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Failure of supplementation with vitamin E to prevent bronchopulmonary dysplasia in infants <1,500 g birth weight

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ABSTRACT: In a randomized trial to determine whether oral vitamin E reduced stages III and IV bronchopulmonary dysplasia (BPD) by 50%, 268 infants were randomly allocated, after stratification by birth weight and severity of disease, to receive vitamin E 25 units or an indistinguishable placebo. The experimental (E) group and the control (C) group were similar in weight, gestational ages, Apgar scores, severity of illness, and initial oxygen and ventilator exposure. Serum vitamin E levels were significantly different within 48 h of administration and remained well above normal adult levels from the first week of life in the experimental group. There was no difference in the rates of early death, BPD at 28 days, or mortality from BPD. Severity was similar and no difference was seen in the incidence of necrotizing enterocolitis or sepsis. There was no evidence that vitamin E supplementation offered protection against chronic lung disease in infants <1,500 g birth weight.

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Bronchopulmonary dysplasia (BPD) is a potentially fatal disorder of newborn infants. The aetiology is unclear, although exposure to increased oxygen and positive pressure ventilation are important aetiological agents. TAYLOR [1] showed that pulmonary oxygen toxicity is enhanced by vitamin E deficiency and reduced by supplemental vitamin E given to deficient rats [2]. Preterm infants have low serum vitamin E levels [3] and an early study by EHRENKRANTZ *et al.* [4] suggested that vitamin E might prevent BPD. We, therefore, performed a randomized, blind, controlled trial of oral vitamin E supplementation in infants <1,500 g birth weight.

Methods

Sample selection. Infants who weighed <1,500 g at birth and were expected to survive at least 48 h, who did not have a major congenital anomaly or Rhesus (Rh) haemolytic disease, were enrolled in the study, after written consent had been received from an informed parent. Four hundred and ninety four infants were admitted to the neonatal unit during the study; 89 died within 48 h; in 64 consent could not be sought, and in 65 consent was refused. Two hundred and sixty six patients were enrolled in the study.

Prognostic stratification. Infants were randomized within birth weight strata (<1,000 g and 1,000–1,500 g) and "sick", *i.e.* receiving more than 60% oxygen and/or intermittent positive pressure ventilation (IPPV), and "well" strata.

Allocation. Randomization within each prognostic stratum was performed in the pharmacy. Infants were allocated to receive either 25 I.U. tocopherol, Hoffman La-Roche (16 mg d-lα tocopherol) or a similar volume of the drug vehicle (Tween 80). Active and control medications were identically presented and dispensed in numbered, light protected syringes. Both were administered by gavage, even in the absence of enteral feeding, for six weeks.

Co-interventions. Respiratory disease was managed with conventional pressure-cycled ventilators when necessary. Infants were fed with maternal breast milk, SMA20, or SMA24, or with Aminosyn® after three days and Nutralipid® after seven days if fed intravenously. No added iron was given.

Outcome measures. Chest roentgenograms performed on days 1, 10, 21, 28 and 42, were reviewed by three radiologists independently and BPD diagnosed if multiple bilateral cystic lesions with (Stage IV) or without

(Stage III) fibrosis were present at 21 days or later. Vitamin E levels were measured as described elsewhere [5] on day one, before the initial dose, and days 2, 3, 7, 21 and 42.

Sample size. Pre-trial calculations, based on the incidence of BPD in the nursery at that time, showed that to detect a 50% risk reduction in BPD, Grades III and IV (from 32 to 16%), with a power of 95%, required at least 119 infants in each group.

Results

Two hundred and sixty six patients entered the study; 132 were allocated to vitamin E supplementation and 134 to placebo. There was no difference between the groups in sex distribution, birth weight or gestational age, proportions inborn or Apgar scores at one and five minutes. The initial oxygen exposure, proportion ventilated, and degree of ventilation, were also similar (table 1). There was no significant difference in the proportions who received intravenous amino acid or fats.

Table 1. – Characteristics of study infants at randomization

	Vitamin E supplemented	Control
n	132	134
Male: female	67:65	67:67
Birth weight g mean±SD	1149±244	1158±251
Birth weight <1,000 g	34	42
≥1,000 g	98	92
Gestational age wks mean±SD	29.2±2.7	29.1±2.7
"Sick":"Well"	60:72	65:69
Received supplementary oxygen after first 24 h	111 (84%)	112 (84%)
F_{IO_2} ≥0.80	53 (40%)	56 (42%)
Number ventilated	68	75
Median number of days on IPPV	8	10

F_{IO_2}: fraction of inspired oxygen; IPPV: intermittent positive pressure ventilation.

Serum vitamin E levels before supplementation were low and were identical (0.049 $mg \cdot l^{-1}$) in each group. Forty eight hours after supplementation the serum vitamin E level in the supplemented group was twice that of the controls. Levels well above the normal adult range were achieved by the end of the first week (vitamin E supplemented group 0.286±0.198 $mg \cdot l^{-1}$; control group 0.0878±0.0662 $mg \cdot l^{-1}$). Even in the control group vitamin E levels were within normal adult limits from seven days onwards.

