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Incidence, severity and time course of ROP in a randomized clinical trial of vitamin E prophylaxis

GRAHAM E. QUINN, LOIS JOHNSON*, CHARI OTIS*, DAVID B. SCHAFFER & FRANK W. BOWEN*

Departments of Pediatrics and Ophthalmology, University of Pennsylvania School of Medicine, Philadelphia, PA 19107, USA*

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Abbreviations: BW, birth weight; E, vitamin E; GA, gestational age; NEC, necrotizing enterocolitis; P, placebo; PPRP, pre-proliferative retinopathy; ROP, retinopathy of prematurity

We report the effect of prophylactic administration of an antioxidant on the incidence and severity of both the acute and chronic phases of ROP, as well as the influence of E on the time course of the disease. These data were collected during a double-masked clinical trial of the use of vitamin E at 5 mg/dl as prophylaxis for retinopathy of prematurity (ROP) and its residua.

Our group had earlier reported two smaller clinical trials [1, 2] in which the antioxidant had been started during the first day after birth and was administered during the period of retinal vascularization at lower, more physiologic levels of 1.5 to 2.5 mg/dl which showed a decreased incidence and severity of ROP. Another protocol from 1976–78 suggested a possible benefit from higher levels of E at the diagnosis of severe ROP [2] as the visual outcome of these infants was better than expected from the literature [3]. This work led to the present trial which employed intravenous, as well as intramuscular and later oral, routes of the active form of the vitamin (free dl alpha tocopherol) to achieve a target serum level of 5 mg/dl from as soon as possible after birth on. Our goals were to: 1) assess the effect of E on both incidence and severity of ROP, 2) assess the possible effect of starting E at the diagnosis of severe disease, defined as Grade 3+ ROP with extraretinal neovascularization in more than 2 quadrants [4], 3) observe the natural history of ROP and its residua in study infants with long term follow up

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including verbal assessment of visual acuity at age 3 years, and 4) maintain careful surveillance for untoward side effects from using the vitamin prophylactically at the target serum level.

As previously reported by Johnson et al. [5], the risk benefit ratio from E prophylaxis at serum levels of 5 mg/dl was found to be unfavorable since there was a higher incidence of necrotizing enterocolitis (NEC) and sepsis in study infants with BW of 1500 g or less who had been on a high dose of E for more than 7 days. However, the findings of this trial do support an effect of antioxidant treatment on initiation, progression and time course of ROP.

Methods

All infants admitted to the University of Pennsylvania Neonatal Complex with a birthweight (BW) of less than 2001 g or > 2000 g BW if gestational age (GA) < 37 weeks and requiring oxygen therapy for more than a day were eligible for the study. If consent was obtained by age 5 days, then the child was randomized within 5 BW strata [6] to receive study medication containing either vitamin E (E) or its placebo (P). Target serum levels in E infants were maintained throughout the period of retinal vascularization or until ROP developed and regressed. Any infant who progressed to severe ROP was taken off study medication and given E at the time of diagnosis.

ROP surveillance began as soon as possible after birth, generally by age one week, and continued on a weekly basis until retinal vascularization was complete or the acute phases of ROP had regressed. All examinations were performed by the DBS or GQ using the classification system designed for this study [4] which closely corresponds to the subsequent International Classification of ROP [7]. Infants with early vascular abnormalities but not diagnostic suggestive of early ROP were classified as having a pre-proliferative retinopathy (PPRP). ROP was divided into three categories of increasing severity: mild ROP (Grades 1 and 2), moderate ROP (from mild to ridge with 2 quadrant extraretinal neovascularization with or without plus disease), and severe ROP as defined above.

Results

914 infants were enrolled during study intake from January 1979 through May 1981 of whom complete acute stage ROP data could be collected on 755 infants (385 P, 370 E). Of these 424 had BW of 1500 g or less (216 P, 208 E).

Table 1. Effect of E prophylaxis on incidence of ROP.

	All enrollees		BW < 1501 g	
	P	E	P	E
Total	385	370	216	208
% ROP	32%	27%	51%	46%
χ^2	$p = 0.10$		$p > 0.10$	
Log Reg	$p = 0.003$		$p = 0.035$	
Prediction	R = 67.2%		R = 60.3%	

Inclusion limit for Log Reg equation $p < 0.05$. Predictors entered: BW, GA, E/P, ml of blood received per kg BW, and days of oxygen therapy, on ventilator and in hospital.
Data after Johnson et al., 1989 [6].

As previously reported [6], 124 of the 385 P-treated infants developed ROP compared to 99 out of those 370 who received E prophylaxis. A model for the logistic regression equation was derived using those predictors for ROP which made a contribution to outcome variance at $p < 0.05$. These predictors were BW, GA, E/P, days of oxygen therapy, days on ventilator, days in the hospital, and amount of blood received per kilogram of BW. Using this model, E treatment provided a significant benefit considering all study infants and those with BW < 1501 g (see Table 1). The incidence of ROP was also affected by the timing of study entry [6]. If the infants were enrolled by age 1 day as compared to those entered on the second to fifth day after birth, they were less likely to develop ROP if they were assigned to the E treatment group ($p = 0.06$ by χ^2 and $p = 0.005$ by Log Reg).

