Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants (Review)

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ABSTRACT

Background
Vitamin A is necessary for normal lung growth and the ongoing integrity of respiratory tract epithelial cells. Preterm infants have low vitamin A status at birth and this has been associated with increased risk of developing chronic lung disease. Several studies have been undertaken to assess whether vitamin A supplementation beyond that routinely given in multivitamin preparations can reduce the incidence of this outcome.

Objectives
To assess the benefit and risk of supplementation with vitamin A in very low birthweight infants.

Search strategy
Searches were made of the Oxford Database of Perinatal Trials, MEDLINE up to November 2006, Cochrane Central Register of Controlled Trials Register (CENTRAL, The Cochrane Library, Issue 4, 2006), and Science Citation Index. The reference lists of relevant trials, recent issues of paediatric and nutrition journals, abstracts and proceedings from relevant conferences in the English language were hand searched.

Selection criteria
Randomised controlled trials which compared the effects of supplemental vitamin A with standard vitamin A regimes in infants with birthweight </= 1500 g and reported clinical outcomes (death, chronic lung disease or bronchopulmonary dysplasia, long-term neurodevelopmental status) and/or vitamin A concentrations were considered for the review, as were trials which compared vitamin A dosing regimes and reported biochemical outcomes (retinol concentrations at 28 days).

Data collection and analysis
Data on mortality, requirement for supplemental oxygen at one month of age and at 36 weeks postmenstrual age, retinopathy of prematurity, nosocomial sepsis and follow-up at 18 to 22 months, as well as retinol concentrations at 28 days in trials comparing dosage regimes, were excerpted by both reviewers independently. Data analysis was conducted according to the standards of the Cochrane Neonatal Review Group.

Main results
Eight eligible trials comparing vitamin A supplementation with standard regimes were identified, one having a much larger sample size than the others combined. The meta-analysis suggests supplementation with vitamin A is beneficial in reducing death or oxygen requirement at one month of age [typical RR 0.93 (95% CI 0.88, 0.99), RD -0.05 (95% CI -0.10, -0.01), NNT 20 (10, 100) and oxygen requirement at 36 weeks postmenstrual age [typical RR 0.87 (95% CI 0.77, 0.98), RD -0.08 (95% CI -0.14, -0.01), NNT 13 (7, 100)], and trends towards reduction in oxygen requirement in survivors at one month of age [typical RR 0.93 (95% CI 0.86, 1.01) and

death or oxygen requirement at 36 weeks postmenstrual age [typical RR 0.91 (95% CI 0.82, 1.00)]. Meta-analysis of the three studies from which data on retinopathy of prematurity are available suggests a trend towards reduced incidence in vitamin A supplemented infants. Neurodevelopmental assessment of 85% of surviving infants participating in the largest trial showed no differences in outcome between supplementation and placebo groups at 18 to 22 months corrected age.

Authors' conclusions

Supplementing very low birthweight infants with vitamin A is associated with a reduction in death or oxygen requirement at one month of age and oxygen requirement among survivors at 36 weeks postmenstrual age, with this latter outcome being confined to infants with birthweight less than 1000 g. Whether clinicians decide to utilise repeat intramuscular doses of vitamin A to prevent chronic lung disease may depend upon the local incidence of this outcome and the value attached to achieving a modest reduction in this outcome, balanced against the lack of other proven benefits and the acceptability of treatment. Information on long-term neurodevelopmental status suggests no evidence of either benefit or harm from the intervention. The benefits, in terms of vitamin A status, safety and acceptability of delivering vitamin A in an intravenous emulsion compared with repeat intramuscular injections, should be assessed in a further trial.

PLAIN LANGUAGE SUMMARY

Vitamin A supplements for preventing illness and death in very low birthweight or preterm infants

Vitamin A is a group of fat soluble compounds used by the body for regulation and promotion of growth and differentiation of many cells, including cells in the retina of the eye and the cells that line the lung. Preterm infants have low vitamin A levels at birth. This may contribute to an increased risk of developing chronic lung disease. It is possible that additional vitamin A supplement may reduce complications of prematurity, including abnormal development of the retina (retinopathy), bleeding in the brain (intraventricular haemorrhage) and damage to the gut from inflammation (necrotising enterocolitis) as well as reducing respiratory infections. Too much vitamin A is potentially harmful as it can raise intracranial pressure and cause skin and mucous membrane changes (injury or lesions) and vomiting. In this review of eight trials, supplementing very low birthweight infants with vitamin A by intramuscular injection or in the milk formula was associated with a trend toward a reduced number of deaths or oxygen requirement at one month of age. For surviving infants with birthweight less than 1000 g (three studies, 824 infants in total of which at least 96% had a birthweight less than 1000 g), fewer infants required oxygen at 36 weeks postmenstrual age. The number needed to treat for one to benefit was 13 (7 to 100). Three studies with information on retinopathy of prematurity suggested a trend towards reduced incidence in vitamin A supplemented infants. The one study which investigated neurodevelopmental status at 18 to 22 months of age correcting for prematurity found no evidence of benefit or harm associated with vitamin A supplementation. No side effects of vitamin A supplementation were reported, but it was noted that intramuscular injections of vitamin A were painful.

BACKGROUND

Vitamin A is the generic name for a group of fat soluble compounds which have the biological activity of the primary alcohol retinol.

Vitamin A is involved in the regulation and promotion of growth and differentiation of many cells and in maintaining the integrity of the epithelial cells of the respiratory tract. Vitamin A is also necessary for formation of photosensitive visual pigment in the retina, reproductive functions and immuno-competence. Caretenoids, dietary precursors of vitamin A, have antioxidant properties.

The fetus accumulates vitamin A in the third trimester. The transport mechanism of vitamin A across the placenta and its regulation are not fully established. Premature infants have reduced hepatic stores (of retinyl ester). In the plasma, vitamin A is bound to a specific carrier protein, retinol-binding protein (RBP), and the resulting complex is further complexed with transthyretin (formerly prealbumin) (Mactier 2005). Premature infants have lower concentrations of plasma RBP than term infants and most preterm infants have low plasma vitamin A concentrations and low plasma retinol/RBP molar ratios, suggesting they are vitamin A deficient (Shenai 1993). Inadequate provision and delivery of vitamin A postnatally may exacerbate the problem.

Preterm infants who are unable to tolerate oral feeds are routinely fed parenterally with both an amino-acid/dextrose mixture and a lipid emulsion. Multivitamin preparations containing retinol or an equivalent are commonly added to the amino-acid/dextrose mixture and infused over 24 - 48 hours, but significant losses in delivered vitamin A have been shown to result from light degradation and from adsorption to the tubing. Alternatively, the multivitamins may be added to the lipid infusate (Greene 1987). Kennedy

1997 demonstrated improved serum retinol concentrations following intramuscular injections given three days per week. This route of administration has been adopted in several recent studies. In preterm infants who are able to tolerate enteral feeds, the absorption of enteral vitamin A by the immature gut may be poor.

The "adequate" concentration of plasma vitamin A in very low birthweight infants is not known. Concentrations below 200 micrograms/L (0.70 micromol/L) have been considered deficient in premature infants and concentrations below 100 micrograms/L (0.35 micromol/L) indicate severe deficiency and depleted liver stores. Both the plasma RBP response (Shenai 1990) and the relative rise in serum retinal concentration (Zachman 1996) following intramuscular vitamin A administration have been described as useful tests to assess functional vitamin A status. However, in a recent review, Mactier 2005 concluded that the relationship between measures of vitamin A concentration and functional vitamin A status in preterm infants is not clear.

Vitamin A deficiency in laboratory animals produces a sequence of histopathological changes in the respiratory tract epithelium including necrotising tracheobronchiolitis and squamous metaplasia. These changes can be reversed by restoration of adequate vitamin A status. Similar changes are observed in ventilated infants with chronic neonatal lung injury, leading to the suggestion that vitamin A deficiency may contribute to such injury and supplementation with vitamin A may facilitate healing and recovery (Shenai 1993; Chytil 1992). Two earlier studies reported that very low birthweight infants who developed chronic lung disease (CLD) had lower concentrations of vitamin A than similar infants without CLD (Shenai 1985; Hustead 1984), although other studies from an era when all infants received more adequate supplementation have given conflicting results (Spears 2004; Chabra 1994).

In the 1920s, vitamin A was considered to be an anti-infective agent. There is increasing evidence that vitamin A does have a role in immune function (Bates 1995). Several studies in areas of the world where there is generally poor nutritional status have suggested vitamin A supplementation in infancy may be associated with decreased mortality and morbidity. In infants in Indonesia, Humphrey 1996 reported that a single dose of 52 micromols (50,000 IU) given orally to term infants at birth reduced infant mortality and the prevalence of severe respiratory infections compared with placebo. A recent Cochrane Review (Huiming 2005) concluded that two oral doses of 200,000 IU in children under two years of age with measles are associated with a reduced risk of overall mortality and of pneumonia-specific mortality.

Vitamin A has a role early in gestation in the development of the cardiovascular system (Mactier 2005). Animal models suggest higher vitamin A concentrations may accelerate postnatal constriction of the ductus arteriosus. The possibility that vitamin A supplementation may ameliorate other complications of prematurity, including retinopathy, intraventricular haemorrhage and necrotising enterocolitis, has been suggested by a number of authors, although the basis for any effect is not clearly established.

Vitamin A is potentially toxic and raised intracranial pressure and vomiting have been described in infants receiving large doses. In children and adults, chronic hypervitaminosis A may include bone and joint pain, mucocutaneous lesions and hepatic dysfunction, but the syndrome has not been recognised in preterm infants.

Although a role for vitamin A in neonatal chronic lung disease is not in doubt, uncertainty exists regarding the efficacy of supplementation and whether additional benefit may be obtained by achieving concentrations beyond sufficiency.

This is an update of a previous review (Darlow 2000) and includes data from an additional trial as well as follow-up data from a previously included trial.

OBJECTIVES

To determine the effect of supplementation with vitamin A on the incidence of death and/or neonatal chronic lung disease and long-term neurodevelopmental disability in very low birthweight infants.

In addition, the review will consider the effect of the route, dose and timing of supplementation influence the outcome

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Only randomised and quasi-randomised studies of the effect of vitamin A supplementation on one or more of: survival, chronic lung disease, bronchopulmonary dysplasia and vitamin A concentrations were included.

Types of participants

Very low birthweight infants (defined as birthweight less than or equal to 1500 g or less than 32 weeks gestation).

Types of intervention

Vitamin A supplementation compared with control (placebo or no supplementation).
Vitamin A supplementation comparing dosage regimes

Types of outcome measures

Death, neonatal chronic lung disease [defined as (a) oxygen use at 28 days, (b) oxygen use at 36 weeks postmenstrual age], retinopathy of prematurity, one or more episodes of nosocomial infection, vitamin A concentrations and neurodevelopment at 18 to 36 months.

Side effects: manifestations of hypervitaminosis A, particularly raised intracranial pressure and mucocutaneous lesions.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

The standard methods of the neonatal review group of the Cochrane Collaboration were used. This involved searching the following databases: MEDLINE up to November 2006 (search terms Vitamin A or retinol; and infant, premature or infant, low birth weight); Oxford Database of Perinatal Trials; Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 4, 2006); Science Citation Index.

In addition, the reference lists of relevant articles were searched and recent issues of pediatric and nutritional journals were hand-searched. Abstracts from the Pediatric Academic Societies' Annual Meeting were handsearched from 2002 to 2007.

METHODS OF THE REVIEW

Both review authors cited all identified articles and the decision regarding inclusion/exclusion of the studies was by consensus. In the event of disagreements, the opinion of a third party was sought.

Both reviewers completed data collection sheets and these were compared and any discrepancies resolved by reference to the original sources.

