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VITAMIN E AND RETINOPATHY OF PREMATURITY

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CONTENTS

Committee	iv
Staff	v
VITAMIN E AND RETINOPATHY OF PREMATURITY	1
Low Birthweight Infants	1
Retinopathy of Prematurity	1
Risk Factors for ROP	3
Prematurity	3
Oxygen	3
Light	4
Incidence of ROP	4
Treatment of ROP	4
Efficacy of Vitamin E Treatment for ROP	5
Results of Six Studies	5
Study Design Differences	9
Staging of ROP	9
Timing of Eye Examinations	9
Administration of Vitamin E	9
Start of Treatment	11
Birthweight	11
Response to Stage 3 Disease	11
Statistical Analysis	11
Efficacy of Vitamin E in ROP: Conclusion	11
Efficacy of Vitamin E in Other Conditions of the Newborn Infant	12
Hemolytic Anemia	12
Bronchopulmonary Dysplasia	13
Intraventricular Hemorrhage	13
Toxicity of Vitamin E in Premature Infants	14
Eferol	15
Recommendations for Future Research	15
Retinopathy of Prematurity	15
Summary	16
References	18

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VITAMIN E AND RETINOPATHY OF PREMATURITY

This report addresses current knowledge about the role of vitamin E, alpha-tocopherol, in the prevention or amelioration of retinopathy of prematurity (ROP) and certain other conditions of the low birthweight premature infant. Attention to the prevention or treatment of life-threatening or disabling neonatal disorders has increased as survival of very low birthweight infants has increased. Vitamin E in particular has been studied as a pharmacologic agent for ROP, hemolytic anemia, and other conditions prominent among premature infants. Because of conflicting reports on its efficacy in ROP and reports of some toxicities, the Food and Drug Administration requested that the Institute of Medicine review available data and identify any additional data needed to determine the safety of vitamin E for neonates and its value, especially for ROP.

Low Birthweight Infants

Survival of very low birthweight infants has increased markedly over the past three decades in the United States (Table 1). In the early 1950s, the survival of infants with birthweights below 1,500 grams was about 30 percent.[1] By the early 1980s, the survival had increased to about 60 percent nationally (Table 1) and was as high as 80 percent in some hospitals.[2] In most neonatal intensive care units today, the birthweight at which half of the infants will survive is about 800 grams.[2]

During the period that survival increased dramatically, there was only a very slight decrease in the incidence of births with weights of 1,500 grams or less. Such births continue to represent about one percent of all births in the United States.[3-7] Thus, the number of surviving infants of birthweight 1,500 grams or less increased from 16,700 in 1960 to about 26,800 in 1982 (Table 1). This trend is expected to continue.

The development of the specialty of neonatology and the creation of neonatal intensive care units in the 1960s led not only to decreased mortality but also to decreased morbidity.[8,9] In the 1950s, more than 70 percent of the surviving infants with birthweights under 1,500 grams had major neurological and developmental defects.[10] In the mid-1980s, only 20 percent of the infants had these long-term problems,[11] but because of the increased survival that still represents many thousands of infants each year.

Retinopathy of Prematurity

Retrolental fibroplasia was first described in the early 1940s as a disease of premature infants that could result in blindness.[12] It

TABLE 1. Incidence and Survival of Low Birthweight Infants

	1960	1971 (Thousands of Infants)	1982
All births in the U.S.	4,260	3,560	3,680
Birthweight < 1,500 g	52.1	40.6	43.3
Percent Survival < 1,500 g	32	39[a]	62[a]
Number of Survivors < 1,500 g	16.7	15.8	26.8

a) Estimates of survival are based on reports from five states on deaths within seven days of birth. The sample population includes black infants and white infants weighing 500 to 1,500 grams at birth.

SOURCES: References 3-7.

is extremely rare in fullterm infants and unusual beyond 33 weeks gestational age.[13] Accordingly, the condition is now called retinopathy of prematurity (ROP), and an International Classification of ROP (ICROP) was developed in 1984.[14] The designation retrolental fibroplasia is reserved for advanced forms of ROP (cicatricial disease) in which scar formation and retinal detachment lead to partial or complete blindness.

