata N, Matsuoka M Wada M, Takahashi K, Nishimura T. Plasma levels of vascular endothelial growth factor and pigment epithelium derived factor before and after intravitreal injection of bevacizumab. *British Journal of Ophthalmology* 2010;**94**:1215–8.

McBrien 1994
McBrien NA, Norton TT. Prevention of collagen crosslinking increases form-deprivation myopia in tree shrew. *Experimental Eye Research* 1994;**59**(4):475–86.

Mintz-Hittner 2011
Mintz-Hittner HA, Kennedy KA, Chuang AZ, BEAT-ROP Cooperative Group. Efcacy of intravitreal bevacizumab for stage 3+ retinopathy of prematurity. *New England Journal of Medicine* 2011;**364**(7):603–15.

Palmer 1991
Palmer EA, Flynn JT, Hardy RJ, Phelps DL, Phillips CL, Schaffer DB, et al. The Cryotherapy for Retinopathy of Prematurity Cooperative Group. Incidence and early course of retinopathy of prematurity. *Ophthalmology* 1991;**98**(11): 1628–40.

Phelps 1997
Phelps DL, Watts JL. Early light reduction to prevent retinopathy of prematurity in very low birth weight infants. *Cochrane Database of Systematic Reviews* 1997, Issue 1. [DOI: 10.1002/14651858.CD000122]

Pietraforte 1995
Pietraforte D, Mallozzi C, Scorva G, Minetti M. Role of thiols in the targeting of S-nitroso thiols to red blood cells. *Biochemistry* 1995;**34**(21):7177–85.

Pinter 2004
Pinter R, Hogge WA, McPherson E. Infant with severe penicillamine embryopathy born to a woman with Wilson disease. *American Journal of Medical Genetics. Part A* 2004; **128A**(3):294–8. [DOI: 10.1002/ajmg.a.10871]

Raju 1997
Raju TNK, Langenberg P, Bhutani V, Quinn GE. Vitamin E prophylaxis to reduce retinopathy of prematurity - a reappraisal of published trials. *Journal of Pediatrics* 1997; **131**(6):844–50.

RevMan 2011 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011.

Sanderud 1995
Sanderud J, Oroszlan G, Bjoro K, Kumlin M, Saugstad OD. D-penicillamine inhibits the action of reactive oxygen species in the pig pulmonary circulation. *Journal of Perinatal Medicine* 1995;**23**(5):385–93.

Sato 2012
Sato T, Wada K, Arahori H, Kuno N, Imoto K, Iwahashi-Shima C, et al. Serum concentrations of bevacizumab (avastin) and vascular endothelial growth factor in infants with retinopathy of prematurity. *American Journal of Ophthalmology* 2012;**153**(2):327–33.

Saugstad 1984
Saugstad OD, Hallman M, Abraham JL, Epstein B, Cochrane C, Gluck L. Hypoxanthine and oxygen induced lung injury: a possible basic mechanism of tissue damage?. *Pediatric Research* 1984;**18**(6):501–4.

Siemeister 1996
Siemeister G, Schnurr B, Mohrs K, Schachtele C, Marme D, Martiny-Baron G. Expression of biologically active isoforms of the tumour angiogenesis factor VEGF in Escherichia coli. *Biochemical and Biophysical Research Communications* 1996;**222**(2):249–55.

Spandau 2012
Spandau U, Tomic Z, Ewald U, Larsson E, Akerbolm H, Holmstrom G. Time to consider a new treatment protocol for aggressive posterior retinopathy of prematurity?. *Acta Ophthalmologica* 2012;**91**(2):170–5.

Staite 1984
Staite ND, Zoschke DC, Messner RP. Scavenging of hydrogen peroxide - a new mechanism of action for D-penicillamine in rheumatoid arthritis. *New England Journal of Medicine* 1984;**311**(8):538–9.

