

ORIGINAL ARTICLES

Randomised controlled trial of oral vitamin A supplementation in preterm infants to prevent chronic lung disease

S P Wardle, A Hughes, S Chen, N J Shaw

Abstract

Background—Intramuscular supplementation with vitamin A in large doses may reduce the incidence of chronic lung disease.

Aim—To investigate whether oral supplementation with vitamin A would reduce the incidence of chronic lung disease in a group of extremely low birthweight infants.

Methods—Infants with birth weight < 1000 g were randomised at birth to receive oral vitamin A supplementation (5000 IU/day) or placebo for 28 days. The primary outcome was oxygen dependency at 28 days of age or death.

Results—A total of 154 infants were randomised; 77 received vitamin A (median birth weight (interquartile range) 806 (710–890) g), and 77 received placebo (median birth weight (interquartile range) 782 (662–880) g). Plasma vitamin A concentrations in the supplemented group were significantly higher at 24 hours of age but did not differ significantly at birth, 12 hours of age, 7 days, or 28 days of life. There were no significant differences in the proportion of infants who survived, required oxygen at 28 days, required oxygen at 36 weeks postmenstrual age, survived without chronic lung disease at 36 weeks, survived without significant retinopathy, or who survived without significant intraventricular haemorrhage.

Conclusions—Oral supplementation with 5000 IU vitamin A in extremely low birthweight infants does not significantly alter the incidence of chronic lung disease. However, this dose may have been inadequate to achieve optimal serum retinol concentrations.

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Keywords: chronic lung disease; lungs; preterm; vitamin A; retinol

Preterm infants have limited hepatic reserves and lower plasma concentrations of vitamin A and plasma retinol binding protein than term infants because vitamin A is transferred across the placenta mainly during the third trimester.¹ In addition, inadequate provision of vitamin A

postnatally is common because of difficulties in establishing enteral feeding. Parenteral administration of vitamin A may be inefficient because of photodegradation and adsorption of the vitamin to the plastic of the intravenous administration set.²

Vitamin A is involved in the regulation of growth and differentiation of many cells and maintains the integrity of the epithelial cells of the respiratory tract.³ It is also necessary for the formation of the photosensitive visual pigment in the retina and development of reproductive functions and immunocompetence, and it may have antioxidant properties.³

Vitamin A deficiency in laboratory animals produces a sequence of histopathological changes in the respiratory tract epithelium including necrotising tracheobronchiolitis and squamous metaplasia, which can be reversed by restoration of adequate vitamin A status. Similar changes are observed in ventilated preterm infants with chronic lung disease (CLD), suggesting that vitamin A deficiency may contribute to this disease.^{1 4 5}

Furthermore there is some evidence that intramuscular supplementation with vitamin A may prevent CLD.^{6–12} There have been no previous controlled trials of oral vitamin A supplementation in preterm infants, probably because absorption at conventional doses has been regarded as insufficient to prevent CLD.¹³ However, with oral vitamin A supplementation at a dose of 5000 IU a day, serum retinol has been shown to increase to concentrations similar to those achieved with intramuscular supplementation.¹⁴ The aim of this study was to determine whether oral supplementation with vitamin A at a dose of 5000 IU a day would reduce the incidence of CLD in extremely low birthweight infants.

Methods

This was a blinded prospective randomised controlled trial. Infants less than 24 hours of age were randomised to receive either a daily dose of vitamin A or the same volume of an inert placebo solution.

PARTICIPANTS

Infants eligible for the study were those with a birth weight less than 1000 g for whom parental consent was obtained for inclusion in the

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study before 24 hours of age. Infants were excluded if they had a major life threatening congenital abnormality.