Data was collected on:

- supplementation dose
- supplementation frequency
- time of initiation of supplementation
- vitamin A intake of control groups
- pre-randomisation vitamin A concentrations of supplemented and control groups (if available)
- post-randomisation vitamin A concentrations
- number of deaths in the supplemented and control groups
- numbers reported as having a significant patent ductus arteriousus at two weeks of age
- numbers developing neonatal chronic lung disease in the supplemented and control groups
- mean, standard deviation and range of gestational age in both supplemented and control groups
- mean, standard deviation and range of birthweight in both supplemented and control groups
- numbers reported as having retinopathy of prematurity in supplemented and control groups
- one or more episodes of defined sepsis in both supplemented and control groups
- numbers with long-term neurodevelopmental disability in both supplemented and control groups

Assessment of methodological quality

Methodological quality was assessed using the procedure of the neonatal review group. This involved using a simple "yes/ can't tell / no" classification to assess the following study characteristics: blinding of randomisation, blinding of intervention, completeness of follow-up and blinding of outcome measurement.

Analysis

Separate analyses were conducted for each of the outcomes; death, neonatal chronic lung disease, retinopathy of prematurity, one or more defined episodes of sepsis, and neurodevelopmental disability. Since there were only a small numbers of deaths, an analyses using the composite endpoint of neonatal chronic lung disease or death, and neurodevelopmental disability or death was conducted. All analyses were conducted on an intention to treat basis. Data did not allow quantitative analysis of vitamin A concentrations among survivors.

For dichotomous outcomes the effect of vitamin A supplementation was analysed via both the relative risk (RR) and the risk difference (RD) with 95% confidence intervals. From 1/RD the number need (NNT) to treat was calculated. For vitamin A concentrations the intention was to focus the analysis on the mean difference between the supplemented and control groups.

Between-study heterogeneity was assessed using standard Chi-square tests and the I^2 test.

DESCRIPTION OF STUDIES

Fifteen potentially relevant trials were identified of which eight met eligibility criteria and were included (Bental 1994; Papagaroufalis 1988; Pearson 1992; Ravishankar 2003; Shenai 1987; Tyson 1999; Wardle 2001; Werkman 1994). The report by Bental 1994 gives complete data published in abstract form in Bental 1990, and further clarification has been obtained from the authors concerning two outcomes: oxygen use at one month in survivors, and death or oxygen use at one month. The data of Papagaroufalis 1988 have been updated with information from the author to Dr K. Kennedy at the time of an earlier review (Kennedy 1997). Information on the age at death for infants in the study by Ravishankar 2003 was obtained from the corresponding author. Further information on the numbers examined for retinopathy of prematurity and numbers with any retinopathy in the study by Wardle 2001 have been obtained from the author.

One trial (Ambalavanan 2003) met the eligibility criteria to address the secondary question regarding dosing. This trial compared three different vitamin A dosing regimes with the primary outcome being serum retinol concentrations at 28 days. Further information on the timing of death, numbers of infants having serum retinol estimations at 28 days, and any retinopathy of prematurity was obtained from the author.

Six trials were excluded from the final analysis. The study of Robbins 1993 was not a randomised trial. The study of Coutsoudis 2000 enrolled low birth weight infants up to 35 weeks gestation and the primary outcome was incidence of respiratory infections in the first year of life. Four studies (Aranda 1992; Koo 1993; Landman 1992; Rush 1994) reported vitamin A concentrations but not clinical outcomes. The unpublished study by Aranda 1992 did not state the route of vitamin A supplementation and reported vitamin A levels appear to contain a decimal point error. The studies of Landman 1992 and Rush 1994 both compared equivalent doses of vitamin A administered either enterally or intramuscularly, and data in the study by Rush 1994 were only reported graphically. The study by Koo 1993 compared three doses of vitamin A added to preterm formula and given for an unstated period of time.

Participants

The eight included studies concerning the main objective reported outcomes on 653 infants treated with vitamin A and 638 control infants. One trial (Ravishankar 2003) studied infants of gestational age < 32 weeks with birthweight 500 to 1500 g who had an indwelling umbilical catheter and were less than 24 hours of age. The remaining seven trials studied infants with birthweight </= 1500 g and "at risk for bronchopulmonary dysplasia". The specific entry criteria varied between studies. Bental 1994 studied infants with birthweight 1000 - 1500 g and </= 34 weeks gestation; Papagaroufalis 1988 studied infants with birthweight </= 1300 g and < 29 weeks gestation; Pearson 1992 studied infants with birthweight 700 - 1100 g; Shenai 1987 studied infants with birthweight 700-1300 g and gestation 26 - 30 weeks; Tyson 1999 studied infants with birthweight 401-1000 g; Wardle 2001 studied infants with birthweight less than 1000 g; and Werkman 1994 studied infants with birthweight 725 - 1300 g. Tyson 1999 enrolled infants who required supplemental oxygen or mechanical ventilation at 24 hours of age; Wardle 2001 required consent before 24 hours of age and absence of life threatening congenital abnormalities; Werkman 1994 required infants to be less than 96 hours of age without contraindications to study; whereas all other studies required infants to be receiving supplemental oxygen and to have been treated with mechanical ventilation for at least 72 hours in the first week. Pearson 1992 and Shenai 1987 excluded growth retarded infants. Bental 1994 included only Black South African infants and Shenai 1987 only Caucasian infants.

The study by Ambalavanan 2003, which addressed the secondary question of vitamin A dosage, had the same entry criteria as Tyson 1999.

Interventions

All included studies except Wardle 2001 and Werkman 1994 gave supplemental vitamin A (water soluble retinyl palmitate) by intramuscular injection soon after birth, usually day four, and over the next 28 days. Injections of 4000 IU (1 IU is equivalent to 0.3 mg) were three times a week in the study by Bental 1994 and on alternate days in the study by Papagaroufalis 1988. Injections of 2000 IU were given on alternate days in the studies by Pearson 1992 and Shenai 1987. Tyson 1999 gave injections of 5000 IU on three days a week for four weeks. Ravishankar 2003 gave 1500 IU to 3000 IU, based on birthweight, but only on three occasions (days one, three and seven). Papagaroufalis 1988; Pearson 1992 and Shenai 1987 compared supplementation vs. normal saline placebo injections, Ravishankar 2003 and Tyson 1999 vs. sham injections and Bental 1994 vs. no supplementation.

In the study by Wardle 2001, supplemental vitamin A was given orally as a bolus through an orogastric tube in a dose of 5000 IU/kg daily from postnatal day one until day 28, with control infants receiving an equivalent volume of a look-alike inert placebo solution. In the study by Werkman 1994, supplemental vitamin A was given as retinyl palmitate in lipid emulsion at a concentration of 80,000 RE/L (1 IU is equivalent to 0.3 RE) over 16 hours and study infants received approximately an additional 1,300 - 3,300 IU/kg/d vitamin A in the first two weeks and additional amounts depending on whether they remained on parenteral nutrition.

Study and control infants were also administered standard vitamin A. However, the amount of vitamin A in standard therapy, and hence received by control groups, varied between studies. When on parenteral nutrition, infants in the study by Shenai 1987 received vitamin A 400 IU /100ml protein-dextrose infusion and usually < 700 IU/Kg/day from all sources. Infants in the study by Pearson 1992 received 1200 - 1500 IU/day of vitamin A in the protein-dextrose solution. In the study by Bental 1994, infants on parenteral nutrition received no vitamin A but some received 1500 - 3000 IU/ day after one week when fed orally. In the study by Papagaroufalis 1988, the amount of standard vitamin A is not stated. In the study by Werkman 1994, standard vitamin A was added to the protein dextrose solution, infants < 1000 g receiving 700 IU/day and infants > 1000 g receiving 1580 IU/day. In the study by Tyson 1999, infants received approximately 700 IU/kg/day in the first week, principally in protein-dextrose solution, and closer to 1000 IU/kg/day in weeks two to four from all sources (data estimated from graph). Infants in the study by Wardle 2001 were stated to receive 23 IU/kg/day added to intralipid when on parenteral nutrition (however, the standard United Kingdom dose was at that time 233 IU/kg/day and it is probable infants in this study received this dose) and 5000 IU/kg/day orally when on full enteral feeds from the 14th postnatal day. In the study by Ravishankar 2003, most infants on parenteral nutrition received 466 IU vitamin A added to 100ml of the protein dextrose solution, and 1500 IU/day orally when fully enterally fed.

In the study by Ambalavanan 2003 infants were randomised to receive a standard vitamin A supplement by intramuscular injection of 5000 IU on three days per week for four weeks (considered as the control group), a higher dose of 10,000 IU on three days per week for four weeks, or a once-per-week dose of 15,000 IU for four weeks.

Outcomes

The primary outcome measure for the studies by Bental 1994, Papagaroufalis 1988, Pearson 1992 and Shenai 1987 was the presence of an oxygen requirement and characteristic chest x-ray at 31 days (28 days after enrollment). (Unpublished data of Papagaroufalis are available for 28, 29, 30 and 31 days and in her previous review Kennedy 1997 used day 28 outcomes rather than 31). Data on this outcome for Bental 1994 were not clear and have been obtained from the authors. Werkman 1994 reported this outcome at 28 days of age. All studies with the exception of Werkman 1994 reported deaths before 31 days of age (with clarification of data for Bental 1994 obtained from the authors). Wardle 2001 and Tyson 1999 reported on supplemental oxygen requirement at, or death prior to, 28 days of age; and oxygen requirement at, or death prior to, 36 weeks postmenstrual age. Pearson 1992 additionally reported on oxygen requirement at, or death prior to, 34 weeks postmenstrual age, but because the incidence of oxygen requirement may decrease rapidly with each week increasing age, these data have not been included.

The primary outcome measure for Ravishankar 2003 was "failure of ductal closure", defined as the presence of a moderate or large patent ductus arteriosus on day 14, receipt of indomethacin therapy or having undergone a surgical ligation. Only the study by Wardle 2001 also reported on a patent ductus arteriosus requiring treatment with indomethacin or surgical closure, but the timing of this is uncertain as to whether some infants had died prior to this outcome, hence these data have not been included. Ravishankar 2003 also reported deaths (and further information on the timing of these has been obtained from the authors) and oxygen requirement at 36 weeks postmenstrual age.

Shenai 1987 and Pearson 1992 reported on retinopathy of prematurity. Pearson 1992 states 61% of each group had retinopathy of prematurity and knowing the number of infants alive at 34 weeks postmenstrual age and assuming all were examined for retinopathy, data have been computed. Wardle 2001 reported on treatment for retinopathy of prematurity, but not overall incidence and further data have been obtained from the author.

Bental 1994 and Tyson 1999 reported on one or more episodes of sepsis, defined as culture proven (Bental 1994) and a positive blood culture plus at least five days antibiotics (Tyson 1999). Papagaroufalis 1988 reported on sepsis episodes but these were undefined and may have included early onset sepsis. Shenai 1987 reported on suspected rather than culture proven episodes of sepsis, and Wardle 2001 reported on the median number of sepsis episodes in each group, hence these data have all been excluded.

All studies analysed plasma vitamin A concentrations at various times; however, no data was reported by Papagaroufalis 1988, Bental 1994, Pearson 1992 and Shenai 1987 only report data as points on a graph; Tyson 1999 reported on mean levels in the first 300 enrolled infants and grouped according to receipt of postnatal steroids two weeks before sampling; Wardle 2001 reported on median vitamin A concentrations for the first 84 infants in the study; and Werkman 1994 has reported data grouped according to pulmonary status. Hence, these outcomes have not been analysed in this version of the review.

Ambalavanan 2003 reported on neurodevelopmental impairment (NDI) [any one of the following: bilaterally blind, deaf in both ears requiring aids, a Bayley II Mental Developmental Index (MDI) < 70, or a Bayley II Psychomotor Developmental Index (PDI) < 70)] at 18 to 22 months for infants enrolled in the study by Tyson 1999.

The primary outcome measure for the study by Ambalavanan 2003 was serum retinol concentrations in micrograms/L at 28 days. Ambalavanan 2003 also reported on death prior to 36 weeks postmenstrual age, oxygen requirement at, or death prior to, 36 weeks postmenstrual age, and threshold retinopathy of prematurity. Further information on timing of death, numbers of infants having serum retinol estimations, and any retinopathy of prematurity have been obtained from the authors.

