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Effects of Vitamin C and E Combination on Element and Oxidative Stress Levels in the Blood of Operative Patients Under Desflurane Anesthesia

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Abstract We investigated effects of vitamin C and E (VCE) administration on desflurane-induced oxidative toxicity and element changes in the blood of operative patients under desflurane general anesthesia. Forty American Society of Anesthesiologists I or II Physical Status adult patients were scheduled for elective surgery. The patients were randomly divided into two groups. Control and VCE group was introduced to anesthesia with desflurane. VCE was administreted to patients in the control and VCE group before 1 hour of anesthesia with desflurane. Baseline (preoperative) and postoperative (at the 1st, the 24th, and 72th h), blood samples were taken from the first and second groups. Erythrocyte and plasma lipid peroxidation levels at the 1st, 24th, and 72th hours were higher in the control than in baseline group, although their levels at the same periods were lower in the VCE group than in the control. Vitamin E levels at the postoperative 1st and 24th hours and erythrocyte glutathione peroxidase (GSH-Px) activity at the postoperative 1st, 24th, and 72th hours was lower than in baseline values. Erythrocyte GSH-Px activity and plasma vitamins A, C, and E levels at the postoperative 1st, 24th, and 72th hours were higher in the VCE group than in the control group. Erythrocyte and plasma reduced glutathione, plasma β-carotene, and serum copper, while zinc, selenium, aluminum, iron, magnesium, and calcium levels did not differ between preoperative and postoperative periods in both groups. In

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conclusion, VCE combination prevented the desflurane-induced vitamin E and GSH-Px consumptions to strengthen the antioxidant levels in the blood of operative patients.

Keywords Element · Desflurane · Antioxidant · Free radicals · Ischemia–reperfusion injury · Vitamins C and E

Abbreviations

CAT	catalase
GSH	reduced glutathione
GSH-Px	glutathione peroxidase
Hb	hemoglobin
I/R	ischemia-reperfusion
LP	lipid peroxidation
MDA	malondialdehyde
ROS	reactive oxygen species
SOD	superoxide dismutase
VCE	vitamin C and E

Introduction

The human body is equipped with a complete arsenal of defenses against external and internal aggressions such as reactive oxygen species (ROS). The concentrations of ROS are kept under strict control by the activity of a complex defense system including enzymes and nonenzymatic species such as vitamins C and E (VCE) [1]. Vitamin C scavenges ROS in the aqueous part of the cell, e.g., the cytoplasm, whereas vitamin E is the major scavenger of ROS in the lipid phase of cell membranes [2, 3]. Elements have been shown to have protective effects against volatile anesthetic-induced oxidative stress injury as cofactors of several enzyme antioxidant systems [4, 5]. For example, zinc plays critical role in the biological membrane stabilization, protein synthesis, and nucleic acid metabolism and growth of normal tissue and as a cofactor of several enzyme systems [6]. The antioxidant role of zinc and copper is mainly due to the presence of Cu–Zn superoxide dismutase (SOD) enzyme [2, 3]. Selenium is an essential trace element for human health [7, 8]. Selenium is also a cofactor for glutathione peroxidase (GSH-Px), an important antioxidant enzyme for removing lipid hydroperoxides and hydrogen peroxide [7, 8]. Catalase contains also zinc and copper as cofactors. It catalyzes also reduction of hydrogen peroxide to water [3]. Magnesium provides the stabilization of DNA, RNA, ribosomes, and activates approximately 300 enzymes including those in energy metabolism and ROS production [9]. Calcium ion has a basic function in neurotransmitter secretion, and magnesium blocks the entrance of calcium ion into cells [10, 11]. Zinc, copper, and selenium as cofactors of antioxidant enzymes are also essential for inhibition of free radical production related to volatile anesthetics [12–15]. However, whether VCE supplementation modulates volatile anesthetics-induced element, lipid peroxidation (LP), and antioxidant changes under general anesthesia is currently unknown and therefore warranted further study forming the basis of this study.

