http:// ijp.mums.ac.ir
Review Article (Pages: 1745-1757)

Effects of Vitamin E in Neonates and Young Infants

*Gian Maria Pacifici[1]

[1] Via San Andrea 32, 56127 Pisa, Italy.

Abstract

Vitamin E (alpha-tocopherol) is a potent and natural antioxidant. Vitamin E is concentrated from soybean oil. The Committee on Fetus and Newborn of the Academy of the American of Pediatrics endorsed 1 to 2 mg/dl as the normal range of serum tocopherol level. Human infants are born with low stores of vitamin E, thus they require an adequate intake of vitamin E soon after birth. The optimum intravenous dose of vitamin E is 2.8 mg/kg per day (maximum 7 mg/kg per day). Treating very-low-birth-weight infants with 100 mg/kg vitamin E for >1 week results in levels >3.5 mg/dl and significantly reduces the risks of severe retinopathy, intracranial hemorrhage, hemolytic anemia, chronic lung disease, retrolental fibroplasia and incidence and severity of intraventricular hemorrhage, but increases the risks of sepsis, necrotizing enterocolitis and can cause retinal hemorrhage in very-low-birth-weight infants. Vitamin E supplementation prevents the isolated vitamin E deficiency that causes spinocerebellar symptoms. The major benefits arising from elevated dosages of vitamin E have been the relief of symptoms of vitamin E deficiency in infants with abetalipoproteinamia and chronic cholestasis. Excessive doses of vitamin E may result in side effects and careful monitoring of vitamin E is thus essential. Neonates born to mothers treated with high doses of vitamin E have significantly lower birth weight compared to neonates born to untreated mothers. Vitamin E is not teratogenic. The aim of this study was to review the effects of vitamin E in neonates and young infants.

Key Words: Effects, Infant, Neonate, Vitamin E.

*Please cite this article as: Maria Pacifici G. Effects of Vitamin E in Neonates and Young Infants. Int J Pediatr 2016; 4(5): 1745-57.

Corresponding Author:

Gian Maria Pacifici, MD, Via San Andrea 32, 56127 Pisa, Italy.

Email: pacificigm@tiscali.it

Received date Feb 22, 2016 ; Accepted date: Mar 22, 2016

1-INTRODUCTION

Alpha-tocopherol (α-tocopherol) is the most active antioxidant of the group of tocopherols known as vitamin E. The amount required by the body is primarily dependent upon the dietary intake of fat, especially polyunsaturated fatty acids. Human milk or currently available infant formulas, contains adequate vitamin E and have appropriate vitamin E to polyunsaturated fatty acid ratios to prevent hemolytic anemia. Infants receiving supplemental iron amounts above 2 mg/kg per day may also require additional vitamin E. Oral absorption of vitamin E is dependent upon hydrolysis that requires bile salts and pancreatic esterases. This can be quite variable in very immature infants and those with fat malabsorption. Free tocopherol is absorbed in the small intestine, taken via chylomicrons into the gastrointestinal lymphatics, than carried by low-density lipoproteins to be incorporated into cell membranes. Significant tissue accumulation may occur with pharmacologic doses (1).

Vitamin E is the name given to a group of fat-soluble antioxidant tocopherols. The natural vitamin E, first isolated in 1936, is concentrated from soybean oil. Excessive intake (100 mg/kg daily) is toxic to the newborn kitten. Plasma levels in excess of 100 mg/l caused hepatomegaly, and levels over 180 mg/l are sometimes lethal. Vitamin E deficiency was first identified as causing fetal death. It is now known that vitamin E causes enhanced platelet aggregation and is also thought to cause a hemolytic anemia, probably as a result of peroxidation of the lipid component of the red cell membrane, a problem that seems to be exacerbated by giving artificial milk containing extra iron. An early a high-dose intravenous or intramuscular use reduces the risk of intravenous hemorrhage, bronchopulmonary dysplasia or retinopathy of prematurity, but the benefits achieved are marginal, and no study has ever looked to see what long-term benefit such treatment delivered. The interest in the vitamin E prophylactic use as an antioxidant has now been defined. High doses of vitamin E can prevent neuromuscular problems in abetalipoproteinamia, an autosomal recessive disorder associated with fat malabsorption and acanthocytosis. Such infants should also be treated with a low-diet and supplementation of vitamin A (7 mg) and vitamin K (5-10 mg) once a day by mouth irrespective of weight (2).

Human milk contains an average of 0.3 mg vitamin E per 100 ml, and formula milks contain vitamin E between 0.5 and 4.0 mg per 100 ml. Neonates are relatively deficient in vitamin E, and plasma levels (2.5 mg/l) are less than a quarter those in the mother. Plasma levels rise rapidly after birth in the breastfed term infants, but remain low for several weeks in artificially fed, especially those weighing <1.5 kg at birth. Significant anemia does not develop with artificially fed preterm infant feeds that provide a daily intake of about 3 IU/kg of vitamin E as long as the ratio of vitamin- E to polyunsaturated fat in the diet is well above 0.4 mg/g even if the milk contains supplemental iron. Hemolytic anemia, when it occurs, usually becomes apparent 4-6 weeks after birth and is usually associated with a reticulocytosis (>8%), an unusually high platelet count and as an abnormal peroxide-induced haemolysis test (>30%) (2).