Only developing blood vessels give rise to ROP. At term, development of the retinal vasculature is nearly complete, accounting for the rarity of the conditions in these infants.[15] In contrast, the retina of a very premature infant must undergo considerable vascular development for a period of time after birth, and is therefore more vulnerable.

ROP, which is a progressive disorder, has been categorized into four acute phases of increasing severity.[14,16] The acute stages range from a line of neovascularization dividing the avascular from vascularized retina, through progression of neovascularization and proliferation of extraretinal fibrovascular tissue, and finally to

retinal detachment. Because retinal detachment has traditionally been classified as part of cicatricial disease, there is overlap between cicatricial disease and the ICROP staging of acute phase ROP. However, during construction of ICROP, it was agreed that without the inclusion of traction detachment in stage 4 the system would be of less use to examining physicians. This overlap reflects the continuum of disease progression.[14]

The time course and outcome of ROP differ from individual to individual. An infant is at risk of developing ROP as long as the peripheral retinal vasculature is immature. The earliest ophthalmoscopically visible signs of ROP rarely occur before four weeks after birth. In most cases, ROP regresses with no known significant long-term consequences. However, cicatricial disease (permanent scarring of the retina resulting in visual impairment) may occur, especially in the more advanced stages of ROP. Retinal changes can continue until about age six months, at which time the condition has either regressed or is stable.

Risk Factors for ROP

Prematurity As noted above, ROP rarely occurs in infants of 33 weeks or greater gestational age.[13]

Oxygen Nursery observations that implicated oxygen in the genesis of ROP were supported by animal studies.[17-20] The association in humans with hyperoxic environments was shown convincingly in a multicenter collaborative clinical trial completed in the 1950s.[21] In this trial, one half of the infants were exposed to high concentrations of oxygen (greater than 50 percent) for four weeks (beginning at 48 hours of age). Following publication of the report, use of oxygen in premature nurseries was sharply curtailed and the incidence of ROP dropped dramatically.[22]

Although the use of supplemental oxygen is a feature in the vast majority of cases of ROP, the condition also can develop in the absence of hyperoxic environments. ROP has occurred in premature infants born in a location in which supplemental oxygen was unavailable or in hospitals in which supplemental oxygen was not used routinely for premature infants.[23] In addition, ROP has been described in an infant with cyanotic congenital heart disease. In this infant, the cardiac condition did not permit arterial oxygen tensions to reach normal, much less elevated levels.[24]

The concern about its toxicity, and the subsequent multiple legal suits alleging injudicious use of oxygen as the cause of ROP, led to a sharply reduced use of oxygen. As a consequence, evidence developed that infant mortality and morbidity were increasing because oxygen was

being withheld from infants who required it.[25,26] Also, the new ability to monitor arterial blood gases documented the severe oxygen deprivation of premature infants with idiopathic respiratory distress syndrome, pointing to the need for more liberal oxygen practices in selected cases. At present, despite the best oxygen monitoring available, ROP continues to occur in very low birthweight infants, underscoring their vulnerability.

Light As another factor contributing to the development of ROP, light was examined in the 1950s and again in a recent study.[27,28] Although the first observations indicated no effect of light, the more recent study reports the lighting in a nursery may increase risk of ROP.[28] There are substantial concerns regarding the design of this study. The data analysis and statistical significance reported also have been questioned.[29] Although this study provides no satisfactory answers for the present, it raises interesting questions.

Incidence of ROP

At least 10,000 infants were partially or completely blinded by ROP in the 1940s and early 1950s.[30] Although reduction in the use of oxygen greatly reduced ROP incidence, many neonatologists and ophthalmologists believe that a new epidemic of ROP is developing in the 1980s as a result of the increased survival of very small premature infants.[31]

Precise national data on the incidence of ROP are not available for either the past or the present. A recent pilot survey conducted by the National Center for Health Statistics to obtain national data on vision was not successful in measuring the prevalence of visual impairment and its causes.[32] Persons identified by at-home vision screening tests as having impaired vision were invited to local clinics for careful follow-up eye examinations. However, less than 50 percent accepted the invitation. The low response rate raises questions about the representativeness of the clinical data that were available on causes of vision impairment.

