Vitamin E supplementation for prevention of morbidity and mortality in preterm infants

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Vitamin E supplementation, particularly in doses that exceed the recommended daily intake, reduces the risk of intraventricular haemorrhage, but increases the incidence of sepsis in preterm neonates. Hence, the present evidence does not support the practice of high-dose vitamin E supplementation, especially intravenously, in preterm and low-birth-weight infants.

RHL Commentary by Sankar MJ and Sankar J

1. INTRODUCTION

Vitamin E, comprising eight biologically active tocopherols, is an important antioxidant for the health and wellbeing of premature neonates. It helps in scavenging free radicals, thereby reducing the risk of lipid peroxidation and oxidant injury in preterm infants (1). However, to achieve these effects, higher serum levels of tocopherols are needed than those reached through routinely recommended oral doses of vitamin E (2). This underlined the need to evaluate higher doses of vitamin E supplementation to eliminate or reduce the risk of conditions such as retinopathy of prematurity (ROP). Randomized controlled trials evaluating the efficacy of such high-dose supplementation have not been uniformly encouraging (3). On the other hand, there have been reports of serious toxicity following megavitamin E supplements in preterm infants (4). The primary objective of this Cochrane review was to evaluate the spectrum of benefits and risks of vitamin E supplementation in preterm infants (5).

2. METHODS OF THE REVIEW

Trials that randomized preterm infants or those with a birth weight <2500 g to supplementation with vitamin E (intervention) or placebo/no treatment were eligible for inclusion in the review. Studies were included regardless of the vitamin E content of the infant’s feedings (human or formula milk) or the route of vitamin E supplementation (parenteral or oral). The reviewers excluded studies in which vitamin E had been provided as a co-intervention.

The primary outcome measures included mortality until discharge from hospital, combined outcome at 18 months including mortality (bronchopulmonary dysplasia, blindness, mental retardation or cerebral palsy, and mortality), and combined outcome at 18 months excluding mortality. The major secondary outcomes were sepsis, severe intraventricular haemorrhage (IVH) (grade III or IV), severe ROP, necrotizing enterocolitis with gastrointestinal perforation, signs of haemolysis, and local reaction at the injection site.

The standard search strategy of the Cochrane Neonatal Collaborative Review Group was used and the authors searched MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials.
The criteria and standard methods of the Cochrane Neonatal Review Group were used to assess the methodological quality of the included trials. The authors assessed the risk of four types of biases: selection, performance, attrition, and detection. Many studies had significant attrition bias. The reviewers extracted data on as many randomized patients as possible, and analysed on an intention-to-treat basis using the total number of randomized patients as the denominator. The data were extracted independently by the authors and then compared and differences resolved. Categorical data were analysed using relative risk (RR), risk difference (RD) and number needed to treat (NNT). Continuous data were analysed using weighted mean difference (WMD) with 95% confidence interval (CI). The authors intended to perform subgroup analyses based on gestational age, birth weight, route of administration of vitamin E, and serum tocopherol levels.

The methods used by the authors to perform the literature search, extract data from eligible studies, assess quality of included studies, and analyse data and present findings were appropriate.

3. RESULTS OF THE REVIEW

Twenty-six randomized trials that had enrolled 3248 infants were included in the review. The majority of these trials were conducted in the 1970s and 1980s. Of the 25 trials that had compared the effects of vitamin E supplementation versus placebo, eight (838 infants) had assessed the effects of vitamin E supplementation provided through the enteral route only, 15 (1159 infants) had assessed the effects of the intramuscular route with or without enteral supplementation, and two (1201 neonates) had evaluated the effect of the intravenous route, with or without other routes of supplementation. Vitamin E supplementation was initiated within the first 48 hours of life in 20 studies, and thereafter in four studies. Vitamin E supplementation was provided for up to 1 week in 11 studies and for a longer period in 13 studies. The dose of vitamin E provided exceeded 11 mg/kg/day – the upper limit of the recommended dietary allowance suggested by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition (6) – in 24 out of 25 studies; the dose was greater than 20 mg/kg/day in nine studies. The total dose of vitamin E intake in the control group was up to 10 mg/100 kcal in 22 studies and greater than 10 mg/100 kcal in three studies. (Although infants in the control group did not receive any vitamin E supplements, they got some vitamin E from parenteral nutrition or intravenous fluids and/or feeds, particularly formula milk.)

Primary outcomes

Pooled analysis of 12 studies involving 994 treated infants and 1034 controls did not find a significant effect on mortality until discharge from hospital following vitamin E supplementation (RR 0.97, CI 0.83–1.14). There was also no effect in the pooled analysis of studies that enrolled only very-low-birth-weight infants (1276 neonates; RR 0.97, 95% CI 0.80–1.16). None of the included trials had assessed a combined outcome at 18 months of age.