2- MATERIALS AND METHODS

2-1. Literature Search

The following databases were searched for relevant papers and reports: MEDLINE, CINAHL, Embase, Google scholar and PubMed as search engines; February 2016 was the cutoff point. Key references from extracted papers were also hand-searched. The bibliographic search

was performed using PubMed database as search engine.

2-2. Search Terms

Combinations of search terms from three categories ("Neonetes" keyword AND "Vitamin E" keyword AND "Effects vitamin E neonate" keyword AND "Infants" keyword), were used to search for the relevant literature. In addition, the books NEOFAX by Young and Mangum (1) and Neonatal Formulary (2) were consulted.

3-RESULTS

3-1. Monitoring

Assess feeding tolerance. Signs of vitamin deficiency include hemolytic anemia and thrombocytosis. Physiologic serum vitamin E concentrations are between 0.8 and 3.5 mg/dl (1).

3-2. Prophylaxis in preterm infants

Only a minority of units now offer routine oral supplementation. The optimum intravenous dose for a parenterally fed infant is about 2.8 mg/kg per day (2).

3-3. Nutritional deficiency

10 mg/kg by mouth once a day will quickly correct any nutritional deficiency (2).

3-4. Abetalipoproteinamia

The dose is usually 100 mg/kg by mouth once a day (2). Infants with parenteral nutrition depend on an adequate supply of micronutrients, in particular, antioxidant vitamins and cofactors such as selenium. In cases of oxidative stress (e.g., chronic inflammations, sepsis, lung distress syndrome, and organ failure), there is a higher need for antioxidants. One of the most important antioxidants is vitamin E. For very-low-birth-weight infants, the plasma level is an indicator for adequate supply and for safety. Safe and indicative blood levels are between 23 and 46 µmol/l, maintained with a dose of 2.8 IU/kg (1-2 mg per day). For safety reasons a plasma level of 80µmol/L should not be exceeded. If parenteral lipid emulsion, are supplied there is an additional need for vitamin E to protect the polyunsaturated fatty acids from lipid peroxidation (3).

The Committee on Fetus and Newborn of the Academy Society of the American of Pediatrics has endorsed 1 to 2 mg/dl as the normal range of serum tocopherol level. Vitamin E supplementation resulting in levels >3.5 mg/dl, but not ≤ 3.5 mg/dl, significantly reduces the risk of severe retinopathy among very-low-birth-weight infants but increases the risk of sepsis and of necrotizing enterocolitis among infants treated for >1 week. As a fixed daily intravenous dose of vitamin E results in an inverse relationship between serum level and birth weight and is a risk for both low and high serum tocopherol levels, a dose adjusted for current weight appears more judicious than a fixed dose per day. Based on currently available data the Academy of the American of Pediatrics and the American Society for Clinical Nutrition currently recommend a routine intake of 2 ml/kg per day (2.8 IU/kg per day) in very-low-birth-weight infants (maximum of 5 ml/day or 7 IU per day) (4).

The use of pharmacologic doses of vitamin E is distinctly different from nutritional vitamin E in regards to issues of efficacy and safety. Repeated administration of pharmacologic doses of vitamin E results in increasing concentrations of vitamin E in all tissues examined. The emergence of a toxic clinical syndrome associated with vitamin E therapy, the effects of vitamin E on important physiologic systems such as granulocyte function and the arachidonic acid cascade, the theoretic possibility of vitamin E becoming a prooxidant at high concentrations, and the continuing controversy regarding the efficacy of pharmacologic doses of vitamin E mandate further study of the dose-response nature

of pharmacologic vitamin E therapy from both an efficacy and toxicity perspective (5). Kitajima et al. (6) assessed the effects of long-term supplementation of α-tocopherol on the neurological development of 259 school-aged extremely-low-birth-weight children. Extremely low birth weight participants were divided into three groups: group A with no α-tocopherol supplementation (n=121); group B with the supplementation for <6 months (n=104), and group C with the supplementation for more than 6 months (n=34). These authors analyzed the participants' data at birth and between the ages of one-and-a-half to 8 years and evaluated potential factors associated with intellectual disabilities. Children from group C had the best outcome. The groups' mean gestational weeks and the mean ventilator days were as follows: 27.5 weeks, 16.1 days (group A); 27.5 weeks, 41.7 days (group B); and 25.1 weeks, 75.5 days (group C). Multivariate regression analysis revealed that the odds ratios for impaired development at 8 years were 1.5 in group B and 0.19 (P=0.017) in group C, compared with 1.0 in group A. The association between the duration of α-tocopherol administration and performance intelligence quotient was dose dependent (P=0.03). Long-term supplementation of α-tocopherol appeared to improve mental development, in particular, performance intelligent quotient, in school-aged extremely-low-body-weight children.

Vitamin E is routinely supplemented to preterm neonates, including those with neonatal sepsis. Bajcetic et al. (7) examined the effects of neonatal sepsis and vitamin E on the antioxidative system in the blood. A prospective, randomized, open label study involved 65 preterm neonates. Control infants were 34 and 31 neonates received of 25 IU per day for 60 days. The activities of superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase were determined in erythrocytes at days 0, 30, and 60, following sepsis diagnosis. There was no difference in the activity of the antioxidative system between controls and neonates ongoing sepsis. At 60 days, septic neonates showed higher catalase activity compared to controls (P=0.027), and lower glutathione peroxidase activity compared to 0 days (P=0.022). The latter was mitigated by vitamin E, which on the other hand provoked lower glutathione peroxidase activity at 30 days, compared to untreated septic neonates (P=0.014). In addition, vitamin E suppressed glutathione reductase in septic neonates (P=0.025 and P=0.017 at 30 and 60 days, respectively). Finally, vitamin E supplementation in control neonates provoked a significant increase of glutathione peroxidase activity (P=0.015 at 60 days). The absence of altered redox settings in the activity of some compounds of antioxidative system, suggest that the supplementation of vitamin E in these patients might not be rational.