Data from a number of ROP studies provide incidence figures for high risk study populations, but even these vary over a wide range. These variations have been attributed to differences in timing and frequency of eye examinations and to differences in the study populations.

Treatment of ROP

When ROP was recognized in the late 1940s, a number of therapies were tried without success, including the administration of vitamin C and ACTH.[33] Vitamin E was administered orally with apparent success

in a small controlled clinical trial conducted by Owens and Owens.[34] But the frequent spontaneous regression of ROP confounds interpretation of early studies.

All tentative therapies were disregarded after publication of the study that indicated hyperoxia was the principal cause of ROP.[21] Withholding supplemental oxygen appeared to make any treatment questions moot.

Investigators began to reexamine the possible pathogenic mechanisms of ROP, its prevention, and the treatment of advanced disease, when the incidence of ROP began to increase again. The association of ROP with a hyperoxic environment provided impetus for renewed investigations into the use of vitamin E, an antioxidant, in preventing ROP.

Efficacy of Vitamin E Treatment for ROP

The Institute of Medicine (IOM) committee reviewed published reports on the efficacy of vitamin E in reducing the incidence or severity of ROP.[35-37] Manuscripts in preparation and a conference presentation also were made available to the committee.[38-40] In addition, six investigators* from three of the groups studying vitamin E and ROP met with the committee to present their data and to participate in discussion and critique of the available data. Clifford Joseph, consultant to Hoffmann-LaRoche, the company that has been responsible for providing and monitoring vitamin E as an Investigational New Drug, also participated in the discussions as a physician knowledgeable about the forms of vitamin E provided to clinical researchers and the experimental uses of the drug.

Results of Six Studies

Information from six studies of vitamin E and ROP is summarized in Tables 2 and 3. Table 2 indicates study characteristics and Table 3 presents key data. To the extent possible, data are presented separately for any ROP, severe acute ROP, and any cicatricial disease. The data presented in Table 3 are for infants under 1,500 grams birthweight who entered into the study within one day of birth. (The Pennsylvania study allowed entry up to five days of birth, but after completion of the study data for infants entered by day one were analyzed separately.)

*Helen Hittner, Lois Johnson, Frank Kretzer, Dale Phelps, Graham Quinn, and David Schaffer.

TABLE 2. Vitamin E and ROP: Study Characteristics

Study (Admission Dates)	Admission Requirements	Vitamin E Administration	Vitamin E Level[a] Control	Vitamin E Level[a] Vitamin E
			(mg/dl)	
Baylor College of Medicine (11/79 - 12/80)	Admitted within 24 hours of birth and birthweight less than 1,500g and require oxygen	d,l alphatocopherol in propylene glycol-polysorbate 80, oral	0.6	1.2
McMaster University (1977)	Birthweight less than 1,500g	d,l alphatocopherol	1.0	3.2
University of Alberta (9/78 - 5/81)	Admitted within 24 hours of birth and birthweight 750-1,500g	Tocopheryl acetate, intramuscular, then oral	0.7	4.8
UCLA (12/80 - 9/83)	Admitted within 24 hours of birth and birthweight less than 1,500g or less than 33 weeks gestational age	d,l alphatocopherol in alcohol, fast intravenous, then oral plus intramuscular	0.6	3-3.5
University of Pennsylvania (11/79 - 5/81)	Admitted within 5 days of birth and birthweight less than 2,000g or less than 36 weeks gestational age	d,l alphatocopherol, intravenous or oral plus intramuscular	0.9	5.0
Yale University	Admitted within 24 hours of birth with respiratory distress syndrome	Vitamin E Injectable, intramuscular	0.7	4.7

a) Mean over the acute treatment period measured in serum for the Alberta, Pennsylvania, and Yale groups, and in plasma for the Baylor, McMaster, and UCLA groups.