STOP-ROP 2000
STOP-ROP Multicenter Trial. Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity (STOP-ROP), a randomised, controlled trial. I: primary outcomes. *Pediatrics* 2000;**105**(2):295–310.

Vekerdy-Lakatos 1987
Vekerdy-Lakatos S, Lakatos L, Oroszlán G, Itzés B. One year longitudinal follow up of premature infants treated with D-Penicillamine in the neonatal period. *Acta Paediatrica Hungarica* 1987;**28**(1):9–16.

Yoshida 1995
Yoshida D, Ikeda Y, Nakazawa S. Copper chelation inhibits tumour angiogenesis in the experimental 9L gliosarcoma model. *Neurosurgery* 1995;**37**(2):287–92.

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Lakatos 1986

Methods	A single-centre, randomised, prospective controlled trial
Participants	204 outborn infants Inclusion criteria: premature infants, 751 to 2000 g BW, born between 1 January 1983 and 6 March 1984 Exclusion criteria: congenital abnormalities, death before 6 h of life
Interventions	Intervention group (n = 100) BW < 1500 g: D-penicillamine intravenously started within 12 h after birth, 300 mg/kg/day (divided in 3 doses) x 3 days, then 50 mg/kg/day (in a single dose) until 2 weeks of age BW 1500-2000 g: D-penicillamine intravenously started within 12 h after birth, 300 mg/kg/day (divided in 3 doses) x 3 days; additional 50 mg/kg/day doses if they required oxygen beyond 3 days Control group (n = 104). No placebo was used in controls Once ROP developed after 6 weeks of age, D-penicillamine 50 mg/kg/day was given to infants in the control group for 3 weeks
Outcomes	Death before discharge Any ROP in survivors
Notes	Follow-up at 1 year of age for anthropometry and neurodevelopment presented in separate study (Vekerdy-Lakatos 1987)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors do not provide the exact method of random sequence generation
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Group assignment not concealed from paediatricians, but ophthalmologists doing ROP examinations were masked to study group
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes of ROP reported on the majority of enrolled infants

Lakatos 1986 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	The study protocol was unavailable

Lakatos 1987 (2nd trial data)

Methods	Randomized controlled trial. 2:1 ratio of randomisation of drug to control
Participants	77 outborn infants Inclusion criteria: premature infants of 751 to 1500 g BW born between 1 July 1984 and 1 March 1985 Exclusion criteria: congenital abnormalities, death before 6 hof life
Interventions	Intervention group (n = 45) D-penicillamine intravenously started by 12 h after birth, 300 mg/kg/day (divided in 3 doses) x 3 days, then 50 mg/kg/day (in a single dose) until 2 weeks Control group (n = 32). No placebo was used for controls D-penicillamine given after 6 weeks to all infants who developed ROP
Outcomes	Death before discharge home Any ROP in survivors
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Authors did not provide the exact method of random sequence generation
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Paediatricians not masked to group assignment. Ophthalmologists determining ROP outcomes were masked
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes of ROP reported on the majority of enrolled infants. 1-year follow-up outcomes reported on majority of survivors
Selective reporting (reporting bias)	Unclear risk	The study protocol was unavailable

Tandon 2010

Methods	Double-blind, single-centre, randomised, placebo-controlled trial with stratification and blocking
Participants	88 inborn infants Inclusion criteria: premature infants of 750 to 1500 g BW born between 1 January 2007 and 31 December 2007, chronological age ≤ 5 days, who were tolerating feeds (≥ 10 mL/day) Exclusion criteria: congenital abnormalities, confirmed or suspected obstructive gastrointestinal malformation, confirmed or suspected necrotizing enterocolitis or severe sickness with estimated life expectancy < 24 h
Interventions	Intervention group (n = 44) D-penicillamine was administered as an oral suspension (50 mg/mL) in sterile water at a dose of 100 mg/kg/dose every 8 h for 3 days, followed by 50 mg/kg once per day for next 11 days Control group (n = 44) was calcium carbonate suspension (50 mg/mL orally) at an identical dose
Outcomes	Any stage ROP or death within 40 weeks' postmenstrual age
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random sequence was generated online from a website
Allocation concealment (selection bias)	Low risk	Quote: "Allocated interventions were placed inside serially numbered opaque envelopes and sealed"
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo given to control group infants. Blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment ensured, and unlikely that the blinding could have been broken
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	The study protocol was unavailable online

BW: birth weight; h: hour; ROP: retinopathy of prematurity.

