Pneumonia e Vitamina A

Vitamin A for non-measles pneumonia in children

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Abstract

Background
Acute respiratory infections, mostly in the form of pneumonia, are the leading cause of death in children under five years of age in low income countries. Some clinical trials have demonstrated that vitamin A supplementation reduces the severity of respiratory infections and mortality in children with measles.

Objective
To determine whether adjunctive vitamin A is effective in children diagnosed with non-measles pneumonia.

Search strategy
We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2007, Issue 3); MEDLINE (1996 to August Week 2, 2007); EMBASE (1990 to January 2007); LILACS (6 May 2007); CINAHL (1990 to August 2007); Biological Abstracts (1990 to July 2007); and the Chinese Biomedicine Database (1994 to June 2007).

Selection criteria
Only parallel-arm, randomised and quasi-randomised controlled trials (RCTs), in which children (younger than 15 years old) with non-measles pneumonia were treated with adjunctive vitamin A, were included.

Data collection and analysis
Two review authors independently extracted data and assessed trial quality. Study authors were contacted for additional information.

Main results
Six trials involving 1740 children were included. There was no significant reduction in mortality associated with pneumonia in children treated with vitamin A compared to those who were not (pooled odds ratio (OR) 1.29; 95% confidence interval (CI) 0.62 to 2.69). Also, there was no statistically significant difference in duration of hospital stay (mean difference (MD) 0.08; 95% CI -0.43 to 0.59).

Vitamin A was associated with a 39% reduction in antibiotic first line failure (OR 0.65; 95% CI 0.42 to 1.01). Disease severity after supplementary high-dose vitamin A was significantly worse compared with placebo. However, low-dose vitamin A significantly reduced the recurrence rate of bronchopneumonia (OR 0.12; 95% CI 0.03 to 0.46). Moderate vitamin A significantly reduced the time to remission of signs in children with normal serum retinol (> 200 ug/L).

Reviewers' conclusions
The evidence does not suggest a significant reduction in mortality, measures of morbidity, nor an effect on the clinical course of pneumonia with vitamin A adjunctive treatment in children with non-measles pneumonia. However, not all studies measured all outcomes, limiting the number of studies that could be incorporated into the meta-analyses, so that there may have been a lack of statistical power to detect statistically significant differences.

Synopsis

Acute respiratory infections, mostly in the form of pneumonia, are the leading cause of death in children under five years of age living in low income countries. Vitamin A supplementation has been found to reduce mortality and the severity of respiratory infections in children with measles. This review was undertaken to assess the effectiveness of vitamin A adjunctive treatment in children with non-measles pneumonia. However, not all studies measured all outcomes, limiting the number of studies that could be incorporated into the meta-analyses, so that there may have been a lack of statistical power to detect statistically significant differences.

Background

Acute respiratory tract infections (ARIs) and vitamin A deficiency are important public health problems in many low income countries. Vitamin A deficiency is associated with impaired humoral and cellular immune function, keratinisation of the respiratory epithelium and decreased mucus secretion, which weaken barriers to infection (Ross 1996). In low income countries, ARIs, mostly in the form of pneumonia, are the leading cause of death in children under five years of age. The incidence of clinical pneumonia in low income countries is estimated at 0.29 episodes per child per year. This equates to an annual incidence of 150.7 million new cases, 11 to 20 million (7% to 13%) of which are severe enough to require hospital admission. No comparable data are available for high income countries. However, from large population-based studies, the incidence of community-acquired pneumonia among children less than five years of age is approximately 0.026 episodes per child per year (Rundan 2004). Pneumonia is associated with and causes about 3.8 million childhood deaths annually; 30.3% of these are in children under the age of five (Kirkwood 1995).

Community-based clinical trials have been conducted in order to determine whether periodic high-dose vitamin A supplementation reduces the incidence, severity or both of acute respiratory infections in children. The association between vitamin A deficiency and child mortality was first observed in the 1930s when vitamin A supplementation significantly reduced mortality among measles patients (Ellison 1932). Two meta-analyses (Fawzi 1993; Glasziou 1993) examined the relationship between vitamin A supplementation and infectious diseases. Glasziou (Glasziou 1993) reported that vitamin A reduced all-cause mortality by one third in children in low income countries. However, the reduction in deaths from respiratory disease was seen only in the measles studies. Fawzi (Fawzi 1993) also reported that supplementation was protective against overall mortality in community-based studies (odds ratio (OR) 0.70) and highly protective against mortality in hospitalised patients with measles (OR 0.39).

From the current evidence it appears that vitamin A supplementation reduces the severity of respiratory infection and other systemic complications of measles. However, the association between vitamin A and non-measles ARIs is unclear. The World Health Organization (WHO) Programme for the Control of Acute Respiratory Infections published a meta-analysis to assess the impact of supplementation on pneumonia morbidity and mortality (VAPWG 1995). They reported no consistent overall protective or detrimental effect on pneumonia-specific mortality and no effect on the incidence or the prevalence of pneumonia.