There was no significant difference in the overall incidence of Stages III or IV BPD (table 2). The numbers of survivors with BPD and the number of deaths from BPD were similar in each group. The combined rate of early death or BPD was 18.9% in the supplemented group and 23.1% in the control group. Severity of disease was assessed by arterial carbon dioxide tension ($Paco_2$) at six weeks, and length of stay in the neonatal intensive care unit (ICU); both appeared similar. All cases of BPD occurred in infants who were ventilated in the first two weeks of life and the disorder was more common in infants of <1,000 g birth weight, occurring in 52% in both control and supplemented groups of this weight.

Table 2. – Incidence of Stage III/IV BPD, occurrence of death <2 wks of age, and length of stay in neonatal intensive care (ICU) and $Paco_2$ at 6 wks of age in infants in ICU

	Vitamin E supplemented	Control
All infants		
n	132	134
No BPD	107	103
BPD (mortality %)	22 (36%)	27 (33%)
Deaths ≤14 days	3	4
Days in neonatal ICU mean±SD	40±32.6	43±34.5
median	31	34.5
$Paco_2$ at 6 wks (mmHg) mean±SD	6.3 (47)±1.8 (14) (n=78)	6.6 (49)±1.8 (14) (n=81)
Ventilated infants only		
n	68	75
No BPD	44	44
BPD	22	27
Deaths ≤14 days	2	4
Days in neonatal ICU mean±SD	56±36.2	60±36.4
$Paco_2$ at 6 wks (mmHg) mean±SD	6.7 (51)±2.0 (15)	7.1 (53)±1.8 (13)

BPD: bronchopulmonary dysplasia; $Paco_2$: arterial carbon dioxide tension.

Discussion

The sample size was based on a predicted reduction of BPD incidence from 32 to 16%, based on our experience before the study. The trial results showed a drop in BPD plus early death from 23 to 18% (20% reduction). The power to detect such a reduction, rather than a 50% reduction, is 0.66. There is, therefore, a possibility that a real reduction of 20% was present but to demonstrate this would have required a trial many times the size of this one. This and three other randomized, controlled trials [6–8] have failed to confirm protective effects of vitamin E against chronic lung disease. This was the only study using an oral preparation, despite which the vitamin E levels in the supplemented group are well above those accepted as normal for adults. The levels in the control group were surprisingly high by one week of age. One possible explanation of the absence of an effect, therefore, would be that vitamin E deficiency must be both severe and chronic in order to predispose to BPD.

Oral and prolonged parenteral administration of vitamin E has been reported to be associated with an increased incidence of necrotizing enterocolitis (NEC) [7, 8] and sepsis [8, 9]. The incidence of both complications was low in this population but there was no trend apparent for an association of either NEC or sepsis with vitamin E.

Bronchopulmonary dysplasia is likely to be multifactorial in origin with positive pressure ventilation and oxygen exposure being necessary, but not sufficient, causative agents. Other agents including vitamin E might be enabling agents or promoters. However, except possibly in severe chronic deficiency of the vitamin, supplementation by vitamin E is ineffective in preventing the development of BPD.

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Echecs des suppléments vitaminiques E dans la prévention de la dysplasie bronchopulmonaire chez les enfants de moins de 1500 grammes. J.L Watts, R. Milner, A. Zipursky, B. Paes, E. Ling, G. Gill, B. Fletcher, C. Rand.

RÉSUMÉ: Lors d'une essai randomisé pour déterminer si l'administration orale de vitamine E réduisait les stades III et IV de dysplasie bronchopulmonaire de 50%, 268 enfants ont été attribués au hasard après stratification par poids de naissance et sévérité de la maladie, soit vers un régime de 25 unités de vitamine E, soit vers un placébo d'apparence similaire. Le groupe expérimental (E) et le groupe contrôle (C) ont des valeurs similaires en ce qui concerne le poids, l'âge gestationnel, les scores d'Apger, la sévérite de la maladie l'exposition initial à la ventilation. Les niveaux sériques de vitamine E sont significativement différents dans les 48 heures d'administration et restent bien au-dessus des valeurs normales de l'adulte à partir de la première semaine de vie dans le groupe expérimental. On n'a pas noté de différence dans les taux de mort précoce et de dysplasie bronchopulmonaire à 28 jours, ou de mortalité globale par dysplasie bronchopulmonaire. La gravité s'avère similaire et il n'y a donc pas de différence de l'entérocolite nécrosante ou de sptisémie. Il n'y a donc pas de preuve qu'un supplément vitaminique E offre une protection quelconque contre les maladies pulmonaires chroniques chez les nouveaux-nés de moins de 1,500 grammes.

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