Plasma levels of vitamin E and lipoperoxide during paediatric anaesthesia

H. Obara MD, N. Maekawa MD, H. Hoshina MD, O. Tanaka MD, R. Chuma MD, S. Iwai MD, H. Hisano MD, K. Nakamura MD, T. Yamamoto MD

We measured plasma levels of vitamin E (total tocopherol) and lipoperoxide in seventeen neonates (<10 days), twenty infants (1–12 months) and ten children (1–5 years) during anaesthesia.

The seventeen neonates were randomly divided into two groups; seven who received 30 mg·kg⁻¹ of α -tocopheryl acetate intramuscularly before anaesthesia and ten who did not. The 20 infants were divided into three groups: Group 1: eight infants who did not receive vitamin E; Group 2: six who received 30 mg·kg⁻¹ of α -tocopheryl acetate orally for three days before anaesthesia; Group 3: six who received 30 mg·kg⁻¹ of α -tocopheryl acetate intramuscularly three hours before anaesthesia.

In the neonates who did not receive α -tocopheryl acetate, plasma vitamin E and lipoperoxide levels were unchanged following surgery. In Group 1 infants, plasma vitamin E levels decreased ($p < 0.05$) and plasma lipoperoxide levels increased ($p < 0.05$).

In both neonates who received vitamin E and Group 3 infants the mean plasma vitamin E levels increased significantly ($p < 0.05$) following surgery. In Group 2 infants, the levels of plasma vitamin E before surgery

were high, as compared to the other groups; however, plasma vitamin E levels decreased following surgery.

In the children, the plasma vitamin E levels were unchanged, while the plasma lipoperoxide levels decreased significantly ($p < 0.05$) during anaesthesia.

It is suggested from our studies that plasma vitamin E levels decrease and plasma lipoperoxide levels increase during anaesthesia and surgery in infants; however, those levels are unchanged in neonates.

Vitamin E is an antioxidant that diminishes the peroxidation of poly-unsaturated lipids by scavenging free radicals. It is also an important structural component of biological membranes, contributing to their stability.^{1,2}

Several studies have reported that neonates are deficient in plasma vitamin E.^{1,2} Neonates undergoing surgical operations may be at risk of developing vitamin E deficiency during operation. However, there are no reports about the changes of plasma vitamin E levels in paediatric surgical patients. Therefore this study was designed to compare the plasma levels of vitamin E and lipoperoxide, produced by the peroxidation of poly-unsaturated lipids, preoperatively and post-operatively in paediatric surgical patients. The effect of intramuscular and oral administration of vitamin E was also compared in different age groups.

Methods

We studied seventeen neonates who were less than ten days old, 25 infants ranging in age from one month to one year, and ten children between one and five years. The operations performed were: 14 neonates had abdominal surgery and three under-

Key words

ANAESTHESIA: paediatric; METABOLISM: vitamin E, lipoperoxide.

From the Departments of Anaesthesia and Pediatric Surgery, Kobe University School of Medicine, Kobe, Japan and Department of Pediatric Surgery, Takatsuki Hospital, Takatsuki City, Osaka, Japan

Address correspondence to: Dr. Hidefumi Obara, Department of Anaesthesia, Kobe University School of Medicine, Kusunoki-cho 7, Chuo-ku, Kobe, Japan 650.

went thoracotomies for a trachea-esophageal fistulae, eighteen infants had abdominal surgery, and five had neurosurgery for either hydrocephalus or spina bifida; seven children had abdominal surgery and three had neurosurgery for hydrocephalus.

Informed consent was obtained at the preoperative visit from the parents.

The seventeen neonates were randomly divided into two groups: seven who received 30 mg·kg⁻¹ of α -tocopheryl acetate (Eizai Inc., Tokyo, Japan) intramuscularly three hours prior to anaesthesia (treated group) and ten who did not (untreated group).

The twenty infants were divided as follows: Group 1: eight infants who did not receive vitamin E prior to anaesthesia; Group 2: six who received 30 mg·kg⁻¹ to α -tocopheryl acetate orally for three days prior to anaesthesia; Group 3: six who received 30 mg·kg⁻¹ of α -tocopheryl acetate intramuscularly three hours prior to anaesthesia.