SOURCES: References 35-40.

TABLE 3. Ophthalmologic Results of Six Studies on Vitamin E and ROP[a]

STUDY	Number Completed Acute Phase Study		Number Any ROP		Number Severe ROP[b]		Number Any Cicatricial Disease[b]	
	Control	Vitamin E	Control	Vitamin E	Control	Vitamin E	Control	Vitamin E
Baylor College of Medicine	51	50	33	32	5	0	--[c]	--
					p<.03			
McMaster University	114	111	19	13	5	3	--[e]	--
					NS[d]			
University of Alberta	51	48	12	9	4	2	5	3
					NS		NS	
UCLA	99	97	28	25	8	11	1	3
					NS		NS	
University of Pennsylvania[f]	216	208	109	95	9	3	13[g]	13
					NS		NS	
(Admitted within one day of birth)	147	141	76	56	7	3	7[h]	4
					p=.05			
Yale University	37	37	8	9	3	1	--[i]	--
					NS			

a) ROP classification systems used are described in Table 4.
b) Statistical tests employed--Baylor: one-sided Fisher's exact test; Alberta: Pearson's Chi square, Fisher's exact and Student's t test; Yale: Fisher's exact test; Pennsylvania: Chi square and Fisher's exact tests; UCLA: Chi square, Fisher's exact, and Student's t tests; McMaster: univariate analyses.
c) Any infant with Grade III or greater "Retrolental Fibroplasia" was treated surgicially.
d) NS=difference between control and vitamin E is not statistically significant.
e) Not determined.
f) Infants 1,500 grams or less birthweight.
g) 177 control and 177 Vitamin E treated infants were available for follow up exams.
h) Grade 2 or greater cicatricial disease.
i) No infant developed more than minor cicatricial changes.

SOURCES: References 35-41.

As shown in Table 3, a benefit of orally administered vitamin E was observed by the Baylor group, manifest by a smaller number of infants with severe acute ROP (5 vs. 0, $p<.03$). No beneficial effect on either incidence or severity of ROP was observed by the UCLA group. For the Pennsylvania group, no statistically significant benefit to infants who received vitamin E was found for the total population of infants under 1,500 grams birthweight; however, when the data were analyzed retrospectively to include only babies whose prophylactic treatment began within one day of birth, significant differences were noted between the control and treatment groups in the incidence (76 vs. 56, $p=.04$) and severity (7 vs. 3, $p=.05$) of ROP. Interpretation of the significance of this data subset must be made cautiously, however, because entry by one day of birth was not a stratification variable in the randomization process.

The data on cicatricial disease--which is of greatest importance with respect to adverse visual outcomes--represent very few cases and reveal no statistically significant difference in the overall incidence of cicatricial disease for vitamin E compared with placebo infants (Table 3). At Baylor, the findings of statistically significant benefit from vitamin E for severe acute stages could not be assessed for cicatricial outcome because the protocol was interrupted with cryotherapy once severe (Grade III) acute ROP was observed. The University of Pennsylvania data (confounded by the administration of vitamin E to placebo infants if they evidenced severe acute stage ROP) indicate a reduction in the severity of cicatricial disease ($p=.025$).* Neither incidence nor severity of cicatricial disease was significantly changed by vitamin E treatment in the UCLA study.

For the remaining three studies of vitamin E and ROP neither the incidence nor the severity of ROP was significantly different in control and treated infants. There was committee consensus that design anomalies made further direct comparisons unproductive. In the Alberta study, control infants received no treatment, rather than receiving a placebo. Furthermore, only the examining ophthalmologists (not other medical staff) were masked concerning whether or not patients received vitamin E.[36] In the Yale study, with only 74 subjects, each infant with ROP demonstrated spontaneous regression and none developed more than minor cicatricial changes; this study population may not be comparable to others studied in which the incidence of cicatricial disease was marginally higher.[37] The McMaster study focused on the acute phase of ROP, and did not report data on long-term retinal findings in relation to vitamin E treatment.[40]

*Severe cicatricial disease was defined as greater than Grade I.