Ischemia (I) and subsequent reperfusion (R), depending on their duration, cause tissue damage called I/R injury that leads to massive accumulation of calcium ion in ischemic tissue and neutrophil infiltration into reperfusion vessels [16]. Inhalation of volatile anaesthetics during mechanical ventilation can augment gene expression of proinflamma-

tory cytokines in the pulmonary system and kupffer cells [16, 17] Previous studies in animals suggested that exposure to volatile anesthetics can active leukocytes or alveolar macrophages, which, in turn, release inflammatory mediators and ROS [14, 15]. The volatile anesthesia induces an I/R injury and is a complex phenomenon resulting production of ROS [5]. This release of inflammatory mediators, I/R injury, and ROS has been clearly demonstrated in generalized inflammatory reactions involving the production of leukocytes.

Volatile agents are frequently used in general anesthesia practice without complications. There are only limited clinical trials of desflurane on oxidative stress and antioxidant systems [18]. In a recent study, we observed that desflurane produced lipid peroxidation (LP) by decreasing vitamin E level. In this study, we aimed to investigate effect of the new volatile anesthetic agent's (desflurane) oxidant property on element, LP, and antioxidative response (as measured by GSH-Px, GSH, β-carotene, and vitamins A, C, and E).

Subjects and Methods

Subjects

The study was performed in the Department of Anaesthesia and Reanimation, Medical Faculty, Suleyman Demirel University. Antioxidant and oxidative stress analyses were performed in the Departments of Biophysics, Medical Faculty, Suleyman Demirel University, and element analyses were performed in the Department of Chemistry, Science Institute, Balıkesir University, Turkey. After obtaining approval of the Suleyman Demirel University Ethical Committee and written informed consent, 40 American Society of Anesthesiologists (ASA) physical status I–II patients aged 33–68 years who were scheduled to undergo elective surgery under general anesthesia were included in the study. Exclusion criteria were malignant or chronic inflammatory diseases, diabetes mellitus, renal dysfunction, autoimmune disease, concurrent medication with anti-inflammatory, immune-suppressant agents and antioxidant agents, or a history of allergy to desflurane.

Anesthesia

All patients were assessed preoperatively; premedication was performed with oral diazepam 5 mg (Diazem tb; Deva, Istanbul, Turkey) and 40 mg famotidine (Famodin tb; İlsan, Istanbul, Turkey) for each patient 1 h before operation. At the arrival to operating room, patients from both groups were attached to standard monitoring device (Datex–Ohmeda Cardiocap/5, Louisville, KY), measuring heart rate, noninvasive blood pressure, peripheral oxygen saturation, electrocardiogram, and end-tidal partial pressure of carbon dioxide. Anesthesia has been induced by 1 $\mu g\ kg^{-1}$ fentanyl, 2.5 $mg\ kg^{-1}$ propofol, and 0.1 $mg\ kg^{-1}$ vecuronium and maintained with 6% desflurane in a 50% mixture of nitrous oxide and oxygen.

Study Groups

The patients were randomly divided into two groups.

Control group In this group, no vitamin supplementation was performed to patients. The venous blood samples were collected preoperatively and also postoperatively at the 1^{st}, the 24^{th}, and 72^{th} hours of desflurane exposure.

Treatment group Venous blood samples were collected preoperatively as baseline values and following single-dose administration of intravenous vitamin C (500 mg, Radoxan; Roche, Istanbul, Turkey) and vitamin E (100 IU; Evigen, Istanbul, Turkey) 1 h preoperatively. Similar to control group, venous blood samples were also collected postoperatively at the 1st, 24th, and 72th hours of desflurane exposure.

Blood Collection and Preparation

Blood anticoagulant (2 ml; EDTA) and 2 ml blood without anticoagulant were taken preoperatively and postoperatively at 1st, 24th, and 72th hours from the antecubital vein, into tubes, protected against light after an overnight fast. The anticoagulated blood was separated into plasma and erythrocytes by centrifugation at 1,500× *g* for 10 min at +4°C. Erythrocytes samples were washed three times in cold isotonic saline (0.9%, v/w), then hemolyzed with a ninefold volume of phosphate buffer (pH 7.4 and 50 mM). Serum was obtained from blood without anticoagulant.

The hemolyzed erythrocytes, plasma, and serum were stored at −30°C for <3 months pending on measurement of element, LP, and antioxidants.

