

Antioxidant Therapy by Oral Vitamin E and Vitamin E-Coated Dialyzer in CAPD and Haemodialysis Patients

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Received August 14, 2006; Accepted September 18, 2006.

Key words: Oxidative stress – Antioxidant defence parameters – CAPD patients – Haemodialysis patients – Plasma and erythrocyte vitamin E – Vitamin E-coated dialyzer

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Abstract: Oxidative stress, increased lipid peroxidation, and impaired function of antioxidant system may contribute to the accelerated development of atherosclerosis in chronic renal failure patients during renal replacement therapy. The aim of the study was to investigate the influence of oral vitamin E (400 mg/day) in 14 patients who underwent continuous ambulatory peritoneal dialysis (CAPD) and effects of the vitamin E-coated dialyzer in 14 haemodialysis patients on several antioxidant biochemical parameters. Six-week treatment with oral vitamin E in CAPD patients and three-month treatment using vitamin E-coated dialyzer in haemodialysis patients led to the significant decrease of plasma malondialdehyde, to the increase of plasma vitamin E and to the increase of erythrocyte vitamin E in haemodialysis patients. No significant changes of erythrocyte antioxidant enzymes – superoxide dismutase, glutathione peroxidase and catalase were found during the both types of antioxidant therapy. At the end of the third month of haemodialysis study the significant increase of erythrocyte glutathione in haemodialysis patients was found, but that value was significantly lower as normal range. Six-week interruption of the administration of oral vitamin E in CAPD patients led to the significant decrease of erythrocyte superoxide dismutase and plasma vitamin E. Ten-week interruption of the use of vitamin E-coated dialyzer led to the significant increase of plasma malondialdehyde and to the decrease of plasma and erythrocyte vitamin E in haemodialysis patients, near to the values at the beginning of the study. Our study confirmed the beneficial effect of oral administration of vitamin E and the use of vitamin E-coated dialyzer against oxidative stress in CAPD and haemodialysis patients.

Introduction

Atherosclerosis is a leading cause of morbidity and mortality in patients with end-stage renal disease including continuous ambulatory peritoneal dialysis (CAPD) and chronic haemodialysis (HD), [1, 2, 3, 4]. Increased oxidative stress and consequent oxidability of low-density lipoproteins (LDL) has been proposed as an explanation for the accelerated cardiovascular complications in chronic renal failure patients undergoing long-term renal replacement therapy [5].

Plasma and erythrocyte antioxidant defence mechanisms, enzymatic [superoxide dismutase (SOD), glutathione peroxidase (GPX), glutathione reductase (GR) and catalase (CAT), [6, 7, 8]] and nonenzymatic [erythrocyte glutathione (GSH), vitamin E [9, 10, 11, 12]] are suppressed in chronic renal failure, in CAPD and HD patients. It is proposed that reduced antioxidant defence mechanism in erythrocytes is one of the important factors leading to peroxidation in the membrane structure of the erythrocytes and thereby to haemolysis and anemia of these patients [13].

Malondialdehyde (MDA) as a product of lipid peroxidation was increased in uremic patients [1, 3, 13, 14, 15, 16, 17, 18], indicating accelerated lipid peroxidation is a consequence of multiply pathogenetic factors [15].

Alpha-tocopherol (vitamin E) is a liposoluble vitamin placed on cell membranes and its main function is to protect polyunsaturated fatty acids against oxidative aggression, thus preserving their integrity [16]. In HD patients the levels of erythrocyte vitamin E are lower than in CAPD patients or in the healthy subjects. Deficiency of erythrocyte tocopherol in HD patients could be due to an insufficiency of this vitamin transfer from plasma HDL fractions to erythrocytes, since it is known that vitamin E is transferred from serum to erythrocyte by HDL. Some other causes could influence too, such as greater consumption of that antioxidant vitamin [17, 18].

The aim of this study was the comparison of the influence of oral vitamin E in CAPD patients and of the use of vitamin E-coated dialyzer in HD patients on the markers of oxidative stress and antioxidative defence parameters in both groups of patients.

Patients and methods

Fourteen CAPD patients were investigated (12 women and 2 men, mean age was 42 ± 9 years), 5 patients suffered from chronic glomerulonephritis and 9 patients from chronic tubulointerstitial nephritis. The duration of CAPD treatment was from 4 to 72 months. CAPD schedule was 6 hourly. Four sessions of peritoneal dialysis were performed during the day. Peritoneal dialysis solution containing 1.5% glucose was used in all patients. CAPD patients were in very good condition and no clinical and laboratory signs of peritonitis were present. The value of Kt/V was 1.75 ± 0.1 . The study consisted of three periods. Each period lasted 6 weeks. In the first and the third period patients received neither vitamin E nor other antioxidant drugs. In the second period patients received orally vitamin E 400 mg/day. Investigated parameters were determined at the end of each period.