METHODOLOGICAL QUALITY

The methods of randomisation were specified in five studies. Pearson 1992, Ravishankar 2003, Shenai 1987 and Wardle 2001 used sealed envelopes prepared in pharmacies. Both Pearson 1992 and Shenai 1987 used an intramuscular injection of normal saline as a placebo in the control group (in two centres in the study by Pearson, the third centre using a mock injection) and Wardle 2001 used an inert oral solution, with treatment blinded from investigators. Tyson 1999 randomised by a telephone call to a hospital pharmacist who assigned the group using a randomisation list (or, in four centres, using sealed envelopes). Both in this study and the study by Ravishankar 2003 the control group received a sham injection and a similar dressing to the study group. In the study by Papagaroufalis 1988, methods of randomisation and blinding of treatment were unclear, although a placebo was used in the control group. The study by Bental 1994 used computer generated random numbers, but whether the randomisation was blinded is unclear. Treatment assignment was blinded to staff caring for the infant but not to the investigators. Methods of randomisation and blinding of treatment groups were also unclear in the study by Werkman 1994.

Ambalavanan 2003 randomised by sealed opaque envelopes (location unclear). The study was only partially masked in that it was blinded with regard to the two three-times-a-week injection

regimes (standard and high dose) but not the one-day-a-week regime. The primary outcome measure was certainly blinded but was not available for all infants.

Outcome measures were certainly blinded only in the studies by Pearson 1992 and Wardle 2001. The study by Werkman 1994 did not report outcomes on all infants entered into the study, excluding ten who transferred to another centre for surgery and two who died and for whom group assignment was not stated.

The studies by Bental 1994 and Papagaroufalis 1988 make no comment on monitoring for side effects of vitamin A supplementation. The study by Shenai 1987 noted that monitoring for toxicity included periodic anterior fontanelle pressure assessment to detect raised intracranial pressure. Infants in the study by Tyson 1999 were independently examined for signs of toxicity, including fontanelle tension, head circumference, liver size, presence of oedema, cutaneous abnormalities, bony tenderness, lethargy or irritability, weekly for four weeks. In the study by Ambalavanan 2003, these examinations were carried out by one of the investigators. The study by Wardle 2001 recorded three potential side effects; persistent vomiting, pulmonary haemorrhage and seizures requiring anticonvulsants.

Assessment of infants in the follow-up study by Ambalavanan 2003 of infants enrolled in Tyson 1999 was by personnel blinded to the infant's group assignment.

RESULTS

SUPPLEMENTAL VITAMIN A VS. NO SUPPLEMENTATION (COMPARISON 01):

Death before one month (Outcome 01.01):
Six studies reported death by one month of age (Bental 1994; Papagaroufalis 1988; Pearson 1992; Shenai 1987; Tyson 1999; Wardle 2001) and none showed a significant difference between vitamin A and control groups. The typical relative risk (RR) and risk difference (RD) for death before one month do not support a significant reduction in neonatal death: [typical RR 0.86 (95% CI 0.66, 1.11); RD -0.02 (95% CI -0.06, 0.02)].

Oxygen use at one month in survivors (Outcome 01.02):
Seven studies (the six above plus Werkman 1994) reported oxygen use at one month of age in survivors and one of these (Shenai 1987) reported a significant reduction in vitamin A treated infants [RR 0.50 (95% CI 0.28, 0.87)]. The pooled data show a trend towards a reduction in oxygen use at one month in survivors that does not reach statistical significance [typical RR 0.93 (95% CI 0.86, 1.01); RD -0.05 (95% CI -0.10, 0.00)].

Death or oxygen use at one month (Outcome 01.03):
The combined outcome of death or oxygen use at one month could be obtained from six studies (Bental 1994, Papagaroufalis 1988, Pearson 1992, Shenai 1987, Tyson 1999, Wardle 2001). One of these (Shenai 1987) reported a significant reduction in this outcome in vitamin A treated infants [RR 0.53 (0.32, 0.89)]. When the meta-analysis was confined to the five studies reporting on intramuscular vitamin A supplementation (excluding Wardle 2001), there was a trend towards a reduction in death or oxygen use at one month that was of borderline statistical significance [typical RR 0.93 (95% CI 0.86, 1.00); RD -0.06 (95% CI -0.11, -0.00), NNT 17 (9, 1000+)]. When Wardle 2001, in which oral vitamin A supplementation was given to treated infants, is included in the meta-analysis, the pooled data showed a significant reduction in this outcome [typical RR 0.93 (95% CI 0.88, 0.99); RD -0.05 (95% CI -0.10, -0.01), NNT 20 (10, 100)].

Death before 36 weeks postmenstrual age (Outcome 01.04):
Three studies (Ravishankar 2003; Tyson 1999; Wardle 2001) reported death before 36 weeks postmenstrual age with no significant difference between vitamin and control groups.

Oxygen use at one month in survivors (Outcome 01.05):
The study by Tyson 1999 reported a significant reduction in oxygen use at this time in vitamin A treated infants [RR 0.85 (0.73, 0.98), RD -0.09 (-0.16, -0.01), NNT 11 (6, 100)], and pooling the data from the three studies did not alter this conclusion [typical RR 0.87 (95% CI 0.77, 0.98); RD -0.08 (95% CI -0.14, -0.01), NNT 13 (7, 100)].

Death or oxygen use at 36 weeks postmenstrual age (Outcome 01.06):
The combined outcome of death or oxygen use at 36 weeks postmenstrual age in the study by Tyson 1999 showed a trend towards reduction in vitamin A treated infants that is of borderline statistical significance [RR 0.89 (0.79, 1.00), RD -0.07 (-0.14, 0.00), NNT 14 (7, 1000+)], and pooling the data from the three studies did not alter this conclusion [typical RR 0.91 (95% CI 0.82, 1.00), RD -0.06 (95% CI -0.12, 0.00), NNT 17 (8, 1000+)]. Inclusion of the outcome data at 34 weeks postmenstrual age reported by Pearson 1992 in this analysis made essentially no difference to these results.

Retinopathy of prematurity (Outcome 01.07):
Two studies (Shenai 1987; Pearson 1992) reported on retinopathy of prematurity (ROP) and data have been obtained from the author for the study of Wardle 2001. Shenai 1987 noted a trend to reduced incidence of ROP in vitamin A supplemented infants [RR 0.44 (0.19, 1.01)]. Pooled data also showed a non-significant trend towards a reduction of ROP in vitamin A supplemented infants [typical RR 0.85 (95% CI 0.68, 1.06), RD -0.10 (95% CI -0.24, 0.03)].

Sepsis (Outcome 01.08):
Two studies (Bental 1994, Tyson 1999) reported on one or more episodes of culture proven nosocomial sepsis. The pooled data showed a non-significant trend towards a reduction in sepsis in vitamin A supplemented infants [typical RR 0.89 (95% CI 0.76, 1.05), RD -0.05 (95% CI -0.11, 0.02)].

Neurodevelopmental outcome (Outcomes 01.10 - 01.12):
The study by Ambalavanan 2003 followed up 88% of surviving infants who participated in the Tyson 1999 study at 18 to 22 months corrected age. Forty-one infants could not be assessed leaving 290 infants in the intervention group and 289 in the control group (15% lost to followup in both groups). There was no difference between the groups in either neurodevelopment impairment [defined as one or more of Bayley II Mental Index (MDI) < 70, Psychomotor Index (PDI) < 70, any cerebral palsy, blind in both eyes, or bilateral hearing aids] [RR 0.89 (95% CI 0.74, 1.08), RD -0.05 (95% CI -0.04, 0.03)], or the combined outcome of death or NDI [RR 0.92 (95% CI 0.81, 1.05), RD -0.05 (95% CI -0.12, 0.03)].

VITAMIN A DOSING REGIME (COMPARISONS 02 AND 03):
The study by Ambalavanan 2003 compared a "standard" intramuscular regime of supplemental vitamin A, as used in the study by Tyson 1999, of 5000 IU 3 x per week for four weeks, with a higher dose (10,000 IU 3 x per week for four weeks) and with a once-per-week dose (15,000 IU weekly for four weeks). The primary outcome was serum retinol concentrations at 28 days and there was no difference between the standard regime and higher dose for this outcome, whilst the once-per-week regime resulted in significantly lower concentrations than the standard regime [SMD -0.97 (-1.56, -0.38)]. The once-per-week dose regime also resulted in a higher proportion of infants with 28 day retinol concentrations below 200 micrograms/L [RR 2.52 (95% CI 1.24, 5.09)]. There were no differences between the groups in oxygen use at 36 weeks postmenstrual age, or in death or oxygen use at 36 weeks postmenstrual age. There was a trend to fewer infants with any retinopathy [RR 0.63 (95% CI 0.39, 1.00)] and fewer cases of threshold retinopathy in the higher dose regime compared with the standard regime, but only small numbers of infants were involved and the study lacked power to assess this outcome.

No side effects of vitamin A supplementation were reported. The studies by Bental 1994, Papagaroufalis 1988 and Ravishankar 2003 make no comment on monitoring for side effects. The study by Shenai 1987 noted that clinical monitoring for toxicity included periodic anterior fontanelle pressure assessment to detect raised intracranial pressure and reported no clinical or biochemical evidence of toxicity. The study by Pearson 1992 noted intramuscular injections of vitamin A were painful and both this study and the study by Werkman 1994 found no evidence of biochemical toxicity. The study by Wardle 2001 noted that the incidence of potential side effects, seizures and persistent vomiting, did not differ between the groups. Infants in the study by Tyson 1999 were independently assessed for signs of toxicity on a weekly basis; a suspected or definite increase in fontanelle tension was slightly more frequent in control than supplemented infants (18% vs. 15%, p = 0.26), and potential toxicity unexplained by other factors occurred in 0.8% controls and 1.0% supplemented infants. The study by Ambalavanan 2003 monitored for potential side effects and one infant in the higher dose group was noted to have transient fullness of the anterior fontanelle without other causes and which resolved in 48 hours.

DISCUSSION

The study by Tyson 1999 is by far the largest randomised study of vitamin A supplementation reported, having a sample size (1011) more than twice that of all other studies combined. The first version of this review (Darlow 1998) reported a significant reduction in death or oxygen use at one month of age in vitamin A treated infants [typical RR 0.75 (95% CI 0.62, 0.91)], but addition of the study by Tyson 1999, which found no difference in outcome at one month, to the pooled data resulted in the meta-analysis showing only a trend towards reduction in death or oxygen use at this time, which was of borderline significance [typical RR 0.93 (95% CI 0.86, 1.00)] (Darlow 2000). The study by Wardle 2001 (the only study to give supplemental vitamin K via the enteral route) had a moderate sample size (151) and found no significant benefit for supplementation; however, the further addition of data from this study resulted in the meta-analysis showing a small but significant reduction in this outcome [typical RR 0.93 (95% CI 0.88, 0.99); RD -0.05 (95% CI -0.10, -0.01), NNT 20 (10, 100)].

Three studies (Ravishankar 2003; Tyson 1999; Wardle 2001) reported outcome at 36 weeks postmenstrual age. The study by Tyson 1999, which gave intramuscular vitamin A to supplemented infants, reported a significant reduction in oxygen use in vitamin A treated infants [RR 0.85 (0.73, 0.98)], and a trend towards reduction in death or oxygen use of borderline significance [RR 0.89 (0.79, 1.00)]. Pooling the data from the three studies did not alter these conclusions. From the meta-analysis of the combined data, the number needed to treat to achieve benefit in one infant with regard to oxygen requirement at 36 weeks is 13, and with regard to death or oxygen requirement at 36 weeks is 17. It is important to note that the 95% confidence intervals are wide, being 7 to 100 and 8 to 1000 respectively. It is also noteworthy that there was no difference in other outcomes, including days of ventilation and length of stay, between vitamin A supplemented and control infants in the study by Tyson 1999.