LP Level Determinations

LP levels in the plasma and erythrocytes samples were measured with the thiobarbituric-acid reaction by the method of Placer et al. [19]. The quantification of thiobarbituric acid reactive substances was determined by comparing the absorption to the standard curve for malondialdehyde (MDA) equivalents generated by acid catalyzed hydrolysis of 1,1,3,3-tetramethoxypropane. The values of LP in the plasma and erythrocytes were expressed as nmol/ml and μmol/hemoglobin (Hb), respectively. Although the method is not specific for LP, measurement of the thiobarbituric cid reaction is an easy and reliable method, which is used as an indicator of LP and ROS activity in biological samples.

Reduced Glutathione (GSH), GSH-Px, and Hb Assay

The GSH content of the erythrocytes was measured at 412 nm using the method of Sedlak and Lindsay [20]. GSH-Px activities of erythrocytes were measured spectrophotometrically at 37°C and 412 nm according to the method of Lawrence and Burk [21]. Hb values of erythrocytes were determined according to the cynamethemoglobin method of Cannan [22].

Plasma VCE and β-Carotene Analyses

Vitamins A (retinol) and E (α-tocopherol) were determined in the plasma samples by a modification of the method described by Desai [23] and Suzuki and Katoh [24]. Plasma samples of about 250 μl were saponified by the addition of 0.3 ml 60% (w/v in water) KOH and 2 ml of 1% (w/v in ethanol) ascorbic acid, followed by heating at 70°C for 30 min. After cooling the samples on ice, 2 ml of water and 1 ml of *n*-hexane were added and mixed with the samples and then rested for 10 min to allow phase separation. An aliquot of 0.5 ml of *n*-hexane extract was taken, and vitamin A concentrations were measured at 325 nm. Then reactants were added, and the absorbance value of hexane was measured in a spectrophotometer at 535 nm. Calibration was performed using standard solutions of all-*trans*-retinol and α-tocopherol in hexane.

The concentrations of β-carotene in plasma samples were determined according to the method of Suzuki and Katoh [24]. Two milliliters of hexane was mixed with 250 μl plasma. The concentration of β-carotene in hexane was measured at 453 nm in a spectrophotometer.

Quantification of ascorbic acid in the plasma samples was performed using the method of Jagota and Dani [25]. The absorbance of the samples was measured spectrophotometrically at 760 nm.

Copper, Zinc, Iron, Calcium, Magnesium, and Aluminum Analysis

Copper, zinc, iron, calcium, magnesium, and aluminum levels were estimated by atomic absorption spectrophotometer and the ICP-Atomic emission spectroscopy system after digestion with nitric acid and hydrogen peroxide as described in a previous study [26]. Serum samples were slowly digested with 3 ml nitric acid for 12 h. Then they were digested in microwave oven for 5–10 min. Lastly, they were cooled in room temperature for 1 h. Then, 0.5 ml hydrogen peroxide was added.

Selenium Analysis by Hydride Technique

Graphite furnace programs for serum selenium measurement are used as described in previous study [26]. Serum selenium levels were analyzed by adding 1:1 diluted hydrochloric acid to the serum sample or standard solutions, and it was followed by heating at 90°C for 20 min. Each analysis repeated three times.

Statistical Analyses

All results are expressed as means ± SD. Presence of statistical signifcances was first analzed by Kruskal–Wallis test. To determine the effect of treatment, data were analyzed using Mann–Whitney *U* test. *p*-values of less than 0.05 were regarded as significant. Data were analyzed using the SPSS statistical program (version 9.05 software; SPSS Inc. Chicago, IL).

Results

Demographic data expressed with sex, age, weight, height, and operation time are shown in Table 1. There were no statistically significant differences among the groups ($p>0.05$).

Patients were hemodynamically stable throughout the procedure and all patients completed the study.