The recommended dose of vitamin E in human pregnancy is 22-30 mg per day (8). High doses of vitamin E (≥400 IU per day) have been show to attenuate or even prevent the damaging effect of ethanol and diabetes on the fetus. The mother risk program prospectively enrolled, and followed-up on 82 pregnant women exposed to high doses (≥400 IU per day) of vitamin E during the first trimester of pregnancy. Pregnancy outcome was compared to a matched control group. The study group (n=82) was vitamin E at doses ranging from 400 to 1,200 IU per day. There was one pregnancy with major malformation (omophalocele) in this study group. There was an apparent decrease in mean birth weight (3,173±467 grams) in vitamin E group as compared to control (3,417±565 grams; P=0.001); however, there were no significant differences in rates of live birth, preterm deliveries,

miscarriages and stillbirths. Therefore, it is concluded that consumption of high doses of vitamin E during the first trimester of pregnancy, does not appear to be associated with increased risk for major malformations, but may be associated with decrease in birth weight.

Treating very low-birth-weight infants with pharmacologic doses of vitamin E as an antioxidant agent has been proposed for preventing or limiting retinopathy of prematurity, intracranial hemorrhage, hemolytic anemia, and chronic lung disease (9). However, excessive doses of vitamin E may result in side effects. Routine vitamin E supplementation significantly increased hemoglobin concentration by a small amount. Vitamin E supplementation in preterm infants reduced the risk of intracranial hemorrhage, but increased the risk of sepsis. Evidence does not support the routine use of vitamin E supplementation by an intravenous route at high doses, or aiming at serum tocopherol levels greater than 3.5 mg/dl.

Vitamin E is an essential component of the oxidant defenses, but supplementation can have side effects in preterm infants. Careful monitoring of vitamin E status, is thus essential, however no consensus has been reached on the best clinical method (10). In 47 healthy preterm infants, several methods for assessment of vitamin E levels were measured, vitamin E to lipid ratios were calculated, and two variations of the hydrogen peroxide hemolysis test were conducted. At birth, the plasma and erythrocyte vitamin E levels were low. After birth, the plasma levels rose gradually, whereas the erythrocyte levels remained low. In contrast, the vitamin E-total-lipid ratio was in the low normal range from birth onwards. Vitamin E-lipid ratios using two lipid components (cholesterol with triglycerides, or cholesterol with phospholipids) or one lipid component (cholesterol) correlated with the vitamin E-total-lipid ratio with a good sensitivity and specificity. It is recommended in Europe that low birth weight infants who do not receive human milk should be fed formula enriched with long-chain polyunsaturated fatty acids. The question has been raised whether long-chain polyunsaturated fatty acids to low-birth-weight infants formula may have adverse effects on the antioxidant status in the recipient infant, particular on the major lipid-soluble antioxidant vitamin E. Koletzko et al. (11) studied the vitamin E status in low birth weight infants fed with human milk (n=15) or formula either without (n=8) or with long-chain polyunsaturated fatty acids derived from egg lipids and fish oil (n=9) on day 4 and 21 of life. Plasma vitamin E concentrations increased significantly in infants fed with human milk (day 4: 4.53 ± 1.31, day 21: 6.35 ± 2.18, mg/l, mean$\pm$ SD, $P<0.01$), whereas there were no changes in infants fed with long-chain polyunsaturated fatty acids. Plasma vitamin E to total lipid ratios and erythrocyte membrane vitamin E concentrations did not change significantly between days 4 and 21 in either group. In contrast, erythrocyte membrane vitamin E to total lipid ratios decreased significantly in infants fed with long-chain polyunsaturated fatty acid (0.42 ± 0.13 versus 0.31 ± 0.06, $P<0.05$), whereas no change occurred in the other two groups. These authors conclude that a long-chain polyunsaturated fatty acids supplementation based on egg lipids and fish oil to formula may induce an early postnatal decrease of vitamin E to total lipid ratios in the erythrocyte membrane of low-birth-weight infants. Therefore, the effects of different forms of long-chain polyunsaturated fatty acids to infant formula on infantile vitamin E status should be carefully evaluated. The major benefits arising from elevated dosages of vitamin E have been the relief of symptoms of vitamin E deficiency in humans with abetalipoproteinamia and

chronic cholestasis (12). In addition, supplementation of vitamin E, prevent the isolated vitamin E deficiency that has recently been associated with spinocerebellar symptoms. In keeping with the view that newborn infants, and especially premature infants, suffer from vitamin E deficiency, elevated dosages of vitamin E have been administered to prevent the anemia of premature infants, retrolental fibroplasia, bronchopulmonary dysplasia, and intraventricular hemorrhage. However, the results have been conflicting. Furthermore, some infants die unexpectedly. The life-threatening hazard of such treatment has been attributed mainly to polysorbates that are used as detergents in preparations of vitamin E for intravenous use rather than to vitamin E itself.