Most of the retinopathy observed was mild and all moderate and severe ROP occurred in children with BW < 1501 g. Of the 50 infants who developed more than mild ROP, 16 P and 22 E infants had moderate ROP and 9 P and 3 E had severe ROP. At the time of diagnosis of severe ROP, 8 of the 9 P-treated infants were placed on vitamin E at a target of 5 mg/dl.

The time course of the acute phases of ROP were examined for the possible influence of antioxidant administration and the results are presented in Table 2 for those children with BW less than 1501 g. The mean E/P difference to the first observation of ROP in the right eye of each infant was 8.8 days ± 2.4 SE and demonstrates a significant delay in those infants who had received E treatment ($p = 0.0002$, unpaired t test, two tailed). Similarly, among the infants with BW < 1501 g, the number of days to the observation of the highest grade was 11.7 days ± 3.1 SE ($p = 0.0002$, unpaired t test). Also given in Table 2 are the mean number of days until the first signs of regression was noted and until resolution was complete in those children

Table 2. Time from birth to onset of ROP, peak disease, regression first noted, and resolution in infants with BW $\leqslant$ 1500 g.

Time[a]	Placebo	Vit E	T[b]	*p*
to ROP	46.1 (1.5)	55.0 (1.9)	3.73	0.0002
to peak	53.7 (2.0)	65.4 (2.4)	3.77	0.0002
to regression first noted	71.1 (2.2)	85.6 (2.7)	4.19	< 0.0001
to resolution	99.8 (4.1)	11.1 (5.3)	2.64	0.0083

[a] Days ($\pm$ SE).
[b] Unpaired *t*-test, two tailed.

who did not have posterior pole or peripheral scarring noted on long-term follow up. The mean E/P difference for days to regression first noted was 14.5 days $\pm$ 3.5 SE ($p < 0.0001$) and for time to resolution 17.3 days $\pm$ 6.6 SE ($p = 0.008$). Findings for the left eye, for infants with BW of < 1001 g, and for the study population as a whole were very similar.

Thirteen children in each treatment group developed cicatricial residua of ROP [8, 9]. All of these children had BW of 1500 g or less. They constitute less than 10% of infants with BW < 1501 g on whom this long-term information was available. In the P treated group, 9 had macular heterotopia or worse in their worse eye and 5 of these had a retinal fold or worse. In contrast, 3 of the E treated children had macular heterotopia and one child had a retinal detachment, by worse eye grade. There is a trend toward decreased severity of cicatricial disease in E infants when the whole study population is considered ($p = 0.072$, χ^2) [8]. When severity of residua is considered among only those children who had residua of ROP, there was a significant decrease in severity of ROP residua among infants who received E from birth on ($p < 0.025$, sign test). Those 8 placebo infants who, according to the study protocol, received E treatment at the diagnosis of severe retinopathy complicate the interpretation of this data.

Discussion

These findings indicate that there is a significant effect of antioxidant treatment on initiation and progression of ROP. This is evident by decreased incidence of ROP as shown by the statistical technique of logistic regression analysis which takes into account factors which are likely to contribute to the development of ROP in the study population and by the suggestion at the 0.055 level by multiple Chi square analysis that severity in the E treated infants was less than that observed in the P group. The effect of early

enrollment also supports the view that the process of initiation of ROP is affected by antioxidant prophylaxis.

The time delay observed in the E treated infants during the onset and progression of ROP also supports the contention that E had an effect on abnormal vessel formation in those infants in whom the disease could not be prevented. The cause of the time delay is unclear at present, but one might speculate that the free radical scavenging abilities of this potent physiologic antioxidant decreased the initial and cumulative insult which the developing retina of the premature infants sustained, thereby postponing the time when the criteria for onset and progression of abnormal vascularization of the retina in the extra-uterine environment were met. The time delay in appearance of abnormal vascularization in E treated infants is probably due to the same mechanism as the decrease in ROP incidence observed in this population.

Interpretation of the long term outcome of the study infants with respect to residua of ROP is complicated by the protocol requirement which removed those P infants who developed severe ROP and put them on vitamin E at the time of diagnosis. This decision had been made before our pilot work in cryotherapy for severe disease [10] and allowed the child with the most severe forms of ROP the only treatment felt reasonable at the time. To the extent that antioxidant treatment was effective in already established ROP, we expected that such treatment would diminish any observable differences between E and P treatment group assignment. Though 8 of the 9 P-assigned children who developed severe ROP received E treatment at diagnosis, there still appears to be a decrease in the severity of ROP residua in E infants compared to P-assigned infants [9].

We conclude that the present study provides evidence that antioxidant prophylaxis of ROP using vitamin E has an effect on the development, progression and time course of ROP. Using high target serum levels in premature infants as ROP prophylaxis is not warranted due to the observed increased incidence of NEC and sepsis among E-treated study infants. Such a risk does not appear likely when lower, physiologic levels of 1.5 to 3 mg/dl are maintained from early on and we agree with Ehrenkranz [11] that E sufficiency should be 'a goal of standard nutritional management in all premature infants.' Cryotherapy has recently been shown to be an effective treatment for severe forms of ROP [12], but over 20% of infants who received cryotherapy still had an unfavorable outcome. The feasibility of using an antioxidant as an adjunct to the surgical treatment of ROP or as a medical therapeutic modality when ROP is already established in an effort to decrease progression to severe disease must be further explored.

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Address for correspondence: G.E. Quinn, Dept. of Ophthalmology, University of Pennsylvania, School of Medicine, Philadelphia, PA 19107, USA.