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

Study	Reason for exclusion
Christensen 2006	Pilot study, no control group enrolled
Christensen 2007	Non-random allocation
Lakatos 1980	Retrospective analysis of historical cohort (preliminary report)
Lakatos 1982a	Retrospective analysis of historical cohort
Lakatos 1982b	Review article
Lakatos 1982c	Retrospective analysis of historical cohort
Lakatos 1982d	Letter to the editor
Lakatos 1985	Description of retrospective cohorts enrolled over the years 1974 to 1978, 1979 to 1980, 1981 to 1982
Lakatos 1988	Correspondence to editor referring to the included trials
Lakatos 1989	Review article referring to previous studies

DATA AND ANALYSES

Comparison 1. D-Penicillamine versus controls, < 2000 g birth weight

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any retinopathy of prematurity	3	369	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.03, 3.70]
2 Severe retinopathy of prematurity	3	369	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.03, 4.26]
3 Death	3	369	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.68, 1.32]
4 Abnormal neurodevelopment in survivors	1	120	Risk Ratio (M-H, Random, 95% CI)	0.6 [0.15, 2.40]
5 Death or abnormal neurodevelopmental outcome	1	204	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.58, 1.25]

Comparison 2. D-Penicillamine versus controls, < 1500 g birth weight

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Any retinopathy of prematurity	3	299	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.03, 3.70]
2 Severe retinopathy of prematurity	3	211	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.11, 4.22]
3 Death	3	299	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.65, 1.32]
4 Abnormal neurodevelopment in survivors	1	72	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.18, 3.11]
5 Death or abnormal neurodevelopmental outcome	1	134	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.59, 1.23]

Analysis 1.1. Comparison 1 D-Penicillamine versus controls, < 2000 g birth weight, Outcome 1 Any retinopathy of prematurity.

Review: D-Penicillamine for preventing retinopathy of prematurity in preterm infants

Comparison: 1 D-Penicillamine versus controls, < 2000 g birth weight

Outcome: 1 Any retinopathy of prematurity

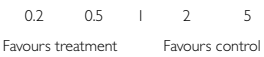
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lakatos 1986	0/100	6/104		28.7 %	0.08 [0.00, 1.40]
Lakatos 1987 (2nd trial data)	0/45	3/32		28.2 %	0.10 [0.01, 1.92]
Tandon 2010	7/44	4/44		43.0 %	1.75 [0.55, 5.56]
Total (95% CI)	**189**	**180**		**100.0 %**	**0.32 [0.03, 3.70]**

Total events: 7 (Treatment), 13 (Control)

Heterogeneity: $Tau^2 = 3.25$; $Chi^2 = 6.87$, df = 2 (P = 0.03); $I^2 = 71\%$

Test for overall effect: Z = 0.91 (P = 0.36)

Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1 D-Penicillamine versus controls, < 2000 g birth weight, Outcome 2 Severe retinopathy of prematurity.

