Vitamin E prophylaxis to reduce retinopathy of prematurity: a reappraisal of published trials
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Authors' objectives
To determine whether the use of vitamin E had beneficial effects on severe, (stage 3+ or worse) retinopathy in very low birth weight (VLBW) infants.

Searching
The following sources were searched: the investigators' personal files; Index Medicus from 1960 to July 1996; and the NLM databases of bibliographic citations from 1961 to July 1996. A list of English language publications related to vitamin E and ROP was prepared. The index search terms and major MeSH terms used were: 'infant', 'premature', 'retinopathy of prematurity', 'retrolental fibroplasia', 'clinical trials', 'antioxidants', 'vitamin E', 'tocopherol', and the interrelated subheadings.

In addition, the references from papers and review articles in major paediatric journals and textbooks were searched to update the list.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Vitamin E and placebo.

Participants included in the review
VLBW infants whose birth weight ranged from 750 to less than 2,000 g on entry to the study.

Outcomes assessed in the review
Retinopathy of prematurity (ROP) was assessed.

How were decisions on the relevance of primary studies made?
Only RCTs were included. Abstracts and trials in which the primary intent was other than the prevention of ROP were excluded. The authors avoided duplicate counting of publications on the basis of their knowledge of most ROP trials, and by close scrutiny of the names of investigators and institutions, trial dates, sample sizes, and findings. When in doubt, the authors contacted the authors of the trial in question for clarification concerning the duplicate publication of data.

In addition, the authors of this review also asked the primary investigator of each trial to make corrections, if any, in the data being analysed and to provide additional information.

Assessment of study quality
The authors do not report the method used to assess validity, or how the validity assessment was performed. However, it was noted that in the six trials included, the outcome evaluations were assessed by ophthalmologists masked to the treatment group assignments, and in five of the studies, the investigators maintained masking of treatment group assignments during dosage adjustments.

Data extraction
Eligible trials were reviewed with regard to the clinical variables and ROP outcome data. The authors noted the ROP
classification scheme used. ROP was computed for all randomly-assigned infants (intention-to-treat analysis) and for those infants completing the trials. When necessary, one of the authors reclassified the eye disease stage with regard to the stage 3+ status, according to the criteria of the International Classification of Retinopathy of Prematurity (ICROP).

Methods of synthesis
How were the studies combined?
Odds ratios (ORs), pooled estimates for event rate reductions, and the respective 95% confidence intervals (CIs) were calculated for the study outcome end points. The authors used an exact analogue of the Mantel-Haenszel procedure, as implemented in the EGRET software, to obtain pooled estimates. This method was used because the incidence of ROP was small or zero in some treatment arms; however, the standard Mantel-Haenszel procedure provided similar results.

How were differences between studies investigated?
The ORs were tested for homogeneity. The authors also examined the sensitivity of their meta-analysis because the incidence of severe ROP was low. When the authors omitted a study with a large treatment effect from the analyses, the OR for severe ROP (intention-to-treat analysis) was 0.86 (95% CI: 0.63, 1.11); this was a statistically non significant value. However, when the authors omitted a study with no treatment effect, the OR for severe, stage 3+ ROP was 0.32 (95% CI: 0.12, 0.75); this was a highly significant effect from vitamin E (p<0.005).

Results of the review
Six RCTs were included: there were 704 VLBW infants in the vitamin E prophylaxis group and 714 VLBW infants in the control group. Of these, 536 (76.1%) infants in the vitamin E group and 551 (77.2%) in the control group completed the trials.

The pooled incidences of ROP of any stage for the infants completing the study protocol (given in 5 of the 6 trials) were not different between the control and vitamin E-treated groups (43.5 and 39.8%, respectively). However, the incidence of stage 3+ ROP was 5.3% in the control group and 2.4% in the vitamin E-treated group.

The pooled OR for developing stage 3+ ROP with vitamin E prophylaxis was 0.44 (95% CI: 0.21, 0.81, p<0.02). The pooled estimate for the event rate reduction of stage 3+ ROP with vitamin E prophylaxis was 2.8% (95% CI: 0.55, 5.1); this represented a 52% reduction. Tests of homogeneity were highly non significant in all cases, therefore it was appropriate to pool the OR data.

The reciprocal of the estimated event rate reduction (2.8%) was 35.3 (95% CI: 19.6, 180), indicating that, on average, 35 (95% CI: 20, 180) infants need to be treated with vitamin E to reduce the occurrence of stage 3+ ROP by one.

Authors’ conclusions
Considering that there was a 52% reduction in the incidence of stage 3+ ROP, the authors suggested that the role of vitamin E in reducing severe ROP should be re-evaluated. The authors could not assess the adverse effect rates from vitamin E therapy in the trials analysed; they therefore recommended that a well-controlled and focused trial be conducted, in which the issues of benefit, adverse effects, and cost can be assessed with vitamin E prophylaxis in extremely low birth weight (less than 1,000 g) infants.

CRD commentary
The authors reviewed 63 articles relating to vitamin E and ROP published between 1961 and 1996, but only 6 met the inclusion criteria for this review. The search strategy described may have overlooked additional studies since non-English language studies and unpublished studies were not included in their search criteria, and they relied on their own knowledge of the existing literature on ROP trials to ensure no duplication in the included trials.

It was unclear from the stated objective whether the authors were looking for a dose response in their meta-analysis; this was not addressed in the analysis before the individual studies were pooled.

While the authors did not specify their procedures or criteria for judging the quality of the included studies, they did
make extensive efforts to perform an intention-to-treat analysis and to obtain clarification of the data from the original investigators.

In their discussion on limitations, the authors acknowledged that there may have been many differences in perinatal and neonatal care practices between the trials analysed, which might have had a confounding effect on ROP. They also acknowledge that since there were fewer than 10 trials, resulting in a possibly low power for homogeneity, they could not rule out the possibility that factors other than the treatment contributed to the observed differences.

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