Some differences between the studies may be explained by the differences in patient populations (birthweight and ethnicity) and by the differences in both the route of vitamin A supplementation (intramuscular, intravenous in lipid emulsion or enteral) and the dose given. The studies by Tyson 1999 and by Wardle 2001 included somewhat lower birthweight infants (401-1000 g and less than 1000 g respectively) than most other studies, whereas other studies used various lower weight limits (500 g Ravishankar 2003; 700 g Pearson 1992, Shenai 1987; 725 g Werkman 1994; 1000 g Bental 1994). The incidence of supplemental oxygen requirement at one month of age in vitamin A supplemented infants was higher at 73% in the study by Tyson 1999 and 83% in the study

by Wardle 2001, which is consistent with their lower birthweight and gestational age, compared with a range of 34% - 67% in the other studies. For the smallest infants, the outcome at 36 weeks postmenstrual age may be more clinically relevant.

In all studies there were higher vitamin A or retinol concentrations at most time periods studied in supplemented infants compared with controls. Kennedy 1997 reported that an intramuscular dose of 5000 IU vitamin A three times per week was required to achieve serum concentrations > 250 micrograms/L in most very low birthweight infants. This was the dose used by Tyson 1999 and was generally greater than the dose used in earlier studies; (Bental 1994 used 4000 IU three times weekly, Papagaroufalis 1988 used 4000 IU on alternate days while the infant was ventilated, Pearson 1992 and Shenai 1987 used 2000 IU on alternate days, and Ravishankar 2003 used between 1500 IU and 3000 IU for only three doses). Nevertheless, in the study by Tyson 1999, 25% of infants who received supplemental vitamin A and 54% of controls (data from the first 300 enrolled infants) had vitamin A concentrations below 200 micrograms/L on day 28. Similar percentages, 22% of those who received supplemental vitamin A and 45% of controls, had a relative dose response (change in the serum retinol concentration divided by the preinjection concentration) of >10% following an intramuscular dose of 2000 IU. Taken together, these data suggested that an even higher dose of vitamin A given intramuscularly may be required to achieve vitamin A sufficiency in very premature infants.

In the study by Wardle 2001, infants received a much higher cumulative dose of supplemental vitamin A than in other studies (140,000 IU in 28 days compared with 60,000 IU in the study by Tyson 1999), but by the enteral route. Vitamin A concentrations were only measured in the first 84 infants enrolled and the median concentration 24 hours after the first dose was significantly higher in supplemented infants (230 micrograms/L versus 150 micrograms/L) but at seven and 28 days of age there were no significant differences in vitamin A concentrations between the groups and the median concentration in both groups was less than 200 micrograms/L at these times. Vitamin A absorption is less efficient using the enteral route. Rush 1994 compared the same dose of vitamin A (2000 IU/kg on alternate days) given by intramuscular injection or orally and reported the former route gave higher plasma vitamin A concentrations after one week and Landman 1992 reported that enteral supplementation with 5000 IU vitamin A daily resulted in similar plasma concentrations at 32 days of age to those resulting from 2000 IU vitamin A on alternate days by the intramuscular route.

There were also quite marked differences in the vitamin A dose received by the control groups. This has previously been suggested to account for differences in outcome between the early studies (Lorch 1994). Infants in the control group in the study by Pearson 1992 received higher doses of vitamin A, and had mean vitamin A concentrations in weeks three and four of > 200 micrograms/L, higher than in infants in the control group in the study by Shenai 1987, where mean vitamin A concentrations were < 150 micrograms/L at these times. One interpretation is that the study of Shenai 1987 demonstrated a benefit of supplemental vitamin A in a population with vitamin deficiency, while the study of Pearson 1992 showed a minimal benefit of additional supplementation in a population with more adequate vitamin status. However, Georgieff 1989 reported that postnatal steroids led to a near doubling of plasma vitamin A concentrations, and this finding was confirmed in the study of Tyson 1999. Certainly variability in exposure to postnatal steroids complicates interpretation of these data. Two studies included in this review reported the incidence of treatment with postnatal steroids (Pearson 1992, 46% in vitamin A group and 44% in controls; Wardle 2001, 39% and 34% respectively), while two others (Bental 1994, Tyson 1999) noted that steroids were used in some infants.

Further information on the optimal dosage of intramuscular vitamin A for infants with birthweight 401-1000 g is now available from the study by Ambalavanan 2003. Ambalavanan 2003 compared the dose regime used by Tyson 1999 (5000 IU 3x weekly for four weeks) with both a higher dose (10,000 IU 3x weekly for four weeks) and a once-a-day-dose (15,000 IU weekly for four weeks) in a total of 120 infants. Only two infants received postnatal steroids between study day 21 to 28. Compared with the standard regime, the higher dose regime was not associated with a significantly higher mean retinol concentration at 28 days and there were no differences between the groups in the proportion of infants having concentrations < 200 micrograms/L at this time (26% vs. 21%). The once-a-day regime, however, was associated with significantly lower mean concentrations at 28 days and increased the risk of infants having concentrations < 200 micrograms/L at this time by a factor of 2.5 (26% vs. 65%).

Many other variables will also affect the rate of chronic lung disease, which is known to vary considerably between centres. These factors include use of antenatal steroids (stated in four studies; Pearson 1992 where they were received by 26% study infants and 41% controls, Tyson 1999 where the rates were 76% and 74%, Wardle 2001 where the rates were 77% and 82%, and Ravishankar 2003 where the rates were 86% and 72%), exogenous surfactant (stated in three studies; Pearson 1992 where > 90% received an artificial surfactant, Tyson 1999 where >80% received a natural surfactant, and Wardle 2001 where all but one infant in the control group received an artificial surfactant), mode of ventilation including early nasal CPAP, postnatal steroids, and criteria for prescribing supplemental oxygen.

Important information on follow-up at 18 to 20 months of infants who participated in the Tyson 1999 study is now available in Ambalavanan 2003. Eighty-five percent of surviving infants were assessed. There was no difference between the groups in either neurodevelopment impairment [defined as one or more of Bayley II Mental Index (MDI) < 70, Psychomotor Index (PDI) < 70, any

cerebral palsy, blind in both eyes, or bilateral hearing aids] [RR 0.90 (0.73-1.08)], or the combined outcome of death or NDI [RR 0.94 (0.80-1.07)]. More infants who received supplemental vitamin A than controls were prescribed home oxygen (36% vs. 32%) and were on home oxygen for more than 6 months (20% vs. 25%), although these differences were not significant. Although this study was not powered appropriately to assess long-term outcomes, there was no evidence of either benefit or harm from repeat intramuscular vitamin A following birth.

The data do suggest that, in the dosages employed, supplemental vitamin A is safe and free from side effects, although Pearson 1992 noted repeat intramuscular injections may have been painful.

AUTHORS' CONCLUSIONS

Implications for practice

Supplementing very low birthweight infants with vitamin A is associated with a benefit in terms of reducing death or oxygen requirements at one month of age and oxygen requirements at 36 weeks postmenstrual age. There was a trend towards reduction in oxygen requirement at one month of age and death or oxygen requirement at 36 weeks postmenstrual age. Supplementation with vitamin A may also reduce the incidence of retinopathy of prematurity and of nosocomial sepsis. Trials do not allow judgement as to the best route of supplementation, although the one trial which gave enteral vitamin A found no significant benefit for supplementation. The one trial which has compared different intramuscular dosing regimes suggests that, at least for infants with birthweight 401 to 1000 g, the optimal dose appears to be 5000 IU 3x weekly for four weeks, although on this regime 26% of infants still had plasma vitamin A concentrations below 200 micrograms/L (0.70 micromols/L), which may indicate deficiency.

The major conclusion of a benefit at 36 weeks postmenstrual age is derived from the results of three studies in which a majority of infants had a birthweight less than 1000 g. The previous version of this review (Darlow 2002) stated that whether clinicians decide to utilise repeat intramuscular doses of vitamin A may well depend upon the incidence of supplemental oxygen requirement at 36 weeks postmenstrual age in extremely low birthweight infants in their unit and their own assessment, based upon the review, of the benefits of a modest reduction in this outcome balanced against lack of other proven benefits and the acceptability of treatment. Long-term follow-up data at 18 to 22 months corrected age of the largest study in this review is now available and showed no evidence of either benefit or harm at this time. If a decision has been made not to treat for the early benefits, the follow-up study is unlikely to change that decision. On the other hand, if a decision has been made to treat for early benefits, the follow-up study is reassuring in that long term harmful effects are unlikely.

Implications for research

Further investigations are warranted as to the relationship between biochemical and functional vitamin A status in very low birthweight infants. In addition, the benefits, in terms of vitamin A status, clinical outcomes and safety and acceptability to caretakers and parents, of delivering vitamin A in an intravenous lipid emulsion from the first days of life compared with delivery by intramuscular injections should be investigated in a randomised controlled trial.

There is an epidemic of retinopathy of prematurity in middle income and developing countries which affects many infants who are more mature at birth and have a greater birthweight than the majority of infants who acquire severe retinopathy in more developed countries. In many of these countries, the vitamin A status of both mothers and infants is particularly poor. The trends towards less retinopathy of prematurity associated with supplemental vitamin A and higher dose regimes seen in this review suggests that further studies should be undertaken in these countries to assess the possible contribution of poor perinatal vitamin A status to retinopathy of prematurity and the need for intervention studies in these populations.

POTENTIAL CONFLICT OF INTEREST

None

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Ambalavanan 2003**
Methods	Single centre randomised controlled trial Blinding of randomisation: yes Blinding of intervention: partial Complete follow-up: yes Blinding of outcome measurements: partial
Participants	Birthweight 401-1000g Requiring mechanical ventilation or supplemental oxygen at 24 hours of age No major congenital anomalies, non-bacterial infection, or terminal illness

Characteristics of included studies (*Continued*)

Interventions	Standard regimen (5000 IU vitamin A i.m. injection 3 times a week for 4 weeks) (n=40) vs high dose (10,000 IU vitamin A i.m. injection 3 times a week for 4 weeks) (n=40) vs once-per-week (15,000 IU vitamin A i.m. injection weekly for 4 weeks) (n=40)
Outcomes	Median retinol concentrations on day 28 Percentage of each group with retinol concentrations <200micrograms/L Death before 36 weeks postmenstrual age Oxygen requirement at, or death before, 36 weeks postmenstrual age Threshold retinopathy of prematurity Examination for potential toxicity at least three times weekly
Notes	Supplemental vitamin A was water soluble retinyl palmitate
Allocation concealment	C – Inadequate

Study	**Bental 1994**
Methods	Single centre randomised controlled trial Blinding of randomisation: unclear Blinding of intervention: no Complete follow-up: yes Blinding of outcome measurement: no
Participants	Birthweight 1000-1500g Gestational age 34 weeks or less Infants receiving supplemental oxygen and mechanical ventilation for at least 72 hours during the first week. No congenital anomalies or infection. Black South African infants
Interventions	Supplemental 4000 IU vitamin A i.m. injection 3 times a week from day 4 for a total of 12 injections (n= 31) vs no supplementation (n=29)
Outcomes	Death before 31 days BPD (oxygen or ventilation on day 31 and characteristic chest x-ray; full data obtained from authors) Culture proven sepsis Vitamin A levels at various times
Notes	Some control and study infants received vitamin A 1500-3000 IU after one week of age when fed orally Supplemental vitamin A for study infants was water soluble retinyl palmitate
Allocation concealment	B – Unclear

Study	**Papagaroufalis 1988**
Methods	Single centre randomised controlled trial Blinding of randomisation: unclear Blinding of intervention: unclear complete follow-up: yes Blinding of outcome measurement: no
Participants	Birthweight </=1300g and gestation <29 weeks Requirement for >40% oxygen and mechanical ventilation for >72 hours in first week
Interventions	Supplemental 4000 IU vitamin A i.m. injection from day 4-6 on alternate days until extubated (n=27) vs normal saline placebo (n=28)
Outcomes	Death before 31 days BPD (oxygen requirement and characteristic chest x-ray on day 31) Vitamin A levels at various times
Notes	Supplemental vitamin A for study infants was water soluble retinyl palmitate Amount of vitamin A in unsupplemented infants not stated

Characteristics of included studies (*Continued*)