All patients received 0.02 mg·kg⁻¹ of atropine intramuscularly 30 minutes prior to anaesthesia. The neonates were intubated after 0.1 mg·kg⁻¹ of pancuronium was given intravenously. The infants and children were induced with nitrous oxide (4 L/min), oxygen (2 L/min), and halothane (in gradually increasing concentrations up to two per cent). Immediately after the onset of sleep, patients were intubated after 0.1 mg·kg⁻¹ of pancuronium was given intravenously. Anaesthesia was maintained with 40 per cent oxygen, 60 per cent nitrous oxide and pancuronium in the neonates and with 40 per cent oxygen, 60 per cent nitrous oxide, pancuronium, and 0.5 to one per cent halothane in the infants and children.

During anaesthesia all patients received an intravenous solution, consisting of 45 mEq Na, 35 mEq Cl and 2.5 per cent glucose in a 500 ml solution at a rate of 10–15 ml·kg⁻¹·hr⁻¹. In neonates blood loss was estimated by weighing sponges and replaced by a similar volume of parents' blood.

Arterial blood samples for determining plasma levels of vitamin E and lipoperoxide were obtained from a femoral artery just after induction of anaesthesia and this was repeated following surgery. A radial artery catheter was used routinely for measuring the arterial blood pressure during anaesthesia. Blood samples were immediately centrifuged and frozen for storage until analysis.

TABLE I Body weight/duration of anaesthesia

	Body weight (kg)	Duration of anaesthesia (hours)
Neonate (n = 17)	3.1 $\pm$ 0.53	2.98 $\pm$ 0.36
Infant (n = 20)	6.5 $\pm$ 0.9	3.85 $\pm$ 0.32
Children (n = 10)	12.7 $\pm$ 1.4	3.47 $\pm$ 0.54

Mean $\pm$ S.E.

Neonate: Within ten days after birth.

Infant: Age one to 12 months.

Children: Age one to five years.

Plasma vitamin E (total tocopherol) and lipoperoxide concentrations were measured by high pressure liquid chromatography (Jasco FLC-120, Tokyo, Japan)⁴ and the spectrophotofluorometric methods.⁵

Statistical analysis was performed using analysis of variance, the paired Student's t-test and the unpaired Student's t-test to compare data within individual groups and between groups.⁶

Results

Table I shows the mean body weight and duration of anaesthesia for the neonates, infants and children studied. There was no significant difference in the mean body weight and duration of anaesthesia among the subgroups. Table II shows the mean plasma vitamin E and lipoperoxide levels in all patients before and following surgery. The figure

FIGURE The mean preoperative vitamin E levels in neonates, infants and children (Mean $\pm$ S.E.). $\otimes$ shows the mean plasma vitamin E levels in the neonates who received intramuscular vitamin E before anaesthesia.

* $\times$ indicate significant differences as compared to the level in the untreated neonates.

TABLE II Plasma Vitamin E and lipoperoxide levels

	Vitamin E ($\mu\text{g}\cdot\text{ml}^{-1}$)		Lipoperoxide ($\text{n mol}\cdot\text{ml}^{-1}$)	
	preop.	postop.	preop.	postop.
Neonates				
Vit E untreated (n = 10)	3.4 $\pm$ 0.71	3.3 $\pm$ 0.41	1.5 $\pm$ 0.5	3.6 $\pm$ 1.5
Vit E treated (n = 7)	7.4 $\pm$ 2.0	10.4 $\pm$ 2.1*	2.3 $\pm$ 1.0	2.5 $\pm$ 0.6
Infants				
Group 1 (control, n = 8)	9.7 $\pm$ 3.5	7.7 $\pm$ 3.7*	1.6 $\pm$ 1.6	4.4 $\pm$ 3.7*
Group 2 (Vit E treated orally, n = 6)	16.0 $\pm$ 2.0	14.7 $\pm$ 2.2*	0.46 $\pm$ 0.23	0.23 $\pm$ 0.17
Group 3 (Vit E treated im. n = 6)	11.9 $\pm$ 1.1	15.6 $\pm$ 0.5*	1.9 $\pm$ 0.8	0.56 $\pm$ 0.27
Children (n = 10)	9.7 $\pm$ 0.72	10.0 $\pm$ 0.8	4.4 $\pm$ 3.3	1.5 $\pm$ 0.8*

Mean $\pm$ S.E.

*p < 0.05, compared to preoperative level.

summarizes the preoperative vitamin E levels. The plasma levels of vitamin E and lipoperoxide in neonates who were not treated with intramuscular α -tocopheryl acetate showed only slight changes. In those who received intramuscular α -tocopheryl acetate, the mean plasma vitamin E levels increased significantly following surgery.