Secondary outcomes

Pooled analysis of six trials did not find a significant difference in the risk of bronchopulmonary dysplasia following vitamin E supplementation (1127 neonates; RR 0.91, 95% CI 0.73–1.14). Sepsis was assessed in four studies, which reported a significantly higher risk of sepsis in infants receiving vitamin E supplementation (1009 neonates; RR 1.52, 95% CI 1.13–2.04). Subgroup analyses showed that the increased risk of sepsis was highest: (i) in infants receiving parenteral supplementation, particularly through the intravenous route; (ii) in those who had received higher doses of vitamin E (total dose exceeding 30 IU/kg/day); and (iii) in infants with high serum tocopherol levels (>3.5 mg/dl). Vitamin E supplementation significantly reduced the risk of all grades of IVH (I–IV) (1755 neonates; RR 0.85, 95% CI 0.73–0.99). Three trials that had assessed severe IVH (grade III–IV) together showed no effect of vitamin E supplementation on the rates of severe IVH (644 neonates; RR 0.91, 95% CI 0.60–1.38). Pooled analysis of
seven studies found no reduction in ROP of any grade (1342 neonates; RR 0.90, 95% CI 0.75–1.09) or severe ROP (grade III or more) (1565 neonates; RR 0.72, 95% CI 0.41–1.25). Necrotizing enterocolitis was assessed in eight studies; pooled analysis indicated no change in its incidence (1443 neonates; RR 1.37, 95% CI 0.96–1.95). Vitamin E supplementation significantly increased the haemoglobin concentration in the intervention groups (416 neonates; WMD 0.46 g/dl, 95% CI 0.24–0.69).

**Secondary outcomes in very-low-birth-weight infants**

Pooled results of the studies that enrolled only very-low-birth-weight infants showed similar results for most of the secondary outcomes listed above. However, vitamin E supplementation failed to reduce the risk of IVH in these infants (777 neonates; RR 0.94, 95% CI 0.75–1.18). There was an indication of reduction (described by the review authors as significant) in the incidence of severe ROP in very-low-birth-weight infants (1062 neonates; RR 0.58, 95% CI 0.34–1.0).

**Subgroup analyses**

Subgroup analyses showed that serum tocopherol levels greater than 3.5 mg/dl in very-low-birth-weight infants were associated with a significantly increased risk of sepsis (RR 1.72, 95% CI 1.24–2.40), increased risk of NEC (RR 1.60, 95% CI 1.02–2.52), and reduced risk for severe retinopathy (RR 0.34, 95% CI 0.13–0.88). Intravenous, high-dose administration of vitamin E in very-low-birth-weight infants was associated with a significantly increased risk of sepsis (RR 1.56, 95% CI 1.07–2.27) and with increased risk of NEC among those treated for more than one week.

4. **DISCUSSION**

4.1 **Applicability of the results**

Vitamin E supplementation, particularly in doses that exceed the recommended daily intake, reduces the risk of IVH, but increases the incidence of sepsis in preterm neonates. As the review authors point out, these results have to be interpreted with caution for two reasons: (i) the majority of the studies were conducted in 1970s and 1980s when the chances of survival of immature and smaller preterm infants were still low; and (ii) the numerous subgroup analyses could potentially yield spurious results. High-dose vitamin E supplementation did not affect the risk of major neonatal conditions attributed to oxidant injury such as bronchopulmonary dysplasia. With better ROP preventive strategies now being practised, even the possible benefit of reducing the risk of severe ROP in very-low-birth-weight infants is likely to be less valued by health-care providers. Moreover, the higher risk of sepsis would deter health-care providers in both developed and developing country settings from using high-dose parenteral vitamin E supplementation in preterm infants. The findings of this review are relevant for all settings.

4.2 **Implementation of the intervention**

The present evidence does not support the practice of high-dose vitamin E supplementation, in particular intravenously, to preterm and low-birth-weight neonates. The recommended dietary allowance of 2–11 mg/kg/day for vitamin E should, however, be provided to prevent vitamin E deficiency in preterm infants (6). This level of dietary allowance is met by the usual daily intake of human or formula milk. In preterm very-low-birth-weight infants who are fed expressed breast milk fortified with a human milk fortifier, the daily requirements are met by the fortified milk (7).
4.3 Implications for research

Of the various trials included in the review, only three had enrolled extremely-low-birth-weight neonates. Given that these infants are more vulnerable to the complications of prematurity such as ROP and IVH (8), the effects of vitamin E supplementation at different doses and routes of administration (except intravenous route) need to be evaluated in these infants in rigorously conducted large randomized controlled trials. However, considering the potential risk for severe adverse effects, these trials should have in-built mechanisms to allow careful monitoring for possible toxicity of the intervention.

References


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