Analysis of nine randomized controlled trials of prophylactic vitamin E supplementation in very low-birth-weight infants (<1,500 grams) showed no statistically significant reduction in the incidence of acute retinopathy of prematurity (13). There was a significant reduction (49%) in the incidence of intraventricular hemorrhage, but no clear evidence for a corresponding reduction in intracerebral hemorrhage and no reduction in the incidence of hemorrhage confined to the germinal matrix. By combining the estimated reduction with the known incidence of long-term neurologic disability associated with intracranial hemorrhage alone, it was shown that only 1.5% and not more than about 4% of all very low birth weight infants are likely to benefit from routine vitamin E supplementation. In view of this, and data suggesting toxicity of vitamin E at concentrations close to those considered therapeutic, the routine use of vitamin E in very-low-birth-weight infants is not justified on present evidence.

A randomized, double study to determine the effect of intramuscular vitamin E on mortality and intracranial hemorrhage was performed by Fish et al. (14). One hundred forty-nine neonates with birth weight ≤ 1,000 grams and ≤ 24 hours of age were grouped by weight (501 to 750 and 751 to 1,000 grams) and randomized to treatment or control. The treatment group received intramuscular injections of vitamin E on days 1, 2, 4, and 6 of life. The control group received injections of placebo on the same schedule. All neonates initially received oral vitamin E (100 mg/kg per day dl-α-tocopherol acetate), which was subsequently adjusted to keep serum levels at 0.5 to 3.5 mg/dl. Ultrasonographic examinations of the head were performed as possible on days 7, and 12 to 14. Hemorrhage was defined as mild if ≤ to grade II intracranial hemorrhage or severe if grade III of IV. No significant differences in neonatal or total hospital mortality between groups were found. However, all intracranial hemorrhages, as well as severe intracranial hemorrhage, were found significantly less in the vitamin E-treated 501 to 750 grams subgroup (all intracranial hemorrhage: 60% versus 29%; severe intracranial: 32% versus 4%). When survivors were analyzed separately, a significant decrease in severe intracranial hemorrhage was seen in the vitamin E-treated neonates (25% versus 5%). Necrotizing enterocolitis and sepsis did not occur more frequently in the neonates treated with intramuscular injection of vitamin E. Vitamin E may have a role in the prevention of severe intracranial hemorrhage in premature neonates weighing between 501 and 750 grams.

The use of pharmacologic doses of vitamin E is distinctly different from nutritional vitamin E in regards to issues of efficacy and safety. Repeated administration of pharmacologic doses of vitamin E results in increasing concentrations of vitamin E in all tissues examined. The emergence of a toxic clinical syndrome associated with vitamin E therapy, the effects of vitamin E

on important physiologic systems such as granulocyte function and the arachidonic acid cascade, the theoretic possibility of vitamin E becoming a prooxidant at high concentrations, and the continuing controversy regarding the efficacy of pharmacologic doses of vitamin E mandate further study of the dose-response nature of pharmacologic vitamin E therapy from both an efficacy and toxicity perspective (5). The human infant is born with low stores of vitamin E. Thus, they require an adequate intake of vitamin E soon after birth. If adequate sources of tocopherol are not provided, a clearly defined deficiency state characterized by hemolytic anemia and, after a period of years, spinocerebellar degeneration results. However, the benefit of pharmacologic doses of vitamin E given as prophylaxis against diseases believed to be related to oxygen toxicity (bronchopulmonary dysplasia, retinopathy of prematurity (ROP), and periventricular-intracranial hemorrhage) is not clear. Possible benefits must be balanced against the potential for serious toxicity (15).

Phelps et al. (16) tested the efficacy and safety of vitamin E in preventing retinopathy of prematurity, 287 infants with birth weights < 1,500 grams or gestational ages of < 33 weeks were enrolled within 24 hours of birth in a randomized, double-masked trial of intravenous, followed by oral, placebo versus tocopherol (adjusted to plasma levels of 3 to 3.5 mg/dl). In 196 infants completing ophthalmic follow-up, tocopherol did not prevent retinopathy of prematurity of any stage (28% placebo treated versus 6% tocopherol treated). Cicatricial sequelae were not significantly different (1/97 placebo treated versus 16/111 tocopherol treated), and retinal hemorrhage correlated positively ($P<0.01$) with plasma levels of tocopherol after the first 2 weeks of age. Prospective monitoring of morbidity including late-onset sepsis, necrotizing enterocolitis, revealed no differences between groups except that in grades 3 and 4 intraventricular hemorrhage occurred more frequently in infants weighing < 1,000 grams at birth who had received tocopherol (14/42, 33%) versus those who had received placebo (4/43, 9%) $p<0.02$. The present data do not support the use of tocopherol for prophylaxis against retinopathy of prematurity in premature infants and suggest that intravenous tocopherol treatment starting on day 1 may increase the incidence of hemorrhagic complications of prematurity, particularly in infants with birth weights of less than 1,000 grams.