In the first 84 infants in the trial, blood samples were obtained on a maximum of five occasions for measurement of serum retinol concentrations: at the time of randomisation before the first dose of vitamin A, at 12 hours, 24 hours, 7 days, and 28 days after the first dose. All of these samples were taken from indwelling arterial lines at the time of routine blood sampling. A 0.5 ml sample of blood was collected into amber glass bottles and refrigerated. Serum was obtained by centrifugation and retinol was extracted using hexane after ethanolic precipitation of serum proteins and analysed using high performance liquid chromatography. These results were only made available to one of the authors (NJS) who, to ensure blinding, did not participate in the analysis of the other outcome measures. These data were not used to alter vitamin A supplementation.

All infants in this trial were managed according to unit guidelines which included: conventional ventilation and extubation when weaned from the ventilator directly into headbox oxygen, and administration of two doses of artificial surfactant (ALEC) to ventilated infants (one at birth and one at 12 hours of age). Antenatal steroids were given routinely to all mothers before preterm delivery if possible. Ventilated infants were sedated with morphine, and neuromuscular paralysis with pancuronium was used only in selected cases where it was felt by the clinical staff that the infant was breathing asynchronously with the ventilator. Postnatal steroids were given to infants who were ventilator dependent by 14 days of age and required > 40% oxygen.

All infants received intravenous glucose with added electrolytes during the first 48 hours and, after this, total parenteral nutrition and intravenous lipid (containing vitamin A (Vitlipid; Pharmacia Ltd UK) at a dose of 23 IU/kg) starting on day 3 of life. Enteral feeds were begun as intermittent orogastric gavage feeds when infants were clinically stable and were advanced in all infants as soon as tolerated. Infants were fed either human milk with fortifier or preterm formula. The vitamin A concentration of the preterm formula milk (Osterprem) was 1 µg/ml (3.5 µmol/l). The vitamin A concentration of the breast milk fortifier (Milupa Eoprotin) at the dose used was 0.3 µg/ml (1.05 µmol/l) of breast milk. When infants were on full enteral feeds they were given multivitamin supplements (Mothers' and Children's Vitamin Drops; Cupol Ltd, Blackburn, Lancs, UK) containing 5000 IU/ml vitamin A from the 14th postnatal day.

RANDOMISATION

Infants were randomised using sealed opaque numbered envelopes containing the treatment allocation, which had been assigned using a computerised random number generator. Randomisation was stratified according to birth weight into two groups ≤ 750 g and > 750 g.

INTERVENTIONS

The vitamin A supplementation group received a daily dose of 5000 IU/kg (3000 µg/kg) vitamin A given orally as a bolus through the orogastric tube from postnatal day 1 starting immediately after randomisation until day 28 inclusively. Each dose was flushed through the orogastric tube with a 1 ml bolus of sterile water. The orogastric tube was not aspirated until at least four hours after each dose. The control group received an equivalent volume of an inert placebo solution (which had been prepared in the hospital pharmacy to look identical with the vitamin A solution) given in the same way.

BLINDING

Both the medical and nursing staff caring for the infants and administering the vitamin A and placebo solutions were unaware of the treatment allocation. In addition, the identity of the treatments was not available to the authors until after the data had been analysed. The two solutions were labelled substance Y and substance Z. Both solutions were prescribed in ml/kg.

OUTCOME MEASURES

The primary outcome measure was the requirement for supplementary oxygen at 28 days. Other outcomes documented were death before discharge from the neonatal unit, supplementary oxygen requirement at 36 weeks postmenstrual age, retinopathy of prematurity (ROP) requiring treatment, intraventricular haemorrhage (IVH) with parenchymal involvement, patent ductus arteriosus (PDA) that required the use of indomethacin or surgery, significant necrotising enterocolitis (NEC) that required surgery, and number of episodes of sepsis. In addition, because of the potential for adverse effects, the incidence of the following symptoms was also recorded: persistent vomiting, pulmonary haemorrhage, and seizures requiring anticonvulsants.