Study Design Differences

Among the three studies examined in detail (Baylor, UCLA, University of Pennsylvania), a number of important study design differences were identified that may help to explain the conflicting results. These differences include criteria for entry into the study, classification system for evaluating ROP, dose and route of administration of vitamin E, timing and frequency of eye examinations, length of follow-up period, and actions taken when Stage 3 Plus ROP was observed (see Table 2). An additional consideration was the possibility of inter- or intra-observer variability in assessing ROP.

Staging of ROP An international classification of ROP (ICROP) was developed in 1984, but this staging system was not available to the investigators while they were collecting data.[14] Various earlier classification systems were used (Table 4).[37,42-46] Although investigators indicated that their classifications could be translated to the ICROP system, the IOM committee is not confident that study-to-study comparisons based on retrospective conversion to ICROP are sound.

Furthermore, the Pennsylvania group and others have described an advanced form of Stage 3 ROP called Plus Disease, which has been incorporated into the ICROP classification system. (Plus Disease is characterized by vascular dilatation and tortuosity in the posterior pole of the retina.) The Pennsylvania and Baylor groups (and others) find that Stage 3 Plus Disease carries a more ominous prognosis for progression to cicatricial sequellae than does Stage 3. The UCLA ophthalmologists did not obtain prior interobserver agreement on the classification of Plus Disease, and did not use this distinction.

Timing of Eye Examinations Because early acute stage manifestations of ROP often are reversed, differences in timing of the ophthalmoscopic examination accounted for at least a portion of the differences observed in the incidence of acute stage ROP. At Baylor, examination began at three weeks after birth and was continued weekly until hospital discharge. Continued follow-up depended on the degree of the disease. The UCLA group began exams at four to six weeks of age, and continued monthly until the condition was stable. The Pennsylvania group began exams when they could be tolerated by the infant, and continued them weekly until the retina was mature, or until regression began. Infants were followed-up every two or four weeks until the condition stabilized.

Administration of Vitamin E Different routes of administration, formulations, and achieved blood levels were used in the several studies (Table 2).

The Baylor group used only the oral route of administration and limited the dose to 100 mg/kg per day. Mean blood levels by one week of age were about 1.0-1.2 mg/dl.

TABLE 4. ROP Classification Systems Employed in Six Vitamin E Studies

Study	Grading System Acute Disease	Severe ROP Definition	Grading System Cicatricial Disease
Baylor College of Medicine	McCormick	Grade III or greater	Not Applicable
McMaster University	McCormick	Grade III or greater	Not Applicable
University of Alberta	Payne and Patz	Stage III or greater	Payne and Patz
UCLA	Clock hour designation converted to ICROP	Stage 3 or greater	Reese, King, and Owens
University of Pennsylvania	Schaffer et al.	Four Quadrant Grade 3 Plus or greater	Reese and Stepanik
Yale University	Puklin, Simon, and Ehrenkranz	Stage II	Not Applicable

SOURCES: References 35-45.

The UCLA group used the intravenous route initially, administered over a period of a few minutes to two to four hours. (The exact rate was not noted.) When the infants were able to take oral feedings, vitamin E was administered orally to maintain a 3-3.5 mg/dl blood level; occasionally, the oral dose had to be supplemented with intramuscular vitamin E to achieve the target level.

The Pennsylvania group administered vitamin E intravenously over a period of 8-12 hours with a goal of achieving a blood level of 5 mg/dl. Then, the same pattern as the UCLA group was used, i.e., oral supplemented with occasional intramuscular administration--adjusted in this case to achieve a plasma level of 5 mg/dl.

Start of Treatment All Baylor infants began treatment by 24 hours after birth. All but two of the UCLA infants started treatment by 24 hours of age; the other two began treatment by 36 hours. Among the Pennsylvania infants 32 precent did not receive the first treatment until after one day of age. (Treatment was initiated any time up to 5 days of age.)

Birthweight Infants in the Baylor and UCLA studies had a birthweight of less than 1,500 grams. In the University of Pennsylvania study, infants were admitted up to 2,000 grams birthweight (or less than 36 weeks gestational age) and then stratified by birthweight.