A prospective study was initiated to monitor serum tocopherol levels in all infants admitted to Indiana University Medical Center with birth weights < 1,500 grams (17). These infants routinely received 100 mg/kg per day of oral vitamin E (Aquasol E tocopherol acetate) every 6 hours. Vitamin E dosage was adjusted regularly to achieve levels ≥ 3.5 mg/dl. During 6 months of this study, a total of 76 infants had 567 serum measurements. Of these, 220 levels (38%) were ≥ to 3.5 mg/dl, 71 (13%) were ≥ to 5.5 mg/dl, and 15 (2.7%) were > 8 mg/dl. Serum tocopherol levels often remained ≥ to 3.5 mg/dl for several days after oral supplementation was discontinued or again became ≥ to 3.5 mg/dl on a reduced dosage of 25 to 50 mg/kg per day. These data indicate that infants weighing < 1,500 grams at birth who are receiving oral vitamin E supplementation at 100 mg/kg per day will have varied serum levels with a significant percentage exceeding 3.5 mg/dl. Serum vitamin E levels were measured in 17 very-low-birth-weight infants in the first 2 weeks of life, before and after the institution of intravenous vitamin E supplementation in a dosage of 4.5 mg per day (18). Serum vitamin E levels were 0.22 ± 0.16 mg/dl before supplementation, and rose to 2.55 ± 0.65

mg/dl in 9 infants > 899 grams birth weight, and rose to 3.68±0.70 mg/dl in six infants < 900 grams at birth. No toxic effects of the preparation or the increased vitamin E levels were found. Two hundred eighty-seven infants were enrolled in a double masked, randomized, placebo controlled trial of early parenteral tocopherol given from day one (19). Among 232 survivors with ophthalmologic follow-up, retinal hemorrhage occurred more frequently in the tocopherol group (16/111; 14.4% than in the placebo group (8/121; 6.6%). The development of retinal hemorrhages correlated strongly with plasma tocopherol levels from three weeks to three months ($P<0.05$).

The incidence of culture-proven neonatal sepsis and necrotizing enterocolitis in preterm infants maintained at pharmacologic (mean± SD 5.1±1.45 mg/dl) serum vitamin E levels for long periods was prospectively studied as part of a double-masked clinical trial of the effect of prophylactic vitamin E versus placebo treatment on the development and course of retinopathy of prematurity (20). Within a few days of birth, 914 preterm infants were enrolled in the study; 545 (275 placebo-treated infants, 270 vitamin E-treated infants had birth weight ≤ 1,500 grams). A significant difference in incidence of neonatal sepsis (17 placebo treated infants, 37 vitamin E-treated infants) and necrotizing enterocolitis (18 placebo-treated infants, 32 vitamin E-treated infants) was observed among infants who had been treated for eight or more days and who had developed neither sepsis nor necrotizing enterocolitis before that time. The association of vitamin E treatment with increased incidence of disease was much higher with sepsis than with necrotizing enterocolitis. The most likely reason for these observations is a pharmacologic serum vitamin E-related decrease in oxygen-dependent intracellular killing ability which results in a decreased resistance to infection in premature infants. In view of the known variability of absorption of oral vitamin E and the association between high serum vitamin E levels and increased incidence of sepsis and late-onset necrotizing enterocolitis, it can be concluded that serum vitamin E levels must be monitored when supplemental vitamin E is administered to premature infants, especially those with birth weight ≤1,500 grams.

Speer et al. (21) determined whether early intramuscular vitamin E supplementation influences the incidence of intraventricular hemorrhage in infants with birth weight ≤ 1,500 grams, data were analyzed from 134 infants enrolled on a protocol to evaluate the efficacy of intramuscular plus oral vitamin E versus oral supplementation alone in the treatment of retrolental fibroplasias. All 134 infants received, via nasogastric tube, 100 mg/kg per day of vitamin E daily (Dl-alpha tocopherol acetate in medium-chain triglyceride oil) for at least 8 weeks with the first dose administered within the first 8 hours of life. Sixty-four infants received placebo injection in a randomized double-blind fashion. In the first week, plasma levels were significantly higher in the 64 infants given intramuscularly vitamin E. In spite of this difference no change in the incidence of sepsis or necrotizing enterocolitis was observed. Both the incidence and severity of intraventricular hemorrhage were reduced significantly in the infants given intramuscular vitamin E as compared to the infants given placebo ($P=0.013$ and $P=0.04$, respectively). These data suggest that vitamin E, a natural antioxidant, may play an important role in protecting the central nervous system microcirculation from the effects of hypoxic/ischemic injury. A study was carried out to evaluate the effects of human milk and cows' milk regimen on plasma tocopherols and hematological status of 176 Brazilian infants from birth

to 12 months of age (22). Plasma total tocopherols and the ratio of tocopherols to total lipids were significantly higher ($P<0.01$) for breast-fed infants than for cows' milk-fed infants at all ages. Hydrogen peroxide-stimulated erythrocyte hemolysis was greater for cows' milk-fed infants at all ages than breast-fed infants; the difference was statistically significant ($P<0.01$) at 3, 6, and 9 months of age. Among the hematological indices examined, hemoglobin levels were significantly higher ($P<0.01$) for the breast-fed infants at 3 and 12 months, while the reticulocyte counts were significantly higher for cows' milk-fed infants at all ages; hematocrit values more or less remained similar for both groups. It is concluded that a human milk regime is ideal as compared to a cows' milk regime for maintaining adequate vitamin E status during the 1st year of early life.