Hospital-based clinical trials examining the effectiveness of high-dose vitamin A, administered during an acute episode of non-measles
ARI, in reducing morbidity or mortality, have been performed. However, no meta-analyses have been carried out. Given the apparent effectiveness of vitamin A in reducing mortality in hospitalised patients with measles, and the inexpensiveness of the intervention, clarification of the association between vitamin A and non-measles ARIs is of some importance.

Results

Discussion

Vitamin A supplementation appears to have had little effect on the clinical course of non-measles pneumonia in children. The lack of a clear beneficial effect after vitamin A treatment is a little surprising given the protective effects of vitamin A in pneumonia associated with measles.

Headaches, loss of appetite, vomiting and bulging fontanelles in infants are some of the adverse effects known to occasionally occur with the administration of high doses of vitamin A. These symptoms are minor and transitory, with no known long-term effects, and require no special treatment (Huimin 2005). From three included studies in this review (Fawzi 1998; Nacul 1999; Stephensen 1998), the incidence of toxicity as an adverse event was not statistically different between the vitamin A and placebo-treated groups.

There was a borderline relative increase in the placebo group of children who failed to respond satisfactorily to first line antibiotic treatment. However, only one study reported on this and whether it represents a consistent effect of vitamin A or is the result of chance, needs further investigation.

Rodríguez (Rodríguez 2005) conducted a subgroup analysis according to the serum retinol concentration, and found vitamin A can shorten the duration of signs in children with normal serum retinol (> 200 ug/L) but no benefit in children with vitamin A deficiency. However, this trial did not report on the nutritional status and severity of illness, which may be confounding factors. This study also found the time to remission of respiratory signs did not differ significantly between the groups of normal weight children and those of underweight children. However, data regarding this issue was unavailable to review.

Supplemental vitamin A in a lower dose seems to result in a beneficial effect on recurrent bronchopneumonia. This finding was from one study of poor methodological quality and lacking nutritional information about the vitamin A status of included children (Zhang 1999). More well-designed, large randomised controlled trials are needed to support this positive finding.

Fawzi (Fawzi 1998) observed a trend towards a higher incidence of death in the vitamin A group (13 of 346 participants versus 8 of 341 in the placebo group) although this was not statistically significant (OR 1.63; 95% CI 0.66 to 3.97). Stephensen (Stephensen 1998) reported more severe clinical scores in children receiving vitamin A than those who received a placebo. We expect that studies in the future will provide more conclusive evidence.

The possible explanation for the lack of benefit of vitamin A in non-measles pneumonia is that the effects of vitamin A may be disease-specific, with vitamin A only being effective when pneumonia is complicated with measles.

The benefit of vitamin A as an adjunct to the treatment of non-measles pneumonia was not clarified, but vitamin A might be beneficial to children with high basal serum retinol. Further randomised controlled trials, possibly with measured vitamin A levels and varying vitamin A doses, may provide sufficient evidence to clarify the role of vitamin A in non-measles pneumonia.

Reviewers’ conclusions

Implications for practice

From the evidence available at this time and given the lack of clinical benefit associated with vitamin A treatment in children with non-measles pneumonia, it is difficult to recommend vitamin A as an adjunctive therapy in this patient group, particularly if the risk of vitamin A deficiency is low.

Implications for research

Even though six studies met the inclusion criteria, the variability in the outcomes reported and measured meant that only results from a few studies were eligible for inclusion in the meta-analyses for each of the outcomes. This limited the power of the meta-analyses to detect statistically significant differences. Large randomised controlled trials reporting clinically important outcomes are needed to increase the likelihood of obtaining a true and precise estimate of the effect of vitamin A. However, designing a trial of vitamin A could also be important and randomised controlled trials with a risk-stratified population, that is children at high risk and low risk of vitamin A deficiency, and varying administered dosage may provide evidence of the effectiveness of vitamin A treatment for non-measles pneumonia in children.

References to studies included in this review

Fawzi 1998 (published data only)


Liu 1997 (published data only)


Nacul 1999 (published data only)


Rodriguez 2005 (published data only)


Stephensen 1998 (published data only)


Zhang 1999 (published data only)


Anonymous 1991 (published data only)


Barreto 1994 (published data only)


Basu 2003 (published data only)


Bhandari 1997 (published data only)


Ghana VAST team 1993 {published data only} Vitamin A supplementation in northern Ghana: effects on clinic attendances, hospital admissions, and child mortality. Lancet 1993;342:7-12.


Li 2004 {published data only} Li Y. Observation for vitamin A as a complementary agent in the treatment of new born baby with pneumonia. Central Plains Medical
Jounal 2004;31:40-1.