SAMPLE SIZE

The combined incidence of CLD or death before 28 days in infants less than 1000 g at Liverpool Women's Hospital before the study was 90% and the incidence of CLD in 28 day survivors was 83%. It was calculated that to reduce the incidence of CLD/death to 70% and to reduce the incidence of CLD in survivors to 50%, 158 infants would need to be included (power 80%, significance 5%).

STATISTICAL ANALYSIS

All the data were analysed on an intention to treat basis using SPSS (version 4.0). Groups were compared using the Mann-Whitney U test for non-parametric data, Student's *t* tests for parametric data, and the χ^2 test for categorical data.

ETHICS

The study was approved by the local research ethics committee, and written informed parental consent was obtained after birth and before randomisation of infants into the trial.

Table 1 Baseline characteristics of preterm infants receiving either oral vitamin A supplementation or placebo

	Vitamin A n=77	Placebo n=77
Median (IQR) gestational age (weeks)	26 (25–27)	26 (25–27)
Median (IQR) birth weight (g)	806 (710–890)	782 (662–880)
Male	37 (48%)	30 (39%)
< 750 g	29 (38%)	33 (43%)
Antenatal steroids	59 (77%)	63 (82%)
Surfactant	77 (100%)	76 (99%)
Mean (range) time receiving TPN (days)	20 (12–30)	20 (15–27)

IQR, interquartile range; TPN, total parenteral nutrition.

Table 2 Results for primary outcome measures in preterm infants receiving either oral vitamin A supplementation or placebo

	Vitamin A (n=77)	Placebo (n=77)	RR (95% CI)	p Value
Survived	52 (68%)	48 (62%)	1.12 (0.81 to 1.61)	0.50
CLD at 28 days in survivors	43 (83%)	42 (88%)	0.84 (0.57 to 1.46)	0.86
Survived without CLD at 28 days	9 (12%)	6 (8%)	1.23 (0.71 to 1.75)	0.41
CLD at 36 weeks in survivors	40 (77%)	37 (77%)	1.0 (0.67 to 1.64)	0.98
Survived without CLD at 36 weeks	12 (16%)	11 (14%)	1.05 (0.65 to 1.52)	0.82
Median (IQR) time ventilated (days)	14 (4–24)	15 (7–33)	—	0.21
Pulmonary haemorrhage	5 (6%)	11 (14%)	0.60 (0.27 to 1.10)	0.13
Pneumothorax	11 (14%)	17 (22%)	0.75 (0.44 to 1.15)	0.24
Treatment for retinopathy	6 (8%)	6 (8%)	1.0 (0.50 to 1.58)	0.98
Survived without significant retinopathy	45 (57%)	45 (53%)	1.02 (0.74 to 1.44)	0.92
PDA	17 (22%)	16 (21%)	1.12 (0.74 to 1.59)	0.84
NEC	9 (12%)	7 (9%)	1.14 (0.66 to 1.66)	0.58
Survived without significant IVH	48 (62%)	41 (54%)	1.19 (0.86 to 1.68)	0.29
Median (IQR) number of sepsis episodes	1 (0–2)	1 (0–2)	—	0.89
Vomiting	1 (1%)	5 (6%)	0.32 (0.06 to 1.11)	0.10
Seizures	15 (19%)	20 (26%)	0.82 (0.52 to 1.20)	0.38

CLD, chronic lung disease; IQR, interquartile range; PDA, patent ductus arteriosus; NEC, necrotising enterocolitis; IVH, intraventricular haemorrhage.