Response to Stage 3 Disease An additional confounding consideration was the decision to add a treatment modality if an infant developed Stage 3 Plus Disease. At Baylor, cryotherapy was provided to both placebo and vitamin E treated infants. At Pennsylvania, vitamin E to achieve a blood level of 5 mg/dl was given to an infant, whether in the control or treatment group, if four quadrant Plus Disease was noted. The protocol was not interrupted at UCLA.

Statistical Analysis

These three clinical trials had different designs and reached conclusions differing from one study to the next--results showing benefit in the Baylor trial, no benefit in the UCLA trial, and benefit for a retrospectively separated subset of patients in the Pennsylvania trial. Although the IOM committee was convinced that the statistical methodologies were internally consistent and sound, the study design differences make direct comparisons of data difficult and pooling of the data sets for further analysis ill-advised.

Efficacy of Vitamin E in ROP: Conclusion

The IOM committee concluded that the evidence from existing studies is not convincing that the incidence or severity of ROP is modified by the prophylactic administration of vitamin E given orally, intramuscularly, or intravenously from birth. Although there is a suggestion in some of the data that the administration of vitamin E might be efficacious, the data from the prospective studies are conflicting and do not warrant a recommendation at the present time for the routine use of vitamin E to prevent or modify ROP.

Efficacy of Vitamin E in Other Conditions of the Newborn Infant

Hemolytic Anemia

Before 1967, although it was recognized that most proprietary formulas fed to low birthweight infants resulted in a prolonged period of vitamin E deficiency, no hematologic abnormalities could be demonstrated.[47] In 1967, the presence of a hemolytic anemia that could be corrected by vitamin E or prevented by maintaining vitamin E sufficiency from early infancy was described.[48,49]

This syndrome was seen almost exclusively in infants with birthweights of less than 1,500 grams and was most pronounced during the period of six to ten weeks of life. In addition to the hematologic abnormalities, many of the small infants also displayed edema of the lower legs and scrotum, watery nasal discharge, and, on occasion, tachypnea. The hematologic findings consisted of anemia (hemoglobin of 6 to 8 grams per deciliter), reticulocytosis of 4 to 5 percent or greater, and thrombocytosis. Red cell morphologic changes included the presence of anisocytosis, poikilocytosis, red cell fragments, and irregularly contracted erythrocytes and spherocytes. The hydrogen peroxide hemolysis test was very abnormal, and the red cell life span was reduced.[49,50]

Treatment with vitamin E, in total doses ranging from 200 to 1,000 mg, produced a prompt rise in hemoglobin, a reduction in the reticulocyte count, and a gradual decline in the platelet count to the normal range.[49,50] Ferrous sulfate administration exaggerated the hemolytic anemia in infants not receiving a vitamin supplement.[51]

Williams and coworkers[52] demonstrated that hemolytic anemia caused by vitamin E deficiency occurred in infants receiving iron-fortified formulas only if the formula was unusually rich in polyunsaturated fats. It has been hypothesized that hemolysis occurs in vitamin E deficiency as a consequence of peroxidation of lipid components of the red cell membrane.

Most manufacturers of proprietary formulas have increased the vitamin E concentration and reduced the polyunsaturated fatty acid (PUFA) content resulting in vitamin E:PUFA ratios in excess of 0.6:1.0, a value generally regarded as sufficient to prevent the development of vitamin E deficiency.[53] The potential for the development of vitamin E deficiency anemia is present when infants receive intravenous lipid preparations without adequate vitamin E supplementation.[54]

Bronchopulmonary Dysplasia

There is no conclusive evidence that the prophylactic administration of vitamin E reduces either the incidence or severity of bronchopulmonary dysplasia (BPD). An initial study by a group at Yale showed a protective effect of vitamin E against BPD.[55] This was not confirmed in a subsequent randomized double-blind trial conducted by the same investigators.[56,57]

Changes in infant formula probably account for the lack of confirmation of a protective effect of additional vitamin E. In the initial trial, control infants received little vitamin E and the formulas used had low ratios of vitamin E to PUFA. In the second trial, control infants received more vitamin E during the first days of life, and by that time formula contained less PUFA. Vitamin E levels of control infants enrolled in the second study reached adequate levels by 24 hours of age whereas the vitamin E levels in the initial study remained low for two weeks.