Forty-four consecutively born infants of birth weight < 1,751 grams were randomly selected to receive a daily intramuscular injection of vitamin E from the day of birth (day 0) until day 3, or were allocated to a non-supplemented control group (23). Frequent ultrasound examinations of the brain were made during the first week of life and infants were classified as having no hemorrhage, subependymal hemorrhage only or intraventricular hemorrhage. The incidence of subependymal hemorrhage or intraventricular hemorrhage was similar in supplemented (42.9%) and control infants (43.5%). Subependymal hemorrhage or intraventricular hemorrhage was observed only in infants < 32 weeks gestation; when only infants < 32 weeks were considered, intraventricular hemorrhage was less common in those supplemented (18.8%) than in controls (56.3%). Infants with intraventricular hemorrhage had lower median plasma vitamin E concentrations when compared with infants without any hemorrhage and compared with those with only subependymal hemorrhage. Three supplemented infants suffered intraventricular hemorrhage and they were the three with the lowest plasma vitamin E concentrations among the infants supplemented with vitamin E from day 0 to day 3. These authors speculate that vitamin E protects endothelial cell membranes of capillaries in the subependymal layer of the brain against oxidative damage and disruption and thereby limits the magnitude of hemorrhage in the subependymal layer, and reduces the risk of extension into the ventricles.

Hittner et al. (24) performed a double-blind study in 101 preterm infants who weighed ≤ 1,500 grams at birth, who had respiratory distress, and who survived for at least four weeks, to evaluate the efficacy of oral vitamin E in preventing the development of retrolental fibroplasia. Weekly indirect ophthalmologic examinations begun, when the infants were three weeks old, revealed a significant decrease in the incidence of retrolental fibroplasia ≥ grade III ($P<0.03$) and ≥ to grade II ($P<0.05$) (McCormick classification) in 50 infants given 100 mg/kg of vitamin E per day as compared with 51 given 5 mg/kg per day (controls). When multivariate analysis was applied to both control and treatment groups, the severity of retrolental fibroplasia was found to be significantly reduced in infants given 100 mg of vitamin E ($P=0.012$).

4-DISCUSSION

Newborn infants are born with low stores of vitamin E, thus they require an adequate intake of vitamin E soon after birth. If adequate intake of vitamin E is not provided, a defined deficiency state characterized by hemolytic anemia and, after a period of years, spinocerebellar degeneration results (15). Vitamin E supplementation resulting in levels >3.5 mg/dl significantly reduces the risk of severe retinopathy among very-low-birth-

weight infants, but increases the risk of sepsis and of necrotizing enterocolitis in infants treated for > 1 week. The Academy of the American Pediatrics and the American Society for Clinical Nutrition recommend a routine intake of 2.8 IU/kg per day of vitamin E (maximum of 7 IU per day) in very-low-birth-weight infants (4). Repeated administration of vitamin E results in increasing of vitamin E in all tissues. Law et al. (13) suggest that the routine use of vitamin E in very-low-birth-weight infants is not justified because the toxicity of vitamin E appears at concentrations close to those considered therapeutic. In cases of oxidative stress such as the chronic inflammation, sepsis, and lung distress syndrome there is a higher need for antioxidants. Vitamin E is the most important natural antioxidant agent. Vitamin E supplementation resulting in plasma levels >3.5 mg/dl significantly reduces the risk of retinopathy of prematurity, intracranial hemorrhage, hemolytic anemia and chronic lung disease (9). However, excessive doses of vitamin E may result in side effects. The preterm septic neonates are particular susceptible to a wide spectrum of different morbidities such as respiratory distress syndrome, bronchopulmonary dysplasia, periventricular leukomalacia, severe intraventricular hemorrhage, cerebral palsy, and vision and hearing impairments. The development of these morbidities has been related to oxidative stress. It appears reasonable to apply antioxidants in order to treat neonatal sepsis and to prevent the development of morbidities. Vitamin E is an active natural antioxidant (7). The neonates born to mothers treated with vitamin E at dosages ranging from 400 to 1,200 IU per day had a significant decrease in birth weight (P=0.001) as compared with neonates born to unsupplied mothers. However, there were no significant differences in rates of live birth, preterm deliveries, miscarriage and stillbirths compared with untreated pregnant women (8). Boskovic et al. (8) concluded that supplementation with high doses of vitamin E during the first trimester of pregnancy does not appear to be associated with increased risk of neonatal major malformations. Elevated dosages of vitamin E prevent the anemia of premature infants, retrolental fibroplasia, bronchopulmonary dysplasia, and intraventricular hemorrhage (12). However, some infants die unexpectedly, the life-threatening hazard of such treatment has been attributed mainly to polysorbates that are used as detergents in preparations of vitamin E for intravenous use rather than vitamin E itself.

Vitamin E supplementation in very-low-birth-weight infants significantly increases the risk of sepsis, and reduces the risks of severe retinopathy and blindness. Evidence does not support the routine use of vitamin E supplementation at high doses in very-low-birth-weight infants. Serum tocopherol concentration should not be higher than 3.5 mg/dl (9). Vitamin E is an essential component of the oxidant defenses, but supplementation can have side effects in preterm infants and careful monitoring of vitamin E status is thus essential (10). Retinal hemorrhage correlated positively with plasma levels of tocopherol after the first 2 weeks of age. These findings do not support the use of tocopherol for prophylaxis against retinopathy of prematurity (16).