Review: D-Penicillamine for preventing retinopathy of prematurity in preterm infants

Comparison: 1 D-Penicillamine versus controls, < 2000 g birth weight

Outcome: 2 Severe retinopathy of prematurity

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lakatos 1986	0/100	6/104		31.5 %	0.08 [0.00, 1.40]
Lakatos 1987 (2nd trial data)	0/45	2/32		30.2 %	0.14 [0.01, 2.89]
Tandon 2010	3/44	1/44		38.3 %	3.00 [0.32, 27.74]
Total (95% CI)	**189**	**180**		**100.0 %**	**0.38 [0.03, 4.26]**

Total events: 3 (Treatment), 9 (Control)

Heterogeneity: $Tau^2 = 2.67$; $Chi^2 = 4.85$, df = 2 (P = 0.09); $I^2 = 59\%$

Test for overall effect: Z = 0.78 (P = 0.43)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 D-Penicillamine versus controls, < 2000 g birth weight, Outcome 3 Death.

Review: D-Penicillamine for preventing retinopathy of prematurity in preterm infants

Comparison: 1 D-Penicillamine versus controls, < 2000 g birth weight

Outcome: 3 Death

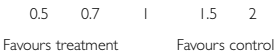
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lakatos 1986	29/100	34/104		65.3 %	0.89 [0.59, 1.34]
Lakatos 1987 (2nd trial data)	18/45	10/32		28.3 %	1.28 [0.68, 2.39]
Tandon 2010	3/44	6/44		6.4 %	0.50 [0.13, 1.87]
Total (95% CI)	**189**	**180**		**100.0 %**	**0.95 [0.68, 1.32]**

Total events: 50 (Treatment), 50 (Control)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.90$, df = 2 (P = 0.39); $I^2 = 0.0\%$

Test for overall effect: Z = 0.31 (P = 0.76)

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 D-Penicillamine versus controls, < 2000 g birth weight, Outcome 4 Abnormal neurodevelopment in survivors.

Review: D-Penicillamine for preventing retinopathy of prematurity in preterm infants

Comparison: 1 D-Penicillamine versus controls, < 2000 g birth weight

Outcome: 4 Abnormal neurodevelopment in survivors

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lakatos 1986	3/60	5/60		100.0 %	0.60 [0.15, 2.40]
Total (95% CI)	**60**	**60**		**100.0 %**	**0.60 [0.15, 2.40]**

Total events: 3 (Treatment), 5 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.72 (P = 0.47)

Test for subgroup differences: Not applicable

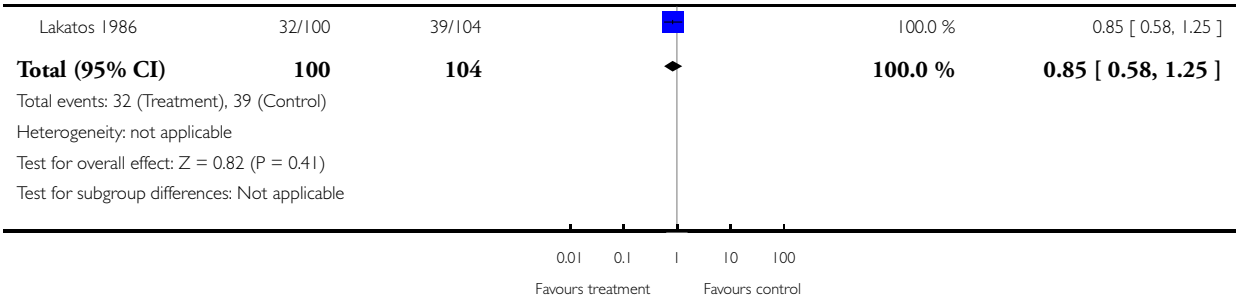
Analysis 1.5. Comparison 1 D-Penicillamine versus controls, < 2000 g birth weight, Outcome 5 Death or abnormal neurodevelopmental outcome.