Table II shows the plasma levels of vitamin E and lipoperoxide which were found in the three subgroups of infants. In Group 1 the mean plasma vitamin E decreased significantly following surgery, while the mean plasma lipoperoxide levels increased significantly. In Group 2, the plasma vitamin E levels were high before surgery and decreased significantly following surgery. Plasma lipoperoxide levels remained low. In Group 3, the plasma vitamin E levels before surgery were similar to those observed in Group 1. However, these levels increased significantly following surgery.

In the children the plasma vitamin E levels were unchanged following surgery while the lipoperoxide levels decreased significantly.

Discussion

Vitamin E includes eight different tocopherol compounds. An α -tocopheryl has the greatest biological activity and constitutes about 90 per cent of the total tocopherol in animal tissue.² One of the important functions of vitamin E is that of an antioxidant. According to the antioxidant theory,^{7,8} poly-unsaturated lipids in animal tissue are continuously under the attack of free radicals produced in metabolic reactions. Vitamin E prevents the

formation of toxic oxidation metabolites, such as lipid-peroxides formed from the unsaturated fatty acids, by scavenging free radicals.^{9,10} Vitamin E, by scavenging lipid peroxides, prevents the reaction process associated with lipid peroxidation. In vitamin E deficiency this is uncontrolled, leading to the inactivation of enzymes and damaging of cell membranes, for example haemolysis of red blood cells.

Some studies^{2,9} indicate that vitamin E plays an important role as a structural component of biological membranes with high levels of poly-unsaturated fatty acids. These membranes require large amounts of vitamin E to stabilize them. The methyl groups of tocopherol interact with the cis double bonds of the fatty acids to form a stable complex in membrane phospholipids.⁹

The neonates had the lowest vitamin E levels (figure). Several studies² have reported that plasma vitamin E levels in neonates are lower than the corresponding maternal levels. These findings suggest that neonates may be in a vitamin E deficiency state, which is attributable to several factors such as a limited tissue storage at birth and a dietary deficiency.

Experimental and clinical studies^{1,2} have shown that vitamin E deficiency affects the reproductive, muscular, cardiovascular and haematopoietic systems. Vitamin E deficiency also potentiates oxygen-induced damage to the lungs, red blood cells and central nervous system. It is possible that these damages may be decreased by vitamin E treatment.

Oski *et al.*¹¹ noted that haemolytic anaemia of

premature infants was induced by low plasma vitamin E levels, and corrected by the administration of vitamin E. In our study we have shown that neonates undergoing surgical operations had low levels of vitamin E before surgery and that this level decreased further during anaesthesia. Therefore we examined the effectiveness of vitamin E administration prior to surgery.

Mino *et al.*² examined the relation between the H₂O₂ hemolysis test and plasma tocopherol levels. They showed that more than 85 per cent of infants with haemolysis had plasma vitamin E levels of less than 450 µg·dl⁻¹. They suggested that haemolysis was more directly related to the tocopherol level in red blood cells than in plasma, and that the tocopherol content of red blood cells was closely related to the tocopherol-lipid ratio in plasma and not to the tocopherol plasma level only. Gross¹³ also reported that the intramuscular administration of α-tocopheryl suppressed an increase in serum bilirubin which occurred during the first week of life of preterm infants weighing less than 1500 g.

It has been shown in clinical studies^{12,14} that the plasma tocopherol levels are related to the total plasma lipid levels, as well as the other plasma lipid fractions such as cholesterol, triglycerides and phospholipids. These studies recommend the use of the tocopherol:total lipid ratio as a determinant of nutritional adequacy. However, the peroxide haemolysis tests are dependent on the plasma vitamin E level and do not take into account the plasma lipid levels. The function of the haematopoietic system appears to be largely dependent on vitamin E plasma levels, and haematological abnormalities due to vitamin E deficiency may be responsive to an increase in the plasma level of vitamin E. However, further studies concerning these speculations are necessary.

In addition to protecting red blood cells from haemolysis, vitamin E is involved in other aspects of the haematopoietic system, such as neutrophils and platelets. In animal studies vitamin E deficiency has decreased chemotactic and phagocytic activities of polymorphonuclear neutrophils.¹⁵ In terms of platelet function, vitamin E deficiency has resulted in thrombocytosis and a hyperaggregability.^{3,16} Some studies on platelets containing a relatively high tocopherol content showed that vitamin E administration decreased the platelet count and inhibited platelet aggregation.

Some studies have suggested that early administration of vitamin E might reduce the incidence or severity of broncho-pulmonary dysplasia^{18,19} and retrolental fibroplasia (RLF),^{20,21} which result from excessive exposure to oxygen. Hittner *et al.* reported that oral administration of 100 mg/kg/day of vitamin E suppressed the development of severe forms of RLF in low-birth-weight infants weighing less than 1500 g.