Allocation concealment	B – Unclear

Study	**Pearson 1992**
Methods	Multicentre randomised controlled trial Blinding of randomisation: yes Blinding of intervention: yes Complete follow-up: yes Blinding of outcome: yes
Participants	Birthweight 700-1100g Requiring supplemental oxygen and mechanical ventilation between 72 and 96 hours of age with previous cumulative duration of ventilation and oxygen longer than 48 hours No growth retardation (undefined), congenital or chromosomal abnormalities, hydrops fetalis, congenital infection, neonatal hepatitis or "do not resuscitate" order
Interventions	Supplemental 2000 IU vitamin A by i.m. injection alternate days from day 4 for 14 doses (n=27) vs normal saline placebo or mock injection (n=22)
Outcomes	Death before 31 days BPD (oxygen requirement at 31 days and characteristic chest x-ray) Oxygen requirement at 34 weeks post-conceptual age Retinopathy of prematurity Plasma vitamin A levels and retinyl binding protein at various times
Notes	Both control and study infants received 1200-1500 IU/d vitamin A in protein-dextrose solution when on parenteral nutrition When fed orally all infants received vitamin A 250-1030 IU per 100 mls milk Supplemental vitamin A for study infants was water soluble retinyl palmitate
Allocation concealment	A – Adequate

Study	**Ravishankar 2003**
Methods	Single centre randomised controlled trial Blinding of randomisation: yes Blinding of intervention: yes Complete follow-up: yes Blinding of outcome measurement: yes
Participants	Birthweight 500-1500g and gestation <32 weeks Having indwelling umbilical line No major congenital malformations or chromosomal anomalies Less than 24 hours of age
Interventions	Supplemental 1500-3000 IU vitamin A (based on weight) by i.m. injection on days 1, 3 and 7 (n=22) vs sham injection (n-18)
Outcomes	Failure of PDA closure, defined as PDA larger than trivial on day 14, indomethacin treatment or surgical ligation Death BPD (oxygen requirement at 36 weeks post-menstrual age
Notes	PDA closure primary outcome Most infants received parenteral nutrition including 466 IU/dl vitamin A and an additional 1000 IU supplement when fed orally
Allocation concealment	A – Adequate

Characteristics of included studies (*Continued*)

Study	**Shenai 1987**
Methods	Single centre randomised controlled trial Blinding of randomisation: yes Blinding of intervention: yes Complete follow-up: yes Blinding of outcome measurement: no
Participants	Birthweight 700-1300g, gestation 26-30 weeks Requiring supplemental oxygen and mechanical ventilation for at least 72 hours in the first week Caucasian infants only Birthweight appropriate for gestational age No congenital abnormalities
Interventions	Supplemental 2000 IU vitamin A by i.m. injection alternate days from day 4 for a total of 14 injections (n= 20) vs normal saline placebo (n=20)
Outcomes	Death before 31 days BPD (oxygen requirement or ventilation at 31 days plus characteristic chest x-ray) Total days oxygen Episodes of sepsis Retinopathy of prematurity Vitamin A levels at various times
Notes	Both control and study infants received vitamin A 400 IU/dL in parenteral nutrition and 240-550 IU/dL from milk plus 1500 IU supplements when fed orally Supplemental vitamin A for study infants was water soluble retinyl palmitate
Allocation concealment	A – Adequate

Study	**Tyson 1999**
Methods	Multicentre randomised controlled trial Blinding of randomisation: yes Blinding of intervention: yes Complete follow-up: yes Blinding of outcome: unclear
Participants	Birthweight 401-1000g Requiring supplemental oxygen or mechanical ventilation at 24 hours of age No major congenital anomalies, non-bacterial infection, or terminal illness
Interventions	Supplemental 5000 IU vitamin A i.m. injection 3 times a week for 4 weeks (n=405) vs sham injection (n= 402)
Outcomes	Oxygen requirement at, or death before, 36 weeks postmenstrual age Oxygen requirement at, or death before, 28 days of age Culture proven sepsis Grade 3 or 4 intracranial haemorrhage Periventricular leukomalacia Vitamin A on study day 28 in subset of infants and relative dose-response to 2000 IU vitamin A i.m. Examination for potential toxicity weekly Assessment of neurodevelopmental status at 18 to 22 months corrected age is available in Ambalavanan 2005
Notes	Control and study infants received similar intakes of vitamin A from non-study enteral and parenteral sources but amounts not stated Supplemental vitamin A for study infants was water soluble retinyl palmitate
Allocation concealment	A – Adequate

Study	Wardle 2001
Methods	Multicentre randomised controlled trial Blinding of randomisation: yes Blinding of intervention: yes Complete follow-up: yes Blinding of outcome: yes
Participants	Birthweight less than 1000g No life threatening congenital abnormalities Consent before 24 hours of age
Interventions	Supplemental 5000 IU vitamin A orally daily until day 28 (n=77) vs same volume look alike placebo liquid (n=77)
Outcomes	Oxygen requirement at 28 days Death pre-discharge Oxygen requirement at 36 weeks post-menstrual age Retinopathy of prematurity requiring treatment
Notes	Control and study infants received 23 IU/kg/day vitamin A (stated amount but probably 233 IU) in intralipid when on parenteral nutrition. When on full enteral feeds and more than 14 days of age all infants received 5000 IU/kg/day vitamin A orally
Allocation concealment	A – Adequate

Study	Werkman 1994
Methods	Single centre randomised controlled trial Blinding of randomisation: unclear Blinding of intervention: unclear Complete follow-up: no Blinding of outcome: no
Participants	Birthweight 725-1300g Less than 96 hours of age No intraventricular or periventricular haemorrhage, history of maternal substance abuse or STD No congenital anomalies
Interventions	Supplemental vitamin A 80,000 RE/L (giving c. 1,300-3,300 IU/kg/d) in intravenous lipid infused over 16 hours from randomisation (48-96hr) and whilst receiving parenteral nutrition (n=44) vs no supplementation (n=42)
Outcomes	BPD (oxygen beyond 28 days and characteristic chest x-ray) Total days oxygen requirement Vitamin A and retinyl binding protein levels at various times
Notes	Both control and study infants received vitamin A as MVIP added to protein-dextrose solution (birthweight <1000g 1.5 ml/d, 210 RE/d; >1000g 3.4 ml/d, 476 RE/d) and oral supplements when fed orally
Allocation concealment	B – Unclear

Characteristics of excluded studies

Study	Reason for exclusion
Aranda 1992	Route of supplementation not stated. No clinical outcomes
Coutsoudis 2000	Compared three doses of oral vitamin A versus placebo in infants of <36 weeks gestation with primary outcome incidence of respiratory infections during the first year of life

Characteristics of excluded studies (*Continued*)

Koo 1993	Compared three doses of vitamin A added to preterm formula for an unstated period. No clinical outcomes
Landman 1992	Compared enteral with intramuscular administration of vitamin A. No clinical outcomes
Robbins 1993	Groups not randomised
Rush 1994	Compared enteral with intramuscular administration of vitamin A. Vitamin A concentrations only reported graphically. No clinical outcomes

ANALYSES

Comparison 01. Supplemental vitamin A vs no supplementation

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Death before one month	6	1165	Relative Risk (Fixed) 95% CI	0.86 [0.66, 1.11]
02 Oxygen use at one month in survivors	7	1070	Relative Risk (Fixed) 95% CI	0.93 [0.86, 1.01]
03 Death or oxygen use at one month	6	1165	Relative Risk (Fixed) 95% CI	0.93 [0.88, 0.99]
04 Death before 36 weeks PMA	3	1001	Relative Risk (Fixed) 95% CI	1.00 [0.77, 1.30]
05 Oxygen use at 36 weeks PMA in survivors	3	824	Relative Risk (Fixed) 95% CI	0.87 [0.77, 0.98]
06 Death or oxygen use at 36 weeks PMA	3	1001	Relative Risk (Fixed) 95% CI	0.91 [0.82, 1.00]
07 Retinopathy of prematurity (any grade)	3	175	Relative Risk (Fixed) 95% CI	0.85 [0.68, 1.06]
08 One or more episodes of sepsis	2	867	Relative Risk (Fixed) 95% CI	0.89 [0.76, 1.05]
09 Failure of ductal closure or treatment by day 14	1	40	Relative Risk (Fixed) 95% CI	0.98 [0.56, 1.72]
10 Neurodevelopmental impairment at 18 -22 months	1	538	Relative Risk (Fixed) 95% CI	0.89 [0.74, 1.08]
11 Death before 18-22 months	1	807	Relative Risk (Fixed) 95% CI	0.95 [0.71, 1.27]
12 Death or neurodevelopmental impairment at 18-22 months	1	687	Relative Risk (Fixed) 95% CI	0.92 [0.81, 1.05]

Comparison 02. Higher dose (10,000 IU 3x wk for 4 wks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 wks)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Retinol concentration on study day 28 (micrograms/L)	1	55	Standardised Mean Difference (Fixed) 95% CI	0.25 [-0.28, 0.78]
02 Retinol <200 micrograms/L on day 28 (%)	1	55	Relative Risk (Fixed) 95% CI	0.83 [0.32, 2.15]
03 Death before 36 weeks PMA	1	80	Relative Risk (Fixed) 95% CI	0.73 [0.33, 1.62]
04 Oxygen use at 36 weeks PMA in survivors	1	61	Relative Risk (Fixed) 95% CI	2.72 [0.81, 9.08]
05 Death or oxygen use at 36 weeks PMA	1	80	Relative Risk (Fixed) 95% CI	1.21 [0.70, 2.12]
06 Retinopathy of prematurity (any grade)	1	63	Relative Risk (Fixed) 95% CI	0.74 [0.48, 1.13]

07 Retinopathy of prematurity (threshold disease)	1	63	Relative Risk (Fixed) 95% CI	0.09 [0.01, 1.53]

Comparison 03. Once-a-week (15,000 IU for 4 weeks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 weeks)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Retinol concentration on study day 28 (micrograms/L)	1	50	Standardised Mean Difference (Fixed) 95% CI	-0.97 [-1.56, -0.38]
02 Retinol <200 micrograms/L on day 28 (%)	1	50	Relative Risk (Fixed) 95% CI	2.52 [1.24, 5.09]
03 Death before 36 weeks PMA	1	80	Relative Risk (Fixed) 95% CI	0.73 [0.33, 1.62]
04 Oxygen use at 36 weeks PMA in survivors	1	61	Relative Risk (Fixed) 95% CI	1.81 [0.50, 6.59]
05 Death or oxygen use at 36 weeks PMA	1	80	Relative Risk (Fixed) 95% CI	1.00 [0.55, 1.82]
06 Retinopathy of prematurity (any grade)	1	64	Relative Risk (Fixed) 95% CI	0.63 [0.39, 1.00]
07 Retinopathy of prematurity (threshold disease)	1	64	Relative Risk (Fixed) 95% CI	0.56 [0.15, 2.16]

INDEX TERMS

Medical Subject Headings (MeSH)

Infant, Newborn; Infant, Premature; Infant, Premature, Diseases [*prevention & control]; *Infant, Very Low Birth Weight; Lung Diseases [*prevention & control]; Randomized Controlled Trials; Vitamin A [*therapeutic use]

MeSH check words

Humans

COVER SHEET

Title	Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants
Authors	Darlow BA, Graham PJ
Contribution of author(s)	Information not supplied by author
Issue protocol first published	1998/4
Review first published	2000/2
Date of most recent amendment	21 August 2007
Date of most recent SUBSTANTIVE amendment	15 July 2007
What's New	This review updates the existing review "Vitamin A supplementation for preventing morbidity and mortality in very low birthweight infants", published in The Cochrane Library, Issue 2, 2002 (Darlow 2002). One further small trial has been identified and data from this trial added to the pooled data for the meta-analysis. There are now data on the neurodevelopmental status at 18 to 22 months postmenstrual age for infants included in the largest vitamin A supplementation

trial, and this information has been included in this review. In addition, data from one trial that compared three different intramuscular vitamin A dosing regimes have been included. The previous version of this review concluded that supplementing very low birthweight infants with vitamin A is associated with a reduction in oxygen requirement among survivors at 36 weeks postmenstrual age, as well as a reduction in death or oxygen requirement at one month of age. With data from the additional study, these conclusions remain the same. The information on follow-up at 18 to 22 months postmenstrual age from the largest included trial showed no evidence or benefit or harm from the intervention.
Based on biochemical data, the one study that investigated different intramuscular vitamin A dosing regimes suggested that the regime used in the largest trial (5000 IU 3x weekly for four weeks) was optimal even though some infants still had poor vitamin A status.
The conclusion remains unchanged: clinicians must decide whether to utilise repeat intramuscular doses of vitamin A based upon the incidence of supplemental oxygen requirement at 36 weeks postmenstrual age in extremely low birthweight infants in their unit and their own assessment, based upon the review, of the benefits of a modest reduction in this outcome balanced against lack of other proven benefits and the acceptability of treatment. The follow-up data would support a decision either to treat or not to treat.

Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	27 May 2007
Date authors' conclusions section amended	27 May 2007
Contact address	Dr Brian Darlow Professor of Paediatrics Department of Paediatrics Christchurch School of Medicine PO Box 4345 CHRISTCHURCH NEW ZEALAND E-mail: bdarlow@chmeds.ac.nz Tel: +64 3 3640 747 Fax: +64 3 3644 634
DOI	10.1002/14651858.CD000501.pub2
Cochrane Library number	CD000501
Editorial group	Cochrane Neonatal Group
Editorial group code	HM-NEONATAL

GRAPHS AND OTHER TABLES

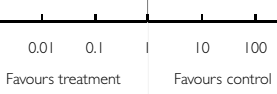
Analysis 01.01. Comparison 01 Supplemental vitamin A vs no supplementation, Outcome 01 Death before one month

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 01 Supplemental vitamin A vs no supplementation

Outcome: 01 Death before one month

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Supplementation via intramuscular injection					
Bental 1994	5/31	10/29		10.5	0.47 [0.18, 1.21]
Papagaroufalis 1988	9/27	8/28		8.0	1.17 [0.53, 2.58]
Pearson 1992	1/27	4/22		4.5	0.20 [0.02, 1.69]
Shenai 1987	1/20	0/20		0.5	3.00 [0.13, 69.52]
Tyson 1999	43/405	46/402		47.0	0.93 [0.63, 1.37]
Subtotal (95% CI)	510	501		70.5	0.86 [0.62, 1.18]
Total events: 59 (Treatment), 68 (Control)					
Test for heterogeneity chi-square=4.69 df=4 p=0.32 I^2 =14.8%					
Test for overall effect z=0.96 p=0.3					
02 Supplementation via intravenous route					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 Supplementation via oral route					
Wardle 2001	25/77	29/77		29.5	0.86 [0.56, 1.33]
Subtotal (95% CI)	77	77		29.5	0.86 [0.56, 1.33]
Total events: 25 (Treatment), 29 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.67 p=0.5					
Total (95% CI)	587	578		100.0	0.86 [0.66, 1.11]
Total events: 84 (Treatment), 97 (Control)					
Test for heterogeneity chi-square=4.69 df=5 p=0.45 I^2 =0.0%					
Test for overall effect z=1.17 p=0.2					



Analysis 01.02. Comparison 01 Supplemental vitamin A vs no supplementation, Outcome 02 Oxygen use at one month in survivors

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 01 Supplemental vitamin A vs no supplementation

Outcome: 02 Oxygen use at one month in survivors

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Supplementation via intramuscular injection					
Bental 1994	11/26	10/19		3.0	0.80 [0.43, 1.49]
Papagaroufalis 1988	12/18	18/20		4.4	0.74 [0.52, 1.06]
Pearson 1992	12/26	8/18		2.5	1.04 [0.54, 2.01]
Shenai 1987	8/19	17/20		4.3	0.50 [0.28, 0.87]
Tyson 1999	265/362	269/356		70.5	0.97 [0.89, 1.06]
Subtotal (95% CI)	451	433		84.7	0.93 [0.86, 1.01]
Total events: 308 (Treatment), 322 (Control)					
Test for heterogeneity chi-square=7.64 df=4 p=0.11 I^2 =47.7%					
Test for overall effect z=1.74 p=0.08					
02 Supplementation via intravenous route					
Werkman 1994	15/44	15/42		4.0	0.95 [0.54, 1.70]
Subtotal (95% CI)	44	42		4.0	0.95 [0.54, 1.70]
Total events: 15 (Treatment), 15 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.16 p=0.9					
03 Supplementation via oral route					
Wardle 2001	43/52	42/48		11.3	0.95 [0.80, 1.11]
Subtotal (95% CI)	52	48		11.3	0.95 [0.80, 1.11]
Total events: 43 (Treatment), 42 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					
Total (95% CI)	547	523		100.0	0.93 [0.86, 1.01]
Total events: 366 (Treatment), 379 (Control)					
Test for heterogeneity chi-square=7.64 df=6 p=0.27 I^2 =21.5%					
Test for overall effect z=1.82 p=0.07					

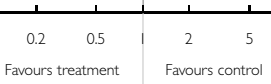
Analysis 01.03. Comparison 01 Supplemental vitamin A vs no supplementation, Outcome 03 Death or oxygen use at one month

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 01 Supplemental vitamin A vs no supplementation

Outcome: 03 Death or oxygen use at one month

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Supplementation via intramuscular injection					
Bental 1994	16/31	20/29		4.5	0.75 [0.49, 1.14]
Papagaroufalis 1988	21/27	26/28		5.5	0.84 [0.67, 1.05]
Pearson 1992	13/27	12/22		2.9	0.88 [0.51, 1.52]
Shenai 1987	9/20	17/20		3.7	0.53 [0.32, 0.89]
Tyson 1999	308/405	315/402		68.2	0.97 [0.90, 1.05]
Subtotal (95% CI)	510	501		84.7	0.93 [0.86, 1.00]
Total events: 367 (Treatment), 390 (Control)					
Test for heterogeneity chi-square=7.70 df=4 p=0.10 I^2 =48.1%					
Test for overall effect z=2.06 p=0.04					
02 Supplementation via intravenous route					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 Supplementation via oral route					
Wardle 2001	68/77	71/77		15.3	0.96 [0.86, 1.06]
Subtotal (95% CI)	77	77		15.3	0.96 [0.86, 1.06]
Total events: 68 (Treatment), 71 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.81 p=0.4					
Total (95% CI)	587	578		100.0	0.93 [0.88, 0.99]
Total events: 435 (Treatment), 461 (Control)					
Test for heterogeneity chi-square=7.88 df=5 p=0.16 I^2 =36.6%					
Test for overall effect z=2.20 p=0.03					



Analysis 01.04. Comparison 01 Supplemental vitamin A vs no supplementation, Outcome 04 Death before 36 weeks PMA

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 01 Supplemental vitamin A vs no supplementation

Outcome: 04 Death before 36 weeks PMA

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Supplementation via intramuscular injection					
Ravishankar 2003	5/22	4/18		5.0	1.02 [0.32, 3.26]
Tyson 1999	59/405	55/402		62.3	1.06 [0.76, 1.50]
Subtotal (95% CI)	427	420		67.3	1.06 [0.77, 1.47]
Total events: 64 (Treatment), 59 (Control)					
Test for heterogeneity chi-square=0.00 df=1 p=0.95 I^2 =0.0%					
Test for overall effect z=0.36 p=0.7					
02 Supplementation via intravenous route					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 Supplementation via oral route					
Wardle 2001	25/77	29/77		32.7	0.86 [0.56, 1.33]
Subtotal (95% CI)	77	77		32.7	0.86 [0.56, 1.33]
Total events: 25 (Treatment), 29 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.67 p=0.5					
Total (95% CI)	504	497		100.0	1.00 [0.77, 1.30]
Total events: 89 (Treatment), 88 (Control)					
Test for heterogeneity chi-square=0.58 df=2 p=0.75 I^2 =0.0%					
Test for overall effect z=0.03 p=1					

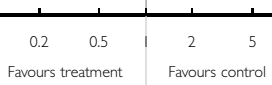
Analysis 01.05. Comparison 01 Supplemental vitamin A vs no supplementation, Outcome 05 Oxygen use at 36 weeks PMA in survivors

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 01 Supplemental vitamin A vs no supplementation

Outcome: 05 Oxygen use at 36 weeks PMA in survivors

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Supplementation via intramuscular injection					
Ravishankar 2003	4/17	5/14		2.3	0.66 [0.22, 2.00]
Tyson 1999	163/346	193/347		81.4	0.85 [0.73, 0.98]
Subtotal (95% CI)	363	361		83.7	0.84 [0.73, 0.97]
Total events: 167 (Treatment), 198 (Control)					
Test for heterogeneity chi-square=0.19 df=1 p=0.66 I^2 =0.0%					
Test for overall effect z=2.33 p=0.02					
02 Supplementation via intravenous route					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 Supplementation via oral route					
Wardle 2001	40/52	37/48		16.3	1.00 [0.81, 1.24]
Subtotal (95% CI)	52	48		16.3	1.00 [0.81, 1.24]
Total events: 40 (Treatment), 37 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.02 p=1					
Total (95% CI)	415	409		100.0	0.87 [0.77, 0.98]
Total events: 207 (Treatment), 235 (Control)					
Test for heterogeneity chi-square=1.98 df=2 p=0.37 I^2 =0.0%					
Test for overall effect z=2.23 p=0.03					



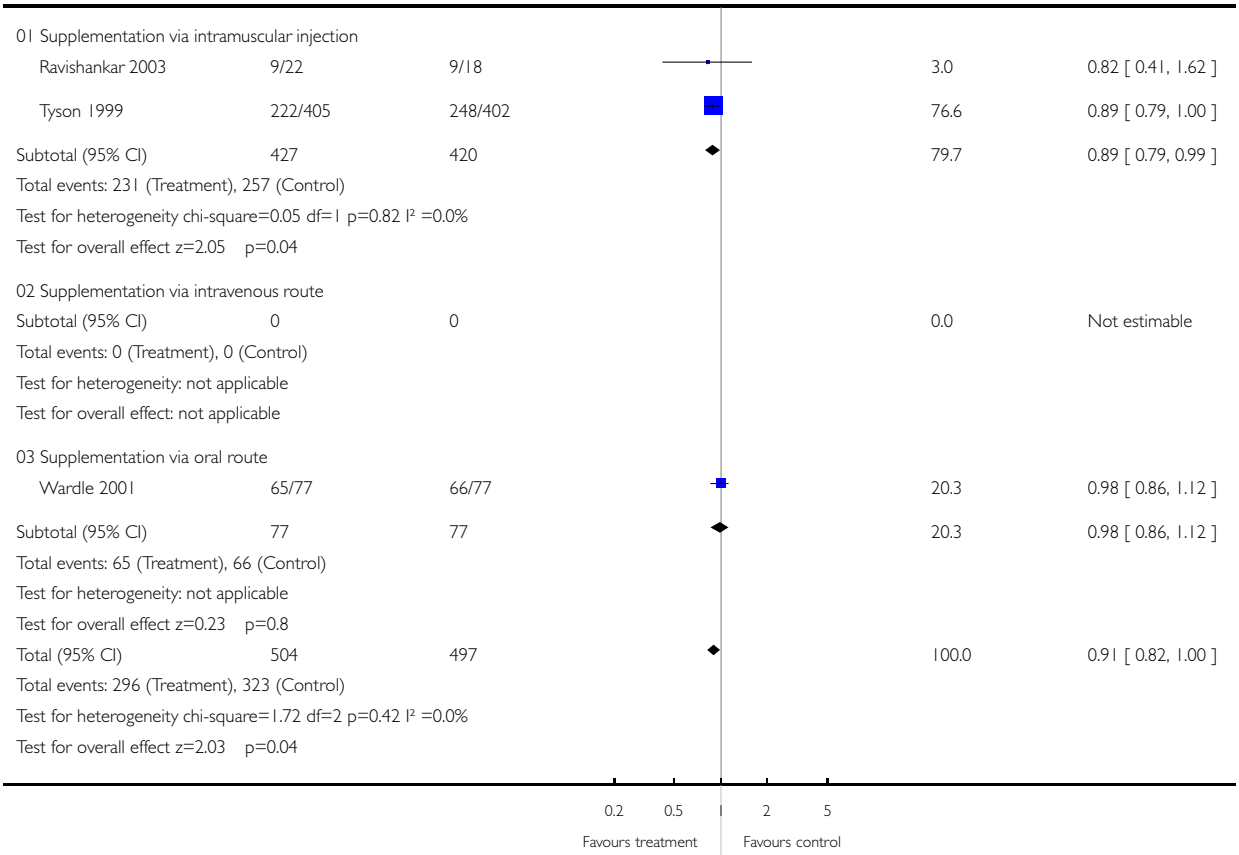
Analysis 01.06. Comparison 01 Supplemental vitamin A vs no supplementation, Outcome 06 Death or oxygen use at 36 weeks PMA