Review: D-Penicillamine for preventing retinopathy of prematurity in preterm infants

Comparison: 1 D-Penicillamine versus controls, < 2000 g birth weight

Outcome: 5 Death or abnormal neurodevelopmental outcome

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lakatos 1986	32/100	39/104		100.0 %	0.85 [0.58, 1.25]
Total (95% CI)	**100**	**104**		**100.0 %**	**0.85 [0.58, 1.25]**
Total events: 32 (Treatment), 39 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.82 (P = 0.41)					
Test for subgroup differences: Not applicable					



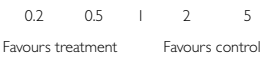
Analysis 2.1. Comparison 2 D-Penicillamine versus controls, < 1500 g birth weight, Outcome 1 Any retinopathy of prematurity.

Review: D-Penicillamine for preventing retinopathy of prematurity in preterm infants

Comparison: 2 D-Penicillamine versus controls, < 1500 g birth weight

Outcome: 1 Any retinopathy of prematurity

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lakatos 1986	0/66	6/68		28.8 %	0.08 [0.00, 1.38]
Lakatos 1987 (2nd trial data)	0/45	3/32		28.2 %	0.10 [0.01, 1.92]
Tandon 2010	7/44	4/44		43.0 %	1.75 [0.55, 5.56]
Total (95% CI)	**155**	**144**		**100.0 %**	**0.32 [0.03, 3.70]**
Total events: 7 (Treatment), 13 (Control)					
Heterogeneity: Tau^2 = 3.26; Chi^2 = 6.90, df = 2 (P = 0.03); I^2 =71%					
Test for overall effect: Z = 0.91 (P = 0.36)					
Test for subgroup differences: Not applicable					



Analysis 2.2. Comparison 2 D-Penicillamine versus controls, < 1500 g birth weight, Outcome 2 Severe retinopathy of prematurity.

Review: D-Penicillamine for preventing retinopathy of prematurity in preterm infants

Comparison: 2 D-Penicillamine versus controls, < 1500 g birth weight

Outcome: 2 Severe retinopathy of prematurity

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lakatos 1986	0/43	1/40		26.3 %	0.31 [0.01, 7.41]
Lakatos 1987 (2nd trial data)	0/27	2/22		29.0 %	0.16 [0.01, 3.25]
Tandon 2010	3/41	1/38		44.7 %	2.78 [0.30, 25.59]
Total (95% CI)	**111**	**100**		**100.0 %**	**0.69 [0.11, 4.22]**
Total events: 3 (Treatment), 4 (Control)					
Heterogeneity: $Tau^2 = 0.63$; $Chi^2 = 2.64$, df = 2 (P = 0.27); $I^2 = 24\%$					
Test for overall effect: Z = 0.40 (P = 0.69)					
Test for subgroup differences: Not applicable					

Analysis 2.3. Comparison 2 D-Penicillamine versus controls, < 1500 g birth weight, Outcome 3 Death.

Review: D-Penicillamine for preventing retinopathy of prematurity in preterm infants

Comparison: 2 D-Penicillamine versus controls, < 1500 g birth weight

Outcome: 3 Death

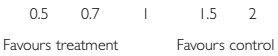
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lakatos 1986	23/66	28/68		62.3 %	0.85 [0.55, 1.31]
Lakatos 1987 (2nd trial data)	18/45	10/32		30.7 %	1.28 [0.68, 2.39]
Tandon 2010	3/44	6/44		7.0 %	0.50 [0.13, 1.87]
Total (95% CI)	**155**	**144**		**100.0 %**	**0.93 [0.65, 1.32]**

Total events: 44 (Treatment), 44 (Control)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.03$, df = 2 (P = 0.36); $I^2 = 2\%$

Test for overall effect: Z = 0.43 (P = 0.67)

Test for subgroup differences: Not applicable



Analysis 2.4. Comparison 2 D-Penicillamine versus controls, < 1500 g birth weight, Outcome 4 Abnormal neurodevelopment in survivors.