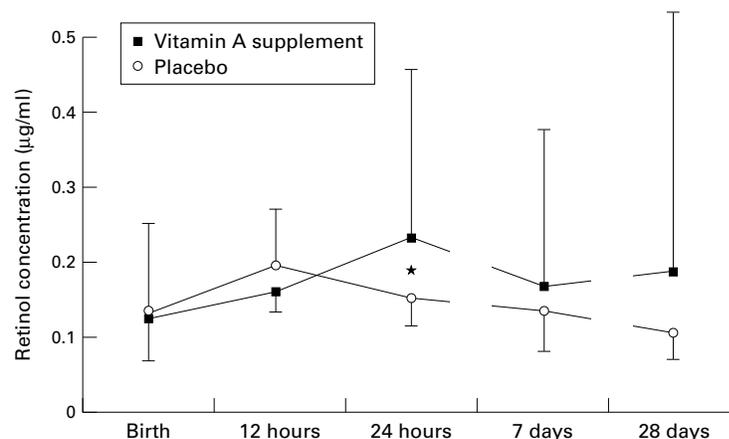


Figure 1 Median plasma retinol concentrations in the vitamin A supplemented group and the placebo group. The error bars represent the interquartile range. The x axis refers to the time after the first dose of vitamin A. *Significantly different, $p = 0.015$.

Results

The study was carried out between January 1994 and September 1997. During this period there were 312 eligible infants treated at the participating hospitals. Of these, 154 (49%) infants were randomised. The reasons for non-enrollment were parental refusal, parental consent not obtained before 24 hours of age, death before 24 hours of age, and transfer from another hospital after 24 hours of age. There were 77 infants in the vitamin A group and 77 infants in the control group. In the vitamin A group, 29 (38%) weighed < 750 g and in the control group 34 (43%) weighed < 750 g. The baseline characteristics of the two groups were similar (table 1). All the infants except one in

the control group were ventilated at birth and all received surfactant as soon after birth as possible. The infants in the vitamin A group received a median (range) of 28 (1–28) doses, which was 93% of the doses intended. Most of the missed doses were because infants were nil by mouth because of possible NEC.

OUTCOMES

Table 2 summarises the results for the primary outcome measures. There was no significant difference in either mortality or the incidence of CLD at 28 days or 36 weeks. In addition, there was no significant difference in other respiratory complications, and infants in both groups were ventilated for a similar period (table 2).

The two groups had a similar incidence of ROP, PDA, and NEC, and a similar proportion survived without significant IVH (table 2). There was no difference in the incidence of sepsis in the two groups (table 2). Of the infants in the vitamin A group, 39% received postnatal steroids compared with 26% in the control group.

SERUM RETINOL CONCENTRATIONS

Figure 1 shows changes in serum retinol concentrations in the subgroup of infants who had these measurements made ($n = 84$). Of these infants, 91% in the vitamin A group and 87% in the control group received antenatal steroids, and 21% in the vitamin A group received postnatal steroids compared with 26% in the control group. The median plasma vitamin A concentration (interquartile range (IQR)) at birth in the control group was 0.13 (0.08–0.22) µg/ml, which was similar to that in the vitamin A supplemented group (0.13 (0.08–0.26) µg/ml ($p = 0.60$)). At 24 hours after the first dose of vitamin A, the concentration in the control group was significantly lower (0.15 (0.11–0.20) *v* 0.23 (0.16–0.55) µg/ml, $p = 0.015$), but the concentrations of vitamin A were not significantly different at 7 days of age ($p = 0.17$) or 28 days of age ($p = 0.54$). The proportion of infants in the treatment group with retinol concentrations < 0.2 µg/ml (< 0.7 µmol/l) were 39%, 52%, and 50% at 24 hours after the first dose, 7 days, and 28 days respectively. The proportion with retinol concentrations < 0.1 µg/ml (< 0.35 µmol/l) in the treatment group were 13%, 26%, and 29% at 24 hours after the first dose, 7 days, and 28 days respectively. In the control group, the proportion with retinol concentrations < 0.2 µg/ml (< 0.7 µmol/l) was 64% at each of 24 hours after the first dose, 7 days, and 28 days.

In the subgroup of infants who had retinol concentrations measured, the median retinol concentration (IQR) at 28 days in those with CLD at 36 weeks was 0.11 (0.06–0.24) µg/ml compared with 0.21 (0.16–0.32) µg/ml in those without ($p = 0.12$). The median retinol concentration (IQR) in those with significant retinopathy at 28 days was 0.2 (0.08–0.63) µg/ml compared with 0.16 (0.06–0.29) µg/ml in those without ($p = 0.46$).