In our study, the plasma levels of vitamin E in Group 1 infants decreased significantly and the plasma lipoperoxide levels increased. Several explanations for the reduction of the plasma vitamin E levels during anaesthesia and surgery may be proposed. PaO₂ in the infants was elevated during anaesthesia, generally to more than 150 mmHg. Therefore plasma vitamin E was consumed as an antioxidant. Another possible explanation is that vitamin E was consumed by halothane free radicals, which were produced in the liver during the metabolism of halothane^{22,23} and lipoperoxides were thus secreted into the plasma. However, in the group of children the plasma vitamin E levels did not decrease in spite of the same form of anaesthesia. We cannot explain, on the basis of the present data, the difference in plasma vitamin E levels following anaesthesia between infants and children.

The side effects of vitamin E therapy have been reported in human subjects and experimental animals, especially those resulting from high-dose vitamin E therapy, such as coagulopathy,²⁴ impaired wound healing²⁵ and hepatic impairment.²⁶ Animal studies²⁴ showed that a large dose of vitamin E reduced intestinal absorption of vitamin A and K, resulting in prolonged prothrombin time. Recently Sobel *et al.*²⁷ suggested that a higher incidence of necrotizing enterocolitis was observed in vitamin E treated infants than in untreated infants. However Finer *et al.*²⁸ did not observe an increased incidence of necrotizing enterocolitis in neonates receiving vitamin E. They also reported that vitamin E administration reduced the early mortality for neonates weighing less than 1500 g and receiving vitamin E. We did not observe side effects of vitamin E administration in our surgical patients; however, Phelps²⁹ has discussed the possible risk of vitamin E supplementation in neonate, according to the current clinical and experimental studies. Therefore further clinical and experimental studies are needed to establish

whether or not vitamin E should be given in paediatric surgical patients with low plasma levels, or to prevent further decreases during anaesthesia.

References

- 1 Bieri JG, Corash L, Hubbard VS. Medical uses of vitamin E. *N Engl J Med* 1983; 308: 1063-71.
- 2 Ehrenkranz RA. Vitamin E and the neonate. *Am J Dis Child* 1980; 134: 1157-66.
- 3 Bieri JG, Farrell PM. Vitamin E. *Vitam Horm* 1976; 34: 31-75.
- 4 Ishibayashi K, Abe K, Ohmae M, Kawabe K, Katsui G. Determination of tocopherol in red blood cells by high-speed liquid chromatography. *Vitamin (Tokyo)* 1977; 51: 415-22.
- 5 Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by thiobarbituric acid reaction. *Anal Biochem* 1979; 95: 351-8.
- 6 Wallenstein S, Zucker CL, Fleiss JL. Some statistical methods useful in circulation research. *Circ Res* 1980; 47: 1-9.
- 7 Green J. Vitamin E and the biological antioxidant theory. *Ann NY Acad Sci* 1972; 203: 29-44.
- 8 Tappel AL. Lipid peroxidation damage to cell components. *Federation Proc* 1973; 32: 1870-4.
- 9 Lucy JA. Functional and structural aspects of biological membranes: a suggested structural role for vitamin E in the control of membrane permeability and stability. *Ann NY Acad Sci* 1973; 32: 4-28.
- 10 Demopoulos HB. Control of free radicals in biologic system. *Fed Proc* 1973; 32: 1903-8.
- 11 Oski FA, Barness LA. Vitamin E deficiency: a previously unrecognized cause of hemolytic anemia in the premature infant. *J Pediatr* 1967; 70: 211-20.
- 12 Mino M, Nakagawa S, Tamai H, Miki M. Clinical evaluation of red blood cell tocopherol. *Ann NY Acad Sci* 1982; 393: 175-8.
- 13 Gross SJ. Vitamin E and neonatal bilirubinemia. *Pediatrics* 1979; 64: 321-3.
- 14 Horwitt MK, Harvey CC, Dahm CH, Searcy MT. Relationship between tocopherol and serum lipid levels for determination of nutritional adequacy. *Ann NY Acad Sci* 1982; 393: 223-36.
- 15 Boxer LA, Harris RE, Bachner RL. Regulation of membrane peroxidation in health and disease. *Pediatrics* 1979; 64: 713-8.
- 16 Lake AM, Stuart MJ, Oski FA. Vitamin E deficiency and enhanced platelet function: reversal following E supplementation. *J Pediatr* 1977; 90: 722-5.
- 17 Fong JSC. Alpha-tocopherol: its inhibition on human platelet aggregation. *Experimentia* 1976; 32: 639-41.
- 18 Erenkranz RA, Ablow RC, Warchaw JB. Effect of vitamin E on the development of oxygen-induced lung injury in neonates. *Ann NY Acad Sci* 1982; 393: 452-65.
- 19 Farrell PM, Mischler EH, Gutcher GR. Evaluation of vitamin E deficiency in children with lung disease. *Ann NY Acad Sci* 1982; 393: 96-108.
- 20 Hittner HM, Speer ME, Rudolph AJ, et al. Retro-lental fibroplasia and vitamin E in the preterm infant - comparison of oral versus intramuscular administration. *Pediatrics* 1984; 73: 238-49.
- 21 Finer NN, Schindler RF, Peter KL, Grant GD. Vitamin E and retrolental fibroplasia. Improved visual outcome with early vitamin E. *Ophthalmology* 1983; 90: 428-35.
- 22 Brown BR. Hepatic microsomal lipoperoxidation and inhalation anesthetics. *Anesthesiology* 1972; 36: 458-65.
- 23 Sharp JH, Trudell JR, Cohen EN. Volatile metabolites and decomposition products of the halothane in man. *Anesthesiology* 1979; 50: 2-8.
- 24 Corrigan JJ, Marcus FI. Coagulopathy associated with vitamin E ingestion. *JAMA* 1974; 230: 1300-1.
- 25 Ehrlich HP, Tarver H, Hunt TK. Inhibitory effects of vitamin E on collagen synthesis and wound repair. *Ann Surg* 1972; 175: 235-40.
- 26 Phelps DL. Toxicity of pharmacologic parenteral doses of vitamin E in the neonatal kitten. *Pediatr Res* 1979; 13: 372.
- 27 Sobel S, Gueriguian J, Troendl G, Nevius E. Vitamin E in retrolental fibroplasia. *N Engl J Med* 1982; 306: 867.
- 28 Finer NN, Peter KL, Hayek Z, Merkel CL. Vitamin E and necrotizing enterocolitis. *Pediatrics* 1984; 73: 387-93.
- 29 Phelps DL. Vitamin E and retrolental fibroplasia in 1982. *Pediatrics* 1982; 70: 420-5.