Lie 1993 {published data only}

Lin 1999 {published data only}

Liu 2002 {published data only}

Lloyd 1991 {published data only}

Long 2006 {published data only}

Long 2007 {published data only}

Ma 2006 {published data only}

Mahalanabis 2001 {published data only}

Qin 1999 {published data only}

Quinlan 1998 {published data only}

Rahman 2001 {published data only}

Rahmatullah 1991 {published data only}

Ramakrishnan 1998 {published data only}

Roy 1997 {published data only}

Ruz 1995 {published data only}

Semba 1993 {published data only}
Semba RD, Graham NM, Caiaffa WT, Margolick JB, Clement L, Vahov D. Increased mortality associated with vitamin A deficiency during human immunodeficiency virus type 1 infection. Archives of Internal Medicine 1993;153:2149-54.

Semba 1995 {published data only}

Semba 1999 {published data only}

Sempertegui 1999 {published data only}

Shah 1994 {published data only}

Si 1997 {published data only}

Stansfield 1993 {published data only}

Stephensen 2002 {published data only}

Tomkins 2000 {published data only}

Velasquez 1995 {published data only}

Vijayaraghavan 1990 {published data only}

Villarmo 2000a {published data only}

Villarmo 2000b {published data only}
Wang 2003a (published data only)

Wang 2003b (published data only)

West 1991 (published data only)

Willumsen 1997 (published data only)

Winkler 2005 (published data only)

Wu 2000 (published data only)

Yang 2002 (published data only)

Ying 1998 (published data only)

Zhen 2003 (published data only)

Additional references

Alderson 2005

Boissel 1989

Cochran 1954

Dickersin 1994

Ellison 1932

Fawzi 1993

Fleiss 1986

Glasziou 1993

Huiming 2005

Juni 2001

Kirkwood 1995

Ross 1996

Rundan 2004

Schulz 1995

VAPWG 1995

Graphs

To view a graph or table, click on the outcome title of the summary table below.

## Vitamin A versus control

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mortality during hospitalisation</td>
<td>3</td>
<td>1446</td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>1.29 [0.62, 2.69]</td>
</tr>
<tr>
<td>Time with signs of pneumonia and treatment issues (continuous)</td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>Subtotals only</td>
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<td>---------------------------------------------------------------</td>
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<tr>
<td><strong>2.1 Time with fever</strong></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-1.11 [-5.66, 3.44]</td>
<td></td>
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</tr>
<tr>
<td><strong>2.2 Time with rapid respiratory rate, &gt; 40 breaths/min/day</strong></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.03 [-0.32, 0.38]</td>
<td></td>
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</tr>
<tr>
<td><strong>2.3 Time with hypoxia, PO2 &lt; 95% per day</strong></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.07 [-0.21, 0.34]</td>
<td></td>
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<tr>
<td><strong>2.4 Length of hospitalisation (days)</strong></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.08 [-0.43, 0.59]</td>
<td></td>
<td></td>
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<tr>
<td><strong>2.5 Time with positive findings on auscultation</strong></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-0.54 [-1.14, 0.05]</td>
<td></td>
<td></td>
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<tr>
<td><strong>2.6 Time with cough</strong></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-2.01 [-3.51, -0.49]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2.7 Time with positive findings at x-ray</strong></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>0.90 [-1.10, 2.90]</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Time with signs of pneumonia and treatment issues (dichotomous)</th>
<th>Odds Ratio (M-H, Fixed, 95% CI)</th>
<th>Subtotals only</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3.1 Short-term effects: slight improvement</strong></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.06 [0.01, 0.30]</td>
</tr>
<tr>
<td><strong>3.2 Long-term effects: no improvement (number of recurrences)</strong></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.12 [0.03, 0.46]</td>
</tr>
<tr>
<td><strong>3.3 Change of antibiotic required</strong></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.65 [0.42, 1.01]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Odds Ratio (M-H, Fixed, 95% CI)</th>
<th>Subtotals only</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4.1 Vomiting</strong></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.77 [0.45, 1.33]</td>
</tr>
<tr>
<td><strong>4.2 Diarrhoea</strong></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.57 [0.31, 1.05]</td>
</tr>
<tr>
<td><strong>4.3 Bulging fontanelles</strong></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>8.25 [0.44, 155.37]</td>
</tr>
<tr>
<td><strong>4.4 Irritability</strong></td>
<td>Odds Ratio (M-H, Fixed, 95% CI)</td>
<td>0.93 [0.56, 1.57]</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Time with fever, tachypnoea and hypoxaemia of pneumonia (serum retinol &gt; 200 ug/L)</th>
<th>Mean Difference (IV, Fixed, 95% CI)</th>
<th>Subtotals only</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5.1</strong></td>
<td>Mean Difference (IV, Fixed, 95% CI)</td>
<td>-61.40 [-119.10, -3.70]</td>
</tr>
</tbody>
</table>