ADVERSE EFFECTS

The incidence of possible adverse events did not differ between the two groups. In particular, there was a similar incidence of seizures and vomiting (table 2).

Discussion

This blinded randomised trial has shown that oral supplementation of vitamin A in a dose of 5000 IU/day did result in an increase in plasma retinol concentrations but did not decrease the incidence of CLD in preterm infants of less than 1000 g birth weight. In addition, mortality and the incidence of other complications such as ROP, IVH, NEC, and PDA were unaffected by vitamin A supplementation. The results of this study of oral supplementation are in contrast with previous studies, which used intramuscular supplementation of vitamin A and showed a significant decrease in the incidence of oxygen dependency at 1 month of age and/or death.⁶⁻¹² Although most of these studies were performed before the routine use of antenatal steroids and postnatal surfactant, the most recent study was performed after the introduction of these important interventions, which may influence the incidence of CLD.⁶ This study is the first randomised controlled trial of oral vitamin A supplementation, and it has been performed in a population who received antenatal steroids and postnatal surfactant.

There are several possible explanations for the failure of this study to produce similar results. Firstly, the serum retinol concentrations achieved may have been insufficient. The optimal concentration of serum retinol in very low birthweight infants is not known, although it has been suggested that concentrations below 0.2 µg/ml (0.70 µmol/l) represent deficiency and concentrations below 0.1 µg/ml (0.35 µmol/l) indicate severe deficiency and depleted liver stores.¹⁵ Plasma retinol concentrations must, however, be interpreted with caution as they do not necessarily reflect hepatic stores particularly in the preterm.¹⁶ Although the measured plasma retinol concentrations were higher in the supplemented group 24 hours after the first dose, further measurements at 7 days and 28 days were not significantly different. There are several possible reasons for this. Firstly, it may be because retinol concentrations were not measured in all infants in the study or multivitamin supplements were begun in both groups after 14 days of age. Also many of the infants in both groups received postnatal steroids, which are known to influence retinol concentrations.¹⁸ Despite these factors, 50% of the vitamin A treated infants in whom retinol concentrations were measured had concentrations less than 0.2 µg/ml at 28 days of age.

The oral supplementation regimen used for this study was based on that described by Landman *et al*,¹⁴ who showed that 5000 IU/day given orally produced plasma concentrations of retinol and retinol binding protein that were similar to those in infants given 2000 IU on alternate days by intramuscular injection. In the study by Landman *et al*, orally supplemented infants had mean (SD) retinol concen-

trations of 0.25 (0.08) µg/ml (0.87 (0.27) µmol/l) on day 32 of life compared with 0.26 (0.13) µg/ml (0.92 (0.44) µmol/l) in the group supplemented intramuscularly. This contrasts with the vitamin A treated group in our study, who had a median retinol concentration (IQR) on day 28 of only 0.19 (0.07-0.54) µg/ml.

A second possibility for the failure to show a difference in CLD in the two groups may be related to the sample size. We aimed to show a reduction in the incidence of oxygen dependency at 28 days or death from 90% to 70%. The actual incidence in the control group in this study was 92% and in the treatment group 88% (this small difference being related to slightly fewer deaths in the supplemented group rather than to a difference in the incidence of CLD in survivors). A clinically significant effect is unlikely to have been shown even with a larger sample size.