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 01 Supplemental vitamin A vs no supplementation

Outcome: 06 Death or oxygen use at 36 weeks PMA

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Supplementation via intramuscular injection					
Ravishankar 2003	9/22	9/18		3.0	0.82 [0.41, 1.62]
Tyson 1999	222/405	248/402		76.6	0.89 [0.79, 1.00]
Subtotal (95% CI)	427	420		79.7	0.89 [0.79, 0.99]
Total events: 231 (Treatment), 257 (Control)					
Test for heterogeneity chi-square=0.05 df=1 p=0.82 I^2 =0.0%					
Test for overall effect z=2.05 p=0.04					
02 Supplementation via intravenous route					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 Supplementation via oral route					
Wardle 2001	65/77	66/77		20.3	0.98 [0.86, 1.12]
Subtotal (95% CI)	77	77		20.3	0.98 [0.86, 1.12]
Total events: 65 (Treatment), 66 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.23 p=0.8					
Total (95% CI)	504	497		100.0	0.91 [0.82, 1.00]
Total events: 296 (Treatment), 323 (Control)					
Test for heterogeneity chi-square=1.72 df=2 p=0.42 I^2 =0.0%					
Test for overall effect z=2.03 p=0.04					

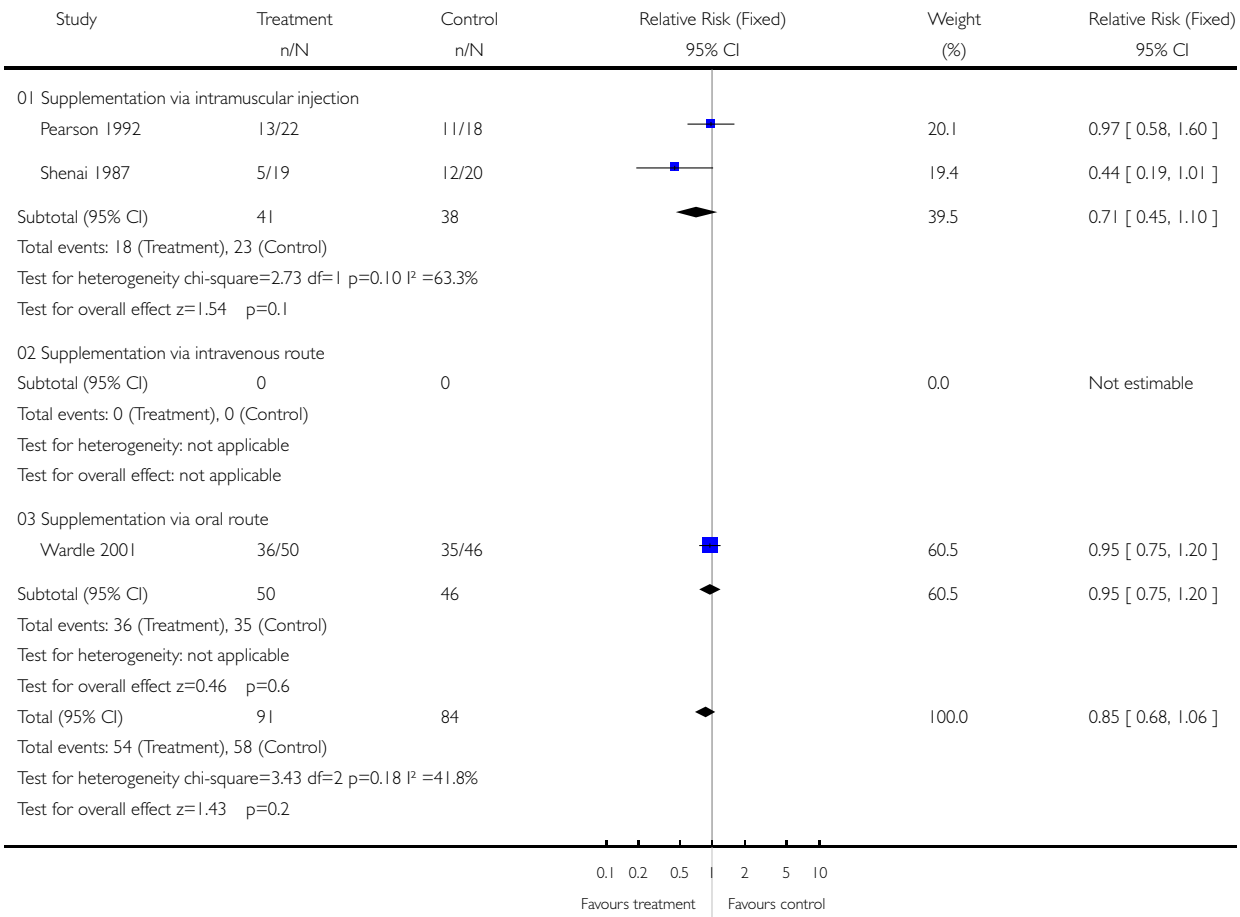


Analysis 01.07. Comparison 01 Supplemental vitamin A vs no supplementation, Outcome 07 Retinopathy of prematurity (any grade)

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 01 Supplemental vitamin A vs no supplementation

Outcome: 07 Retinopathy of prematurity (any grade)

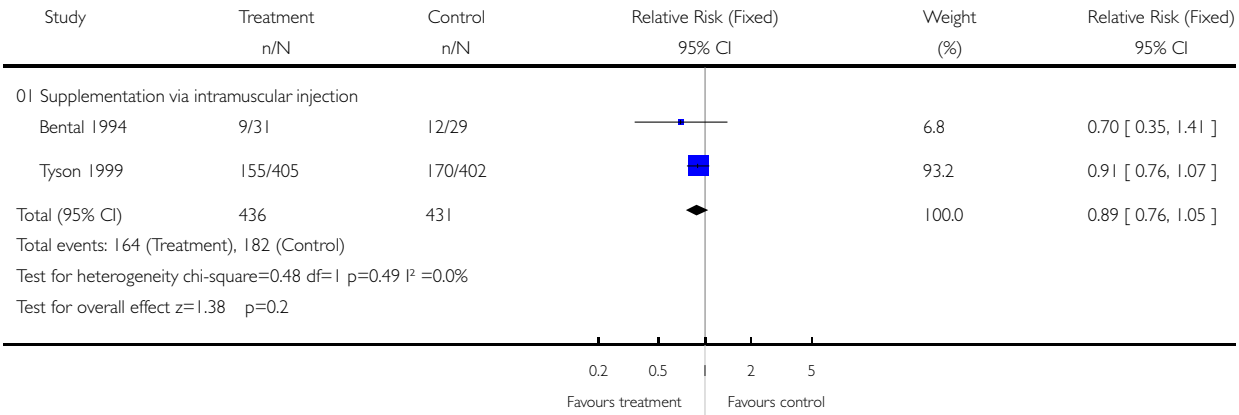


Analysis 01.08. Comparison 01 Supplemental vitamin A vs no supplementation, Outcome 08 One or more episodes of sepsis

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 01 Supplemental vitamin A vs no supplementation

Outcome: 08 One or more episodes of sepsis

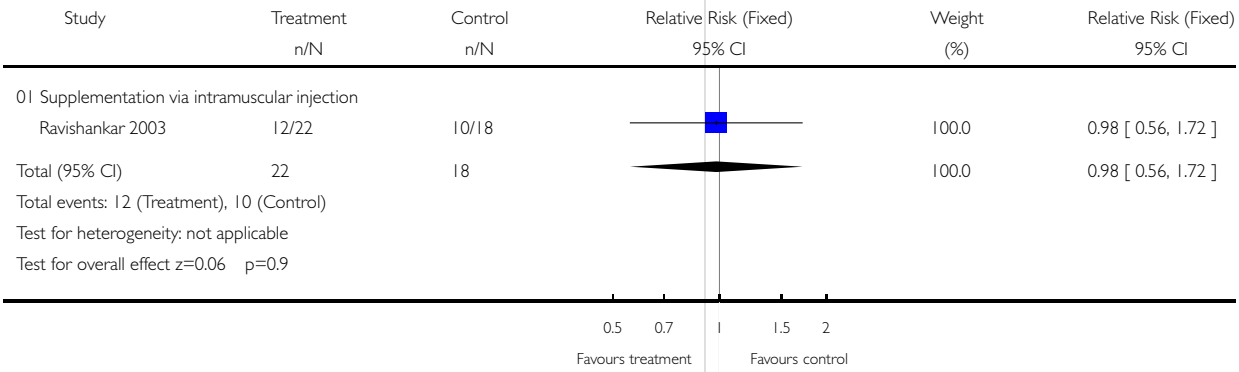


Analysis 01.09. Comparison 01 Supplemental vitamin A vs no supplementation, Outcome 09 Failure of ductal closure or treatment by day 14

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 01 Supplemental vitamin A vs no supplementation

Outcome: 09 Failure of ductal closure or treatment by day 14

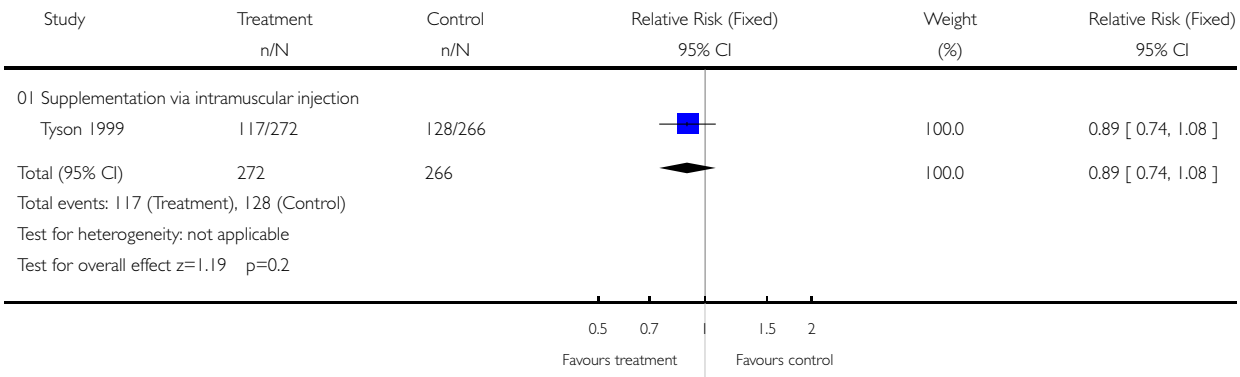


Analysis 01.10. Comparison 01 Supplemental vitamin A vs no supplementation, Outcome 10 Neurodevelopmental impairment at 18 -22 months

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 01 Supplemental vitamin A vs no supplementation