It appears likely that pharmacological supplementation of vitamin E over that which is now available in the course of normal newborn nutrition confers no additional benefit for the prevention of BPD.

Intraventricular Hemorrhage

The effect of vitamin E on intraventricular hemorrhage (IVH) has been studied directly and also has been monitored during studies of ROP. The results are not entirely consistent.

A preliminary report of a protective effect of vitamin E in IVH suggested that vitamin E reduces the severity of IVH but not the overall incidence.[58] Among infants receiving vitamin E, the hemorrhage was confined principally to the membrane lining the brain's ventricular spaces; among control infants, the hemorrhage extended into the ventricles. A follow-up study, not yet published, reports reduction in both incidence and severity of IVH in low birthweight infants receiving vitamin E from birth.[59]

The Baylor study of ROP, which involved oral administration of vitamin E, indicated no effect with regard to IVH. However, another report by this group indicates oral vitamin E supplemented with intramuscular vitamin E reduces both the incidence and severity of IVH.[60]

In contrast, in the Pennsylvania study of ROP, no difference was apparent between treatment and control infants with respect to IVH. Moreover, the UCLA group had a significantly increased incidence of severe IVH (grades 3 and 4) in the subset of vitamin E treated infants who weighed less than 1,000 grams at birth. No difference between

placebo and vitamin E recipients was observed for less severe IVH (grade 1 to 2) or for larger infants (1,000-1,500 grams). The observed effect may be a reflection of the mode of administration of vitamin E (rapid intravenous) in the UCLA study.

The committee concluded that no firm conclusion about the efficacy of vitamin E with respect to IVH is possible at this time. Publication of the recently completed study[59] and completion of an ongoing study at Indiana University may lead to greater clarity in the future.

Toxicity of Vitamin E in Premature Infants

There is no evidence to suggest that the mortality rate is affected by the administration of vitamin E (in its currently available formulations) to infants of any birthweight. Three possible toxic effects have been noted: necrotizing enterocolitis (NEC), neonatal sepsis, and IVH (see above).

In a retrospective study, an increased incidence of NEC was associated with oral, but not intramuscular, administration of vitamin E, particularly for infants of birthweight less than 1,250 grams.[61] Some caution is required in interpreting these results, however, because there was a marked increase in mortality in the placebo compared to the vitamin E treated population. Conceivably, the control infants that died were at greatest risk for NEC. The earlier case matched prospective study by the same investigators (an ROP study) found no enhanced risk for NEC with vitamin E.[36]

The Pennsylvania group studying ROP observed an increased incidence of NEC and neonatal sepsis.[38] These complications may be a consequence of the high vitamin E blood levels (5 mg/dl) used by that group. This explanation is not wholly satisfactory, however, because the UCLA group did not observe an increased incidence of NEC or late sepsis, even though there must have been high blood levels of vitamin E in some of their babies during the initial phases of therapy.

Although administration of vitamin E resulting in pharmacologic blood levels appears to be tolerated with relative impunity in infants, a number of toxic effects of vitamin E therapy have been described in adults.[53,62] These include prolongation of plasma clotting time,[63] which may reflect a direct effect of vitamin E on the fibrinolytic system;[64] inhibition of platelet prostaglandin synthesis and decreased platelet aggregation;[65,66] and impaired immune function, as indicated by reduced bacteriocidal activity of leukocytes and depressed mitogen-induced transformation of lymphocytes.[67] However, the clinical importance of these potentially harmful effects to the human newborn is not known inasmuch

as these side effects have not been monitored during clinical trials of vitamin E supplementation. Of note, Zipursky et al.[68] have measured plasma coagulation function in infants with birthweights below 1,500 grams who received either daily parenteral vitamin E or placebo during the first six weeks of life. There were no significant differences between the vitamin E treated and placebo groups in any of the coagulation tests examined before, during, or at the end of treatment.