Seventy-six infants, with body weight < 1,500 grams, received 100 mg/kg per day oral tocopherol every 6 hours. The treatment lasted 6 months. Tocopherol serum levels were ≥3.5 mg/dl in 38% infants, 13% infants had a tocopherol serum level ≥ 5.5 mg/dl, and 2.7% infants had a serum level of tocopherol ≥ 8 mg/dl. Serum tocopherol levels remained ≥ 3.5 mg/dl for several days after oral supplementation was discontinued. These data indicate that infants weighing < 1,500

grams at birth supplied with oral 100 mg/kg tocopherol have varied serum levels of tocopherol with a significant percentage exceeding 3.5 mg/dl (17). Vitamin E treatment had an increased sepsis as compared to controls. The most likely reason for this observation is that vitamin E-related decrease in oxygen-dependent intracellular killing ability results in a decreased resistance to infection in premature infants (20). The incidence and severity of intraventricular hemorrhages were significantly reduced in infants given intramuscular vitamin E as compared to infants given placebo (21). This finding suggests that vitamin E, a natural antioxidant, plays an important role in protecting the central nervous system microcirculation from the effects of hypoxic/ischemic injury.

All infants with body weight between 501 and 750 grams were treated with oral vitamin E at the dose of 100 mg/kg and the serum levels were adjusted to be between 0.5 and 3.5 mg/d. The treated group received intramuscular vitamin E (100 mg/kg) and controls received placebo intramuscularly. Total intracranial hemorrhage was 29% in treated infants and 60% in control infants. Severe intracranial hemorrhage was 4% in treated infants and 32% in control infants. A decrease of intracranial hemorrhage was significantly lower in treated than control infants. Vitamin E has a role in the prevention of intracranial hemorrhage in premature infants weighing between 501 and 750 grams (14). Martinez et al. (22) compared the effects of breast milk and cows' milk regimen on plasma tocopherols from birth to 12 months. Plasma total tocopherols and the ratio of tocopherol to total lipids were significantly higher for breast-fed infants than for cows' milk-fed infants at all ages. These authors conclude that a human milk regimen is ideal as compared to cows' milk regimen for maintaining adequate vitamin E status during the first year of life. Retinal hemorrhage correlated positively with plasma levels of tocopherol after the first 2 weeks of age. This finding does not support the use of tocopherol for prophylaxis against retinopathy of prematurity in premature infants (16). Rosenbaum et al. (19) observed that retinal hemorrhage occurred more frequently in infants treated with tocopherol than in infants treated with placebo. Both the incidence and severity of intraventricular hemorrhages were reduced significantly in the infants given intramuscular vitamin E as compared to the infants given placebo (21). These data suggest that vitamin E, a natural antioxidant, plays an important role in protecting the central nervous system microcirculation from the effects of hypoxic/ischemic injury. Intraventricular hemorrhage was observed only in infants of less than 32 weeks gestation. Intraventricular hemorrhage was less common in infants treated with vitamin E than in controls. Infants with intraventricular hemorrhage had lower plasma vitamin E concentrations when compared with infants without intraventricular hemorrhage (23).

In infants < 32 weeks of gestation with birth weight < 1,751 grams, intraventricular hemorrhage was less common in those supplemented (18.8%) with vitamin E than in controls (56.3%). Infants with intraventricular hemorrhage had lower plasma vitamin E concentrations when compared with infants without intraventricular hemorrhage (23). Chiswick et al. (23) speculate that vitamin E protects endothelial cell membrane of capillaries in the subependymal layer of the brain against oxidative damage and disruption and thereby limits the magnitude of hemorrhage in the subependymal layer, and reduces the risk of extension into the ventricles. Hitter et al. (24) compared the development of retrolental fibroplasia in infants, weighing

< 1,500 grams birth weight, who received 100 mg/kg vitamin E with infants receiving 5 mg/kg per day vitamin E (controls). When multivariate analysis was applied to both treated and control groups, the severity of retrolental fibroplasia was found to be significantly reduced in infants given 100 mg of vitamin E.

5-CONCLUSION

In conclusion, vitamin E (α-tocopherol) is the most active antioxidant of the group of tocopherols. The functions of vitamin E may be to take up (scavenge) the free radicals generated by normal metabolic processes and by substances in the environment, e.g. hydrocarbons. This prevents free radicals from attacking polyunsaturated fats in cell membranes with resultant cell injury. A deficiency syndrome causes peripheral neuropathy with spinocerebellar degeneration, and a hemolytic anemia in premature infants. Vitamin E has some beneficial effects and some toxic effects in infants. Vitamin E reduces the risks of severe retinopathy, intracranial hemorrhage, hemolytic anemia, chronic lung disease, retrolental fibroplasia and the incidence and severity of intraventricular hemorrhage in very-low-birth-weight infants, but increases the risks of sepsis, necrotizing enterocolitis and causes retinal hemorrhage in infants. After oral administration, serum levels of vitamin E range in a wide interval. Neonates are born with low stores of vitamin E, thus they require an adequate intake of vitamin E. The recommended routine intake of vitamin E is 2.8 IU/kg per day (maximum 7 IU/kg per day). Vitamin E is not teratogenic, but infants born to mothers treated with high doses of vitamin E, have a decrease in birth weight as compared to neonates born to untreated mothers. Although there are several studies on the effects of vitamin E in infants more investigations are required for an evidence-based treatment of neonates and young infants with this vitamin.

6-CONFLICT OF INTERESTS

Prof. Gian Maria Pacifici declares no conflicts of financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employments, gifts and honoraria.

7-ACKNOWLEGMENTS

The author thanks Dr. Patrizia Ciucci and Dr. Francesco Varricchio of the Medical Library of the University of Pisa for retrieving the scientific literature.

8-REFERENCES

1. Young TE, Mangum B. Neofax, Vitamins & minerals. In: a manual of drugs used in neonatal care. Edition 23rd. Montvale: Thomson Reuters; 2010. P. 332.