Table 1 Demographic Characteristics of Patients with Desflurane Anesthesia and VCE Treatment (mean±SD)

	Control	VCE
Male/Female	10/10	10/10
Age (y)	57.2±16.1	56.3±8.9
Weight (kg)	74.1±11.6	72.1±12.2
Height (cm)	162.4±8.9	167.2±9.9
Operation time (min)	80.3±17.4	88.5±20.4
Anesthesia time (min)	90.0±19.0	98.5±16.5

The plasma and erythrocyte mean LP values of control and VCE groups are shown in Tables 2 and 3, respectively. The results showed that in the control group, plasma and erythrocytes LP levels at the postoperative 1st, 24th, and 72th hours were significantly ($p<0.05$) higher than the baseline (control) values. There was no statistical difference in LP values of VCE group between control and treatment groups. The plasma ($p<0.05$) and erythrocyte ($p<0.05$ and $p<0.01$) LP levels were also significantly higher in control group than the treatment group at the postoperative 1st, 24th, and 72th hours.

The mean erythrocyte GSH-Px activities in control and VCE groups are shown in Table 3. In control group, the GSH-Px activities at the postoperative 1st, 24th, and 72th hours were significantly ($p<0.05$) lower than the baseline (preoperative) values. GSH-Px activities in VCE group did not differ between preoperative and postoperative hours. The erythrocyte GSH-Px activities were also significantly ($p<0.05$ and $p<0.01$) higher in the VCE group than in control. Plasma and erythrocytes GSH values are shown in Tables 2 and 3, respectively. The GSH-Px values in control and VCE groups did not change between preoperative and postoperative hours.

The mean plasma β-carotene and vitamin A, E, and C levels of control and VCE groups are shown in Table 2. In control group, the mean plasma vitamin E levels were significantly ($p<0.05$) low at the 1st and 24th postoperative hours compared with baseline level. The plasma vitamin A ($p<0.05$), vitamin C ($p<0.01$), and vitamin E levels ($p<0.05$) were also significantly higher in the VCE group than in the control. β-Carotene levels did not change between preoperative and postoperative hours in control and VCE groups.

The mean serum copper, zinc, selenium, aluminum, iron, magnesium, and calcium levels are shown in Table 4. The serum copper, zinc, selenium, aluminum, iron, magnesium, and calcium levels were not statistically different in control and VCE groups between preoperative and postoperative periods.

Discussion

MDA is one of the end products in LP and can inactivate membrane transporters by forming intramolecular and intermolecular crosslink [2, 27]. MDA results from the breakdown of lipid peroxyl radicals and oxidizes protein molecules, and as such it is both an indicator and effector of oxidative stress [3]. To counteract the harmful effects of ROS

Table 2 Effects of Desflurane and VCE Treatment on Plasma-Reduced Glutathione (GSH), LP, Vitamins E and A, and β-carotene Levels in Patients (mean ± SD, $n=20$)

Parameters	Control (desflurane; $n=20$)				Treatment (desflurane + VCE; $n=20$)			
	0 h	1st h	24th h	72th h	0 h	1st h	24th h	72th h
LP (nmol/ml)	1.8±0.2	2.9±0.5*	2.5±0.4*	2.3±0.2*	1.8±0.5	1.8±0.2**	1.2±0.2***	1.3±0.2***
GSH (μmol/l)	0.10±0.01	0.10±0.01	0.10±0.01	0.11±0.01	0.10±0.01	0.10±0.01	0.10±0.01	0.10±0.01
Vitamin A (nmol/l)	8.1±1.6	8.2±0.8	8.2±0.8	7.8±0.5	9.1±0.5**	9.0±0.5**	8.8±0.5**	8.6±0.3**
β-Carotene (μmol/l)	2.5±0.7	2.4±0.8	2.3±0.6	2.5±0.5	1.9±0.4	2.0±0.4	1.9±0.4	1.9±0.3
Vitamin E (μmol/l)	9.8±2.3	8.8±3.6*	8.7±1.0*	9.5±1.2	10.6±2.7	9.7±1.0**	9.9±1.0**	10.9±1.2**
Vitamin C (μmol/l)	1.6±0.4	1.5±0.3	1.5±0.3	1.6±0.3	2.2±0.3***	2.1±0.3***	2.3±0.3***	2.4±0.4***

* $p<0.05$ versus 0 h in control and treatment groups

** $p<0.05$ and *** $p<0.01$ versus control at same hour

Table 3 The Effects of Desflurane and VCE Treatment on Erythrocyte GSH-Px Activity, Reduced Glutathione (GSH), and LP Levels in Patients (mean ± SD)