Résumé

On a mesuré le niveau plasmatique de la vitamine E (tocophérol total) et du lipoperoxide chez 17 nouveau-nés (<10 jours), 20 nourrissons (1–12 mois) et dix enfants (un à cinq ans) pendant l'anesthésie.

Les 17 nouveau-nés ont été divisés au hasard en deux groupes; sept ont reçu $30 \text{ mg} \cdot \text{kg}^{-1}$ de α -tocophéryl acétate par voie intramusculaire avant l'anesthésie et dix n'en ont pas reçu. Les 20 nourrissons ont été divisés en trois groupes: groupe 1: huit nourrissons qui n'ont pas reçu de vitamine E; groupe 2: six qui ont reçu $30 \text{ mg} \cdot \text{kg}^{-1}$ de α -tocophéryl acétate par voie orale avant l'anesthésie; groupe 3: six au ont reçu $30 \text{ mg} \cdot \text{kg}^{-1}$ de α -tocophéryl acétate par voie intramusculaire avant l'anesthésie.

Chez les nouveau-nés et le groupe 1 des nourrissons qui n'ont pas reçu de α -tocophéryl acétate, le niveau plasmatique de la vitamine E a diminué après la chirurgie et le niveau plasmatique du lipoperoxide a augmenté.

Tant chez les groupe de nouveau-nés ayant reçu la vitamine E que chez le groupe 3 des nourrissons, le niveau plasmatique moyen de la vitamine E a augmenté significativement ($p < 0.05$) après la chirurgie. Pour le groupe 2 des nourrissons, le niveau plasmatique de la vitamine E avant la chirurgie était élevé, comparativement aux autres groupes; cependant le niveau plasmatique de la vitamine E a diminué après la chirurgie.

Chez les enfants, le niveau plasmatique de la vitamine E a augmenté significativement et le niveau plasmatique du lipoperoxide a diminué significativement ($p < 0.05$) pendant l'anesthésie.

Il ressort de nos études que le niveau plasmatique de la vitamine E diminue et le niveau plasmatique du lipoperoxide augmente pendant l'anesthésie et la chirurgie, spécialement chez les nouveaux-nés et les nourrissons.