A recently updated Cochrane Database meta-analysis summarised the studies that have attempted to use vitamin A supplementation to prevent CLD.⁷ In five of the six studies included, supplementary vitamin A (water soluble retinyl palmitate) was given by intramuscular injection from soon after birth, usually day 4 to 31,^{6 8-11} and, in the other study, retinyl palmitate in lipid emulsion was given intravenously as part of the total parenteral nutrition regimen.¹² The study by Tyson *et al*, the most recent intramuscular supplementation study, was the largest.⁶ Unlike the other studies, it included infants who had received antenatal steroids and postnatal surfactant, and its results are therefore relevant to current practice. It showed a significant reduction in the incidence of CLD at 36 weeks postmenstrual age when 5000 IU vitamin A was given intramuscularly three times a week. The incidence of death or CLD at 36 weeks postmenstrual age was 55% in the vitamin A group and 62% in the control group (RR (95% confidence interval) 0.89 (0.80 to 0.99); $p = 0.03$), with no difference in deaths between the groups (17% *v* 16% (RR (95% confidence interval) 1.01 (0.74 to 1.38); $p = 0.96$). The number needed to treat to prevent one case of CLD is 14 or 15. The main disadvantage of the intervention is that vitamin A was given intramuscularly three times a week. The incidence of side effects appeared to be low, but the intervention is relatively invasive (intramuscular injections) and the benefit relatively small.

The authors of the meta-analysis concluded that supplementation with vitamin A was associated with a reduction in the incidence of oxygen requirement at 36 weeks postmenstrual age and a trend towards reduction in death or oxygen use at 28 days. However, they also comment that whether clinicians decide to repeat intramuscular doses of vitamin A depends on the incidence of CLD in their unit balanced against the lack of other proven benefits and the acceptability of treatment.⁷ This risk/benefit decision may explain why the use of vitamin A supplementation to prevent CLD is not widespread. An alternative method of administration of vitamin A (by the oral route)

would therefore be appealing. A recent editorial by Shenai¹⁷ recommended that supplemental vitamin A should be given by intramuscular injection until establishment of full enteral feeds and that vitamin A should then be given by orogastric administration at a dose of 4000 IU/kg/day. This regimen has been suggested in order to increase the acceptability of vitamin A supplementation. However, as this study has shown, supplementation with oral vitamin A failed to produce any significant clinical improvements. We therefore feel that supplementation in this way cannot be recommended to prevent CLD.

This study did not show a difference in ROP in the supplemented group. There was also no relation between retinol concentrations and the risk of developing ROP. Although many studies have looked at the relation between CLD and vitamin A in the preterm baby, little attention has been given to ROP. One observational study reported that a fall in retinol levels was associated with an increased risk of ROP when several other factors were controlled but, as in our study, there was no direct relation between retinol concentration and ROP.¹⁸ Of the five studies included in the Cochrane meta-analysis, two reported retinopathy outcomes.^{10–11} Meta-analysis of these two studies supports a trend towards a reduction in the incidence of ROP in vitamin A supplemented infants.⁷ None of the trials, however, have included ROP as a primary outcome measure and it is therefore possible that they were underpowered to show a difference in this outcome. This requires further study.

Vitamin A is potentially toxic, and raised intracranial pressure and vomiting have been described in infants receiving large doses.¹⁹ In children and adults, symptoms of chronic hypervitaminosis A may include bone and joint pain, mucocutaneous lesions, and hepatic dysfunction, but these problems have not been recognised in preterm infants. Preterm infants may be at increased risk of toxicity, however, because of undernutrition, reduced peroxidative protection, and liver disease.¹⁹ No increased incidence of adverse effects was noted in the infants in this trial and indeed in any of the trials of intramuscular supplementation.^{6–12}

In conclusion, although previous trials have shown a difference in the incidence of CLD and a trend towards less ROP with intramuscular vitamin A supplementation, this has not yet been accepted as routine practice, probably

because of the relatively modest benefit and the invasiveness of the intervention. Our trial of oral vitamin A supplementation has failed to show a difference in the incidence of CLD, and oral supplementation at the doses used in this study therefore does not seem to be a viable alternative to intramuscular supplementation. Further study of higher dose oral supplementation or supplementation using the intravenous route may be useful.

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