Review: D-Penicillamine for preventing retinopathy of prematurity in preterm infants

Comparison: 2 D-Penicillamine versus controls, < 1500 g birth weight

Outcome: 4 Abnormal neurodevelopment in survivors

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Lakatos 1986	3/36	4/36		100.0 %	0.75 [0.18, 3.11]
Total (95% CI)	**36**	**36**		**100.0 %**	**0.75 [0.18, 3.11]**

Total events: 3 (Treatment), 4 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.40 (P = 0.69)

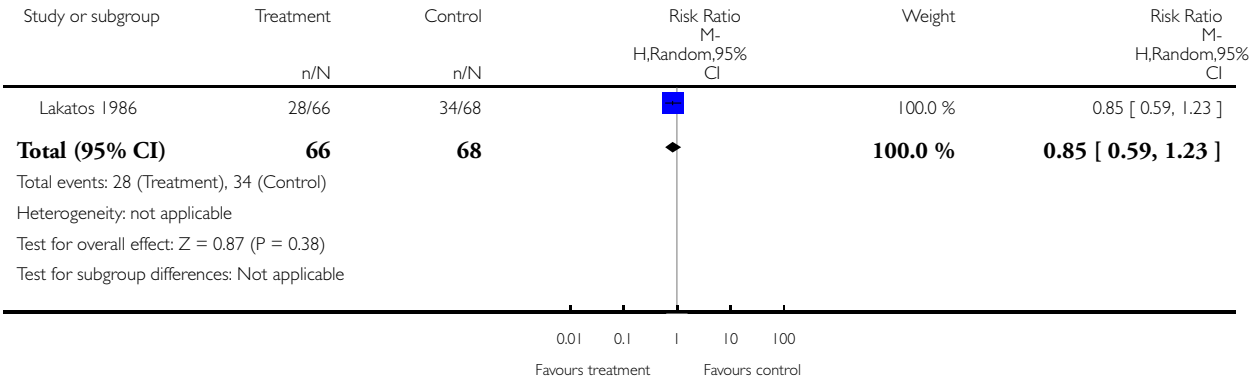
Test for subgroup differences: Not applicable

Analysis 2.5. Comparison 2 D-Penicillamine versus controls, < 1500 g birth weight, Outcome 5 Death or abnormal neurodevelopmental outcome.

Review: D-Penicillamine for preventing retinopathy of prematurity in preterm infants

Comparison: 2 D-Penicillamine versus controls, < 1500 g birth weight

Outcome: 5 Death or abnormal neurodevelopmental outcome



WHAT'S NEW

Last assessed as up-to-date: 27 May 2013.

Date	Event	Description
27 November 2012	New search has been performed	This is an update of the existing review of "D-Penicillamine for preventing retinopathy of prematurity in preterm infants", the Cochrane Library, Issue 1, 2009
27 November 2012	New citation required but conclusions have not changed	A new trial was located in the search done in November 2012 (Tandon 2010) leading to some changes in the review. However, there was no change to the conclusion that the evidence to date does not justify routine use of D-penicillamine to prevent ROP

HISTORY

Protocol first published: Issue 2, 1998

Review first published: Issue 2, 1998

Date	Event	Description
13 November 2000	New search has been performed	This is an update of the existing review of "Carbohydrate supplementation of human milk to promote growth in preterm infants", The Cochrane Library, Issue 2, 1999 No new trials were located in the search done in April 2002, and as a result, no substantive changes were made in the review. There was no change to the conclusion that the addition of carbohydrate supplements to human milk in preterm infants has not been studied sufficiently to make recommendations for practice

CONTRIBUTIONS OF AUTHORS

Both review authors (MQ, MK) participated in all stages of the review and approved the

final data, report and conclusions. Only the new review authors prepared this update (2013).

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

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

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INDEX TERMS

Medical Subject Headings (MeSH)

Chelating Agents [*therapeutic use]; Infant, Premature; Penicillamine [*therapeutic use]; Randomized Controlled Trials as Topic; Retinopathy of Prematurity [*prevention & control]

MeSH check words

Humans; Infant, Newborn