In summary, there is no clear evidence of vitamin E toxicity in infants.

Eferol

In late 1983 and early 1984, low birthweight infants in several neonatal intensive care units developed an enigmatic and ultimately fatal syndrome that was associated with the administration of Eferol. The syndrome was characterized by unexplained thrombocytopenia, renal dysfunction, hepatomegaly, cholestasis, ascites, hypotension, and metabolic acidosis.[69,70]

Eferol is a preparation of tocopheryl acetate solubilized in polysorbates. The toxicity has been attributed to the high polysorbate load to which the infants were exposed, rather than the vitamin E itself.[69,71,72] Because Eferol is no longer marketed, it was not considered further by the IOM committee.

Recommendations for Future Research

Retinopathy of Prematurity

The IOM committee concluded that a multicenter clinical trial would be necessary to provide a sufficiently large study population for definitive information on the efficacy of vitamin E in ROP. Should such a trial be undertaken, the committee recommends the following.

o Vitamin E treatment should begin within 24 hours of birth. It is quite clear from the data reported to the committee that vitamin E blood levels in control subjects have increased over time; this is probably a reflection of many factors, including improved nutrition of mothers, increased frequency of human milk feeding, addition of vitamin E to proprietary formulas, and the addition of vitamin E to parenteral alimentation solutions. It appears likely that control infants will become vitamin E sufficient by one to two weeks of age. Thus the only time that additional treatment with vitamin E may have a demonstrable effect is early in the infant's life.

o There should be uniform criteria for inclusion and exclusion of infants from the study, including birthweight and gestational age.

o The ICROP classification should be used and examiners should meet prior to initiation of the study to develop reproducibility and comparability of the ROP observations.

o The outcome measure should be ROP Plus Disease.

o The committee did not make specific recommendation of a therapeutic dose of vitamin E. However, the committee does recommend that the blood level of vitamin E not exceed 3 mg/dl. The committee further notes that several groups, including the American Academy of Pediatrics (AAP) and the National Research Council (NRC) have made proposals for recommended daily allowances of vitamin E for maintenance of good nutrition.[73,74] For infants under six months, 0.5 mg alpha-tocopherol per kilogram was recommended by the NRC in 1980 and 0.5 mg per 100 kilocalories by the AAP in 1985; these are essentially the same recommendation.

A controlled clinical trial of the efficacy of cryotherapy for treatment of ROP Plus Disease has been initiated. Because the inter- and intra-observer comparability in use of ICROP has been established among ophthalmologists participating in this trial, the centers involved in the cryotherapy study might be a group well prepared to undertake a study of vitamin E prophylaxis for ROP.

In view of the reports of efficacy of vitamin E in preventing IVH, the committee further recommends that if a clinical trial of vitamin E is undertaken, IVH be monitored in addition to ROP Plus Disease.

Current research on pathophysiology of ROP is largely descriptive,[75] and experimental research on basic mechanisms would be of value. Animal models used to date appear to be limited in their usefulness,[76] so development of better model systems also would be worthwhile.

Summary

Success in perinatal care presents a population of about 35,000 infants yearly with birthweights below 1,500 grams. This committee met to consider the safety and efficacy of vitamin E treatment for those infants.

Vitamin E as prophylaxis for retinopathy of prematurity was subject to a detailed analysis. This committee found no conclusive evidence either of benefit or harm from vitamin E administration.

Regarding other conditions of the newborn infant, the committee found that vitamin E prevents hemolytic anemia if a deficiency is

present, but infant formulas now in use supply sufficient vitamin E. There is no evidence to suggest that supplemental vitamin E should be provided to prevent or treat bronchopulmonary dysplasia. Conclusions are not possible at this time with regard to the effect of vitamin E on intraventricular hemorrhage, necrotizing enterocolitis, or late sepsis.

Risks from vitamin E appear to be minimal for premature infants provided that doses are kept moderate to achieve a blood level no higher than 3 mg/dl.

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