2. Neonatal Formulary. Sixth edition. John Wiley & Sons, Limited European Distribution Centre New Era Estate, Oldlands Way Bognor Regis, West Sussex, PO22 9NQ, UK; 2011.p. 539-40.

3. Biesalski HK. Vitamin E requirements in parenteral nutrition. Gastroenterology 2009;137(5 Suppl):S92-104.

4. Brion LP, Bell EF, Raghuveer TS, Soghier L. What is the appropriate intravenous dose of vitamin E for very-low-birth-weight infants? J Perinatol 2004; 24(4):205-7.

5. Roberts RJ, Knight ME. Pharmacology of vitamin E in the newborn. Clin Perinatol 1987;14(4):843-55.

6. Kitajima H, Kanazawa T, Mori R, Hirano S, Ogihara T, Fujimura M. Long-term alpha-tocopherol supplements may improve mental development in extremely low birthweight infants. Acta Paediatr 2015;104(2):e82-9.

7. Bajčetić M, Otašević B, Prekajski NB, Spasić S, Spasojević I. Antioxidative system in the erythrocytes of preterm neonates with sepsis: the effects of vitamin E supplementation. Ann Clin Biochem 2014;51(Pt 5):550-6.

8. Boskovic R, Gargaun L, Oren D, Djulus J, Koren G. Pregnancy outcome following high

doses of Vitamin E supplementation. Reprod Toxicol 2005; 20(1):85-8.

9. Brion LP, Bell EF, Raghuveer TS. Vitamin E supplementation for prevention of morbidity and mortality in preterm infants. Cochrane Database Syst Rev 2003; (4):CD003665.

10. van Zoeren-Grobben D, Jacobs NJ, Houdkamp E, Lindeman JH, Drejer DF, Berger HM. Vitamin E status in preterm infants: assessment by plasma and erythrocyte vitamin E-lipid ratios and hemolysis tests. J Pediatr Gastroenterol Nutr 1998; 26(1):73-9.

11. Koletzko B, Decsi T, Sawatzki G. Vitamin E status of low birthweight infants fed formula enriched with long-chain polyunsaturated fatty acids. Int J Vitam Nutr Res 1995;65(2):101-4.

12. Mino M. Clinical uses and abuses of vitamin E in children. Proc Soc Exp Biol Med 1992; 200(2):266-70.

13. Law MR, Wijewardene K, Wald NJ. Is routine vitamin E administration justified in very low-birthweight infants? Dev Med Child Neurol 1990; 32(5):442-50.

14. Fish WH, Cohen M, Franzek D, Williams JM, Lemons JA. Effect of intramuscular vitamin E on mortality and intracranial hemorrhage in neonates of 1000 grams or less. Pediatrics 1990; 85(4):578-84.

15. Phelps DL. Current perspectives on vitamin E in infant nutrition. Am J Clin Nutr. 1987; 46(1 Suppl):187-91.

16. Phelps DL, Rosenbaum AL, Isenberg SJ, Leake RD, Dorey FJ. Tocopherol efficacy and safety for preventing retinopathy of prematurity: a randomized, controlled, double-masked trial. Pediatrics 1987; 79(4):489-500.

17. Neal PR, Erickson P, Baenziger JC, Olson J, Lemons JA. Serum vitamin E levels in the very low birth weight infant during oral supplementation. Pediatrics 1986; 77(5):636-40.

18. DeVito V, Reynolds JW, Benda GI, Carlson C. Serum vitamin E levels in very low-birth weight infants receiving vitamin E in parenteral nutrition solutions. JPEN J Parenter Enteral Nutr 1986;10(1):63-5.

19. Rosenbaum AL, Phelps DL, Isenberg SJ, Leake RD, Dorey F. Retinal hemorrhage in retinopathy of prematurity associated with tocopherol treatment. Ophthalmology 1985; 92(8):1012-14.

20. Johnson L, Bowen FW Jr, Abbasi S, Herrmann N, Weston M, Sacks L, Porat R, Stahl G, Peckham G, Delivoria-Papadopoulos M. Relationship of prolonged pharmacologic serum levels of vitamin E to incidence of sepsis and necrotizing enterocolitis in infants with birth weight 1,500 grams or less. Pediatrics 1985; 75(4):619-38.

21. Speer ME, Blifeld C, Rudolph AJ, Chadda P, Holbein ME, Hittner HM. Intraventricular hemorrhage and vitamin E in the very low-birth-weight infant: evidence for efficacy of early intramuscular vitamin E administration. Pediatrics 1984; 74(6):1107-12.

22. Martinez FE, Jorge SM, Gonçalves AL, Desai ID. Evaluation of plasma tocopherols in relation to hematological indices of Brazilian infants on human milk and cows' milk regime from birth to 1 year of age. Am J Clin Nutr 1984; 39(6):969-74.

23. Chiswick ML, Johnson M, Woodhall C, Gowland M, Davies J, Toner N, Sims D. Protective effect of vitamin E on intraventricular haemorrhage in the newborn. Ciba Found Symp 1983; 101:186-200.

24. Hittner HM, Godio LB, Rudolph AJ, Adams JM, Garcia-Prats JA, Friedman Z, et al. Retrolental fibroplasia: efficacy of vitamin E in a double-blind clinical study of preterm infants. N Engl J Med 1981; 305(23):1365-71.