Parameters	Control (desflurane; n=20)				Treatment (desflurane + VCE; n=20)			
	0 h	1st h	24th h	72th h	0 h	1st h	24th h	72th h
LP (μmol/g Hb)	10.1±1.7	13.2±2.9*	11.9±1.5**	8.9±1.2***	8.4±1.6†	10.3±1.2†	8.3±1.4†	6.8±1.8†
GSH (μmol/g Hb)	4.8±0.6	4.8±0.8	5.2±1.1	5.0±0.8	4.7±0.8	5.1±1.0	4.9±0.8	4.9±0.9
GSH-Px (IU/ g Hb)	4.5±0.7	3.2±0.5*	3.3±0.4*	3.2±0.6*	5.9±0.6†	5.3±0.9††	5.3±0.9††	5.1±0.9††

* $p<0.05$ versus 0 h in control and treatment groups

[a] $p<0.05$ and [b] $p<0.01$ versus 1st h.

† $p<0.05$ and †† $p<0.01$ versus control at same hour

produced in body, defense mechanisms have evolved to detoxify or scavenge radicals and other reactive species. Reduced blood flow elicits during volatile anesthesia characterized by activation of neutrophils [27, 28]. Activated neutrophils are known to induce tissue injury through production of ROS into extracellular fluid [29]. In the present study, LP levels in plasma and erythrocytes of patients were increased by desflurane exposure. Desflurane induced-neutrophil activation and I/R injury might lead to overproduction of ROS leading to loss of biological membrane fluidity and production of LP.

I/R injury contains free radical production, polymorphonuclear leukocytes chemotaxis/degranulation, and production of proteolytic enzymes, complement components, coagulation factors, and cytokines [17, 27]. The role of neutrophils and oxidative damage in the lung and liver following lower I/R injury is well documented [28–31]. Increased alveolar fluid gene expressions for tumor necrosis factor-α, interferon-γ, interleukin-1β, and macrophage inflammatory protein-2 have been found in anesthetized rats after inhalation of volatile anesthetics [32]. However, the authors did not study anesthesia conducted with desflurane. In biological membranous structures, such as mitochondria, there is close correlation between the degree of LP and concentration of α-tocopherol [2]. It is possible that production of ROS was membrane related, probably in the endoplasmic reticulum,

Table 4 Effects of Desflurane and VCE Treatment on Serum Element Levels in Patients (mean ± SD, n=20)

Parameters	Control (desflurane; n=20)				Treatment (desflurane+ VCE; n=20)			
	0 h	1st h	24th h	72th h	0 h	1st h	24th h	72th h
Copper (μg/l)	165.6±11.4	163.5±10.3	166.1±11.8	164.5±11.5	165.6±10.4	165.7±8.8	167.3±9.5	167.1±9.9
Zinc (μg/l)	609±17	608±13	612±13	607±17	614±8	603±12	613±9	600±18
Selenium (μg/dl)	9.4±0.9	8.9±0.9	10.0±0.8	9.3±1.2	10.1±1.2	9.3±1.2	9.8±1.4	9.5±1.3
Aluminum (μg/dl)	22.4±0.4	22.1±0.7	22.4±0.5	22.5±0.4	22.3±0.6	22.4±0.3	22.3±0.9	22.3±0.3[d]
Iron (μg/l)	1121±18	1102±31	1118±24	1118±20	1115±28	1119±13	1145±37	1113±20
Magnesium (mg/dl)	4.4±0.1	4.3±0.1	4.4±0.1	4.4±0.1	4.5±0.1	4.6±0.3	4.4±0.1	4.4±0.1
Calcium (mg/dl)	10.1±0.3	10.1±0.2	10.2±0.2	10.1±0.3	10.2±0.2	9.3±1.1	9.8±1.4	9.5±1.3