Outcome: 10 Neurodevelopmental impairment at 18 -22 months

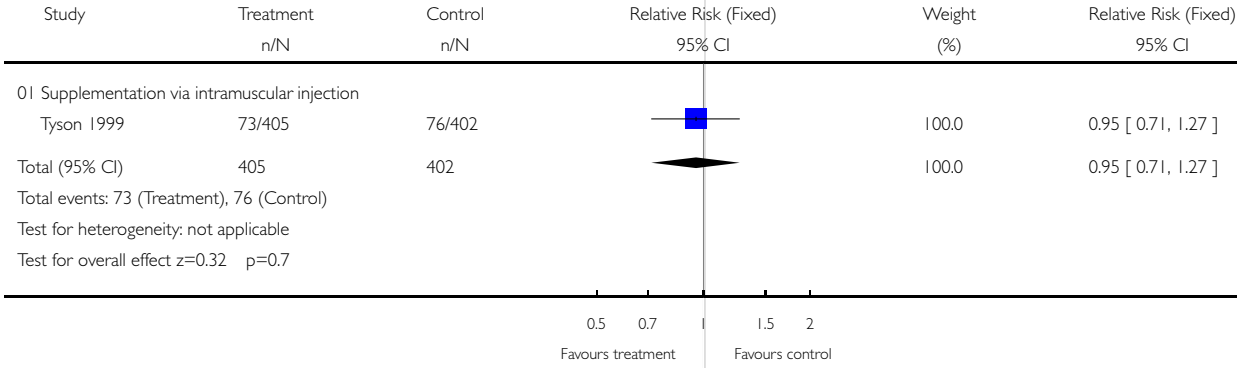


Analysis 01.11. Comparison 01 Supplemental vitamin A vs no supplementation, Outcome 11 Death before 18-22 months

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 01 Supplemental vitamin A vs no supplementation

Outcome: 11 Death before 18-22 months

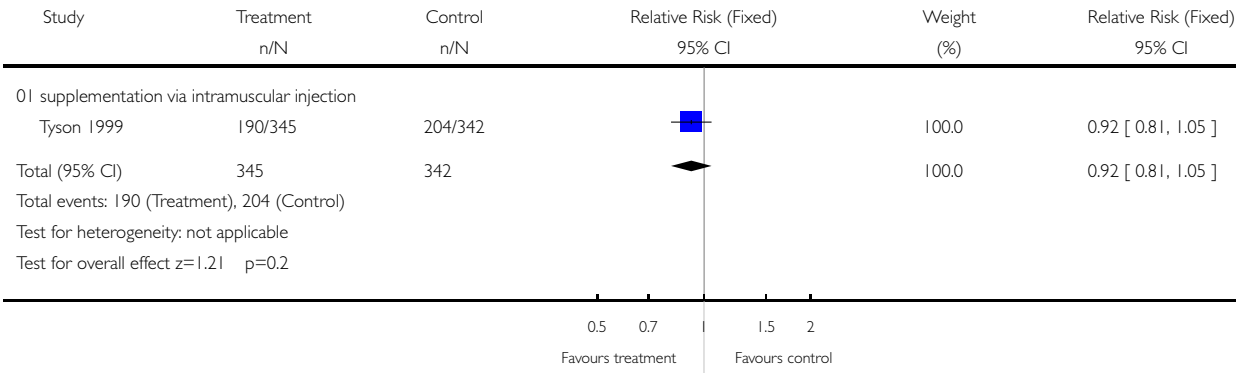


Analysis 01.12. Comparison 01 Supplemental vitamin A vs no supplementation, Outcome 12 Death or neurodevelopmental impairment at 18-22 months

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 01 Supplemental vitamin A vs no supplementation

Outcome: 12 Death or neurodevelopmental impairment at 18-22 months

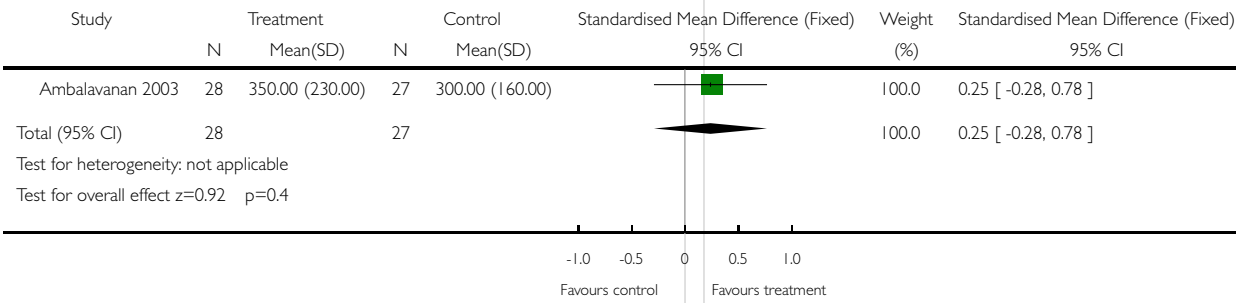


Analysis 02.01. Comparison 02 Higher dose (10,000 IU 3x wk for 4 wks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 wks), Outcome 01 Retinol concentration on study day 28 (micrograms/L)

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 02 Higher dose (10,000 IU 3x wk for 4 wks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 wks)

Outcome: 01 Retinol concentration on study day 28 (micrograms/L)



Analysis 02.02. Comparison 02 Higher dose (10,000 IU 3x wk for 4 wks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 wks), Outcome 02 Retinol <200 micrograms/L on day 28 (%)

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 02 Higher dose (10,000 IU 3x wk for 4 wks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 wks)

Outcome: 02 Retinol <200 micrograms/L on day 28 (%)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ambalavanan 2003	6/28	7/27		100.0	0.83 [0.32, 2.15]
Total (95% CI)	28	27		100.0	0.83 [0.32, 2.15]
Total events: 6 (Treatment), 7 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.39 p=0.7					

Analysis 02.03. Comparison 02 Higher dose (10,000 IU 3x wk for 4 wks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 wks), Outcome 03 Death before 36 weeks PMA

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 02 Higher dose (10,000 IU 3x wk for 4 wks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 wks)

Outcome: 03 Death before 36 weeks PMA

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ambalavanan 2003	8/40	11/40		100.0	0.73 [0.33, 1.62]
Total (95% CI)	40	40		100.0	0.73 [0.33, 1.62]
Total events: 8 (Treatment), 11 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.78 p=0.4					

Analysis 02.04. Comparison 02 Higher dose (10,000 IU 3x wk for 4 wks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 wks), Outcome 04 Oxygen use at 36 weeks PMA in survivors

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 02 Higher dose (10,000 IU 3x wk for 4 wks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 wks)

Outcome: 04 Oxygen use at 36 weeks PMA in survivors

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ambalavanan 2003	9/32	3/29		100.0	2.72 [0.81, 9.08]
Total (95% CI)	32	29		100.0	2.72 [0.81, 9.08]
Total events: 9 (Treatment), 3 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.63 p=0.1					

Analysis 02.05. Comparison 02 Higher dose (10,000 IU 3x wk for 4 wks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 wks), Outcome 05 Death or oxygen use at 36 weeks PMA

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 02 Higher dose (10,000 IU 3x wk for 4 wks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 wks)

Outcome: 05 Death or oxygen use at 36 weeks PMA

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ambalavanan 2003	17/40	14/40		100.0	1.21 [0.70, 2.12]
Total (95% CI)	40	40		100.0	1.21 [0.70, 2.12]
Total events: 17 (Treatment), 14 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.69 p=0.5					

Analysis 02.06. Comparison 02 Higher dose (10,000 IU 3x wk for 4 wks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 wks), Outcome 06 Retinopathy of prematurity (any grade)

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 02 Higher dose (10,000 IU 3x wk for 4 wks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 wks)

Outcome: 06 Retinopathy of prematurity (any grade)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ambalavanan 2003	16/32	21/31		100.0	0.74 [0.48, 1.13]
Total (95% CI)	32	31		100.0	0.74 [0.48, 1.13]
Total events: 16 (Treatment), 21 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.41 p=0.2					

Analysis 02.07. Comparison 02 Higher dose (10,000 IU 3x wk for 4 wks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 wks), Outcome 07 Retinopathy of prematurity (threshold disease)

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 02 Higher dose (10,000 IU 3x wk for 4 wks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 wks)

Outcome: 07 Retinopathy of prematurity (threshold disease)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ambalavanan 2003	0/32	5/31		100.0	0.09 [0.01, 1.53]
Total (95% CI)	32	31		100.0	0.09 [0.01, 1.53]
Total events: 0 (Treatment), 5 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.67 p=0.1					

Analysis 03.01. Comparison 03 Once-a-week (15,000 IU for 4 weeks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 weeks), Outcome 01 Retinol concentration on study day 28 (micrograms/L)

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 03 Once-a-week (15,000 IU for 4 weeks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 weeks)

Outcome: 01 Retinol concentration on study day 28 (micrograms/L)

Study	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Standardised Mean Difference (Fixed) 95% CI	Weight (%)	Standardised Mean Difference (Fixed) 95% CI
Ambalavanan 2003	23	170.00 (90.00)	27	300.00 (160.00)		100.0	-0.97 [-1.56, -0.38]
Total (95% CI)	23		27			100.0	-0.97 [-1.56, -0.38]
Test for heterogeneity: not applicable							
Test for overall effect z=3.21 p=0.001							

Analysis 03.02. Comparison 03 Once-a-week (15,000 IU for 4 weeks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 weeks), Outcome 02 Retinol <200 micrograms/L on day 28 (%)

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 03 Once-a-week (15,000 IU for 4 weeks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 weeks)

Outcome: 02 Retinol <200 micrograms/L on day 28 (%)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ambalavanan 2003	15/23	7/27		100.0	2.52 [1.24, 5.09]
Total (95% CI)	23	27		100.0	2.52 [1.24, 5.09]
Total events: 15 (Treatment), 7 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.57 p=0.01					

Analysis 03.03. Comparison 03 Once-a-week (15,000 IU for 4 weeks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 weeks), Outcome 03 Death before 36 weeks PMA

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 03 Once-a-week (15,000 IU for 4 weeks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 weeks)

Outcome: 03 Death before 36 weeks PMA

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ambalavanan 2003	8/40	11/40		100.0	0.73 [0.33, 1.62]
Total (95% CI)	40	40		100.0	0.73 [0.33, 1.62]
Total events: 8 (Treatment), 11 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.78 p=0.4					

Analysis 03.04. Comparison 03 Once-a-week (15,000 IU for 4 weeks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 weeks), Outcome 04 Oxygen use at 36 weeks PMA in survivors

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 03 Once-a-week (15,000 IU for 4 weeks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 weeks)

Outcome: 04 Oxygen use at 36 weeks PMA in survivors

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ambalavanan 2003	6/32	3/29		100.0	1.81 [0.50, 6.59]
Total (95% CI)	32	29		100.0	1.81 [0.50, 6.59]
Total events: 6 (Treatment), 3 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.90 p=0.4					

Analysis 03.05. Comparison 03 Once-a-week (15,000 IU for 4 weeks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 weeks), Outcome 05 Death or oxygen use at 36 weeks PMA

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 03 Once-a-week (15,000 IU for 4 weeks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 weeks)

Outcome: 05 Death or oxygen use at 36 weeks PMA

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ambalavanan 2003	14/40	14/40		100.0	1.00 [0.55, 1.82]
Total (95% CI)	40	40		100.0	1.00 [0.55, 1.82]
Total events: 14 (Treatment), 14 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.00 p=1					

Analysis 03.06. Comparison 03 Once-a-week (15,000 IU for 4 weeks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 weeks), Outcome 06 Retinopathy of prematurity (any grade)

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 03 Once-a-week (15,000 IU for 4 weeks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 weeks)

Outcome: 06 Retinopathy of prematurity (any grade)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ambalavanan 2003	14/33	21/31		100.0	0.63 [0.39, 1.00]
Total (95% CI)	33	31		100.0	0.63 [0.39, 1.00]
Total events: 14 (Treatment), 21 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.97 p=0.05					

Analysis 03.07. Comparison 03 Once-a-week (15,000 IU for 4 weeks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 weeks), Outcome 07 Retinopathy of prematurity (threshold disease)

Review: Vitamin A supplementation to prevent mortality and short and long-term morbidity in very low birthweight infants

Comparison: 03 Once-a-week (15,000 IU for 4 weeks) i.m. vitamin A supplementation vs Standard (5000 IU 3x wk for 4 weeks)

Outcome: 07 Retinopathy of prematurity (threshold disease)

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ambalavanan 2003	3/33	5/31		100.0	0.56 [0.15, 2.16]
Total (95% CI)	33	31		100.0	0.56 [0.15, 2.16]
Total events: 3 (Treatment), 5 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.84 p=0.4