especially since cytochrome P450 can convert volatile anesthetics to ROS [5]. In many diseases and toxic conditions, there often occurs membrane damage in cells that provokes LP and accelerates the disorders in membrane structure and function [1–3, 33]. When lipid peroxides accumulate to a certain level, they leak from cells into the blood and increase the LP in blood plasma and erythrocyte. The increased LP in the blood is not readily excreted in the urine, and blood level is regulated by the rates of their formation and antioxidant decomposition in the body [1–3]. In the present study, we observed that plasma vitamin E (α-tocopherol) levels were lower in the 1st and 24th hours of postoperative period than in baseline period of desflurane exposed (control) group. The decrease in the vitamin E concentration in plasma as a result of hypoxia and I/R injury may account for the increased LP levels. Desflurane is relatively a new short-acting anesthetic characterized by a rapid onset and a short duration of action, along with a quick postanesthetic recovery. Hence, vitamin E decrease was postoperatively significant at 1st and 24th hour but not in postoperatively at 72th hour. This may be related to the rapid recovery of desflurane [34]. However, plasma vitamin E levels did not decrease in VCE-administered patients of the current study. Similarly, vitamin E consumption after exposure to desflurane reported in an experimental study [13]. Nazıroğlu and Günay [15] reported that serum vitamin E levels were decreased in dogs with enflurane anesthesia during postoperative period, whereas serum LP levels increased. Liver α-tocopherol levels decreased in enflurane exposed rats, although its levels were increased by vitamin E and selenium administration [14]. Eroglu et al. [35] reported in a clinical study that serum α-tocopherol levels were decreased by desflurane. Plasma vitamin E results in the present study were confirmed by the previous experimental and clinical trials [13–15, 35].

The antioxidant enzyme system inherent in the cellular defense system is the most important defense mechanism against ROS. GSH and GSH-Px act as antioxidants and have preventive effect against extensive production of ROS by anesthetics. Effects of anesthetics on GSH-Px activities and GSH in human and animal studies are conflicting. Nazıroğlu and Günay [15] reported that halothane administration to dogs under hypoxic conditions has led to an increase in the consumption of GSH-Px and GSH in the liver tissue. De La Cruz et al. [36] found that propofol reduced GSH-Px activity in platelets in surgical patients. Allaouchiche et al. [13] reported that bronchoalveolar fluid GSH-Px activity increased during propofol exposure. They observed also decreased bronchoalveolar fluid GSH-Px activity in the patients during exposure to desflurane. In a recent study, Eroglu et al. [35] reported that GSH-Px activities did not postoperatively change in erythrocytes of desflurane anesthetized patients. In the current study, the erythrocyte GSH-Px activities in patient with desflurane anesthesia at 1st, 24th, and 72th hours were lower than in the baseline time of desflurane exposed (control) group. Erythrocyte GSH-Px activity in VCE group did not decrease between preoperative and postoperative hours. Plasma and erythrocytes GSH values did not change between preoperative and postoperative hours in the control and VCE groups. Adaptative antioxidant responses of GSH were accompanied by GSH-Px enzymatic activity up-regulation.

The plasma vitamin A, C, and E levels in plasma and GSH-Px activity in erythrocytes were increased in the patients by VCE supplementation. VCE acts as a chelator of cytosolic iron, which plays an important role in free radical chemistry [1–3]. VCE has the capacity to enhance enzymatic and nonenzymatic antioxidants such as GSH-Px, vitamin A, vitamin C, and vitamin E levels [2, 3, 8]. VCE could influence the homeostasis of lung and blood cells with an antiapoptotic and/or antioxidative activity or by interfering on the biochemical modifications of lung and blood proteins [3, 31]. These results are supported with a study that reported that supplementation with VCE protected cells exposed to enflurane in the anesthetized patients, possibly by affecting the lifetime of the ROS [1, 2].

Element levels were regulated in the body by homeostasis mechanism, and their levels were changed by long-term exposure to volatile anesthetics. Turkan et al. [4] analyzed blood of 30 anesthesia and surgery personnel who had been exposed to inhalation anesthetics for 3 years, and they observed that selenium, copper, and zinc levels were decreased in the operating room personnel compared with healthy volunteer subjects. In the current study, short-term exposure to desflurane anesthetic did not affect serum copper, zinc, selenium, aluminum, iron, magnesium, and calcium levels in control and VCE-administered groups between preoperative and postoperative periods.

In conclusion, LP, vitamin E, and GSH-Px findings in the current study supported the existence of systemic oxidative stress in patients after exposure to desflurane, although the changes have not been observed in patients treated with VCE before desflurane exposure. Further clinical trials in wider series are required to understand the role of vitamin supplementation in order to avoid the side effects of volatile anesthetic agents.

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