We investigated 14 HD patients in the haemodialysis study. Among them were 7 women and 7 men, mean age was 43 ± 5 years. Six patients suffered from chronic glomerulonephritis, 5 patients suffered from chronic tubulointerstitial nephritis, 2 patients from diabetic nephropathy and one from vascular nephrosclerosis. All patients underwent regular bicarbonate HD treatment 3-times for 4h/wk. The Kt/V value was 1.40 ± 0.18 . Haemodialysis study lasted 3 months. Regular HD was carried out using the vitamin E-coated regenerated cellulose hollow fiber dialyzer [Terumo Clirans CL-E15NL, Terumo Corporation, (currently Asahi Corporation), Tokyo, Japan]. Before and after of our 3-month HD study the HD were carried out using standard dialyzer Terumo Clirans 15CL-S with cellulose membrane. All investigated parameters were determined at the beginning of the study, at the end of the 3rd month of the study and 10 weeks after interruption of the use of vitamin E-coated dialyzer.

Six CAPD patients and all HD patients were treated by erythropoietin (EPO), the value of the haematocrit and haemoglobin concentration was in the range from 0.29 to 0.39 and from 93.5 to 122.8 g/l respectively, and they were supplemented

with pyridoxine (20 mg/d), folic acid (5 mg/wk) and HD patients also were supplemented with vitamin C (50 mg/d). CAPD patients were advised to maintain a protein free diet and they did not receive oral vitamin C.

Erythrocyte antioxidant enzymes (SOD, GPX and GR) were determined by spectrophotometric methods using RANSOD, RANSEL and GR kits (Randox Laboratories), [19, 20, 21] on a Cobas Mira automatic analyzer (Roche, Basel, Switzerland) and erythrocyte CAT by spectrophotometric ultraviolet method [22]. Erythrocyte GSH level was determined by the spectrophotometric method with 5,5-dithio-bis(2-nitro)benzoic acid [23]. Plasma MDA level as the thiobarbituric acid reactive substance was determined by the spectrofluorometric method [24]. Plasma and erythrocyte vitamin E levels were determined by the modified spectrofluorometric method [25, 26]. Results were analysed statistically by ARCUS QUICKSTAT BIO (Addison Wesley Longman Ltd., USA). Statistical significance between investigated parameters was performed using paired test ANOVA.

Results

The activity of erythrocyte enzymes SOD, GPX, and CAT were within or in under the lower margin of normal range during the whole study in both groups of patients (Figures 1, 2, 3). The activity of erythrocyte GR was in the normal range in HD patients. Erythrocyte GSH level in investigated HD patients was very low in comparison with the control group and the use of vitamin E-coated dialyzer led to significant increase of its value, but that was still significantly lower as the normal range (Figure 2). Plasma uric acid was in the normal range in both groups of the patients during CAPD and HD study (Figure 4). Six-week treatment with oral vitamin E (400 mg/d) in CAPD patients and 3-month treatment using a vitamin E-coated dialyzer in HD patients led to the significant decrease of plasma MDA and to the significant increase of plasma vitamin E. Concentration of erythrocyte

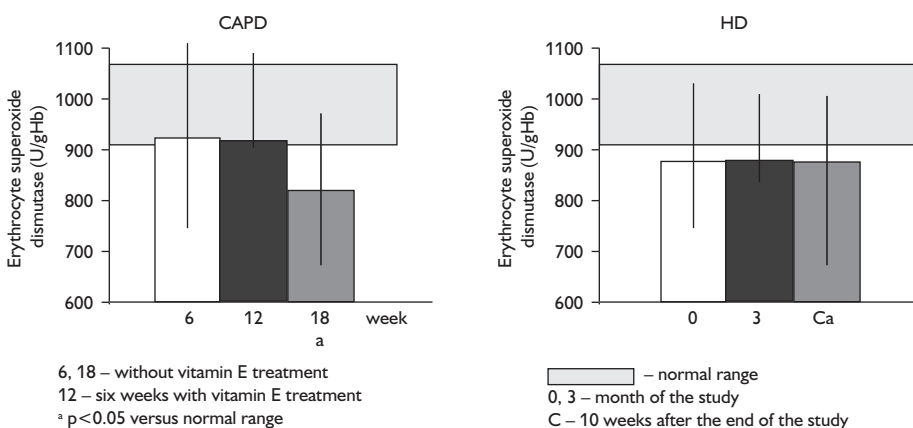


Figure 1 – Erythrocyte superoxide dismutase in CAPD and haemodialysis patients.

vitamin E in HD patients was decreased at the beginning of the study and 3-month use of vitamin E-coated dialyzer improved its value within the normal range (Figures 5, 6). Six-week interruption of the administration of oral vitamin E in CAPD patients led to the significant decrease of erythrocyte SOD and plasma vitamin E (Figures 1, 6). Ten-week interruption of the use of vitamin E-coated dialyzer led to the significant increase of plasma MDA and to the decrease of erythrocyte GSH, plasma and erythrocyte vitamin E in HD patients, near to the initial values (Figures 2, 5, 6). Except for this we found direct relationships between erythrocyte GPX and serum albumin in CAPD and HD group of patients at the beginning of the studies (Figure 7). Results are showed as a mean values \pm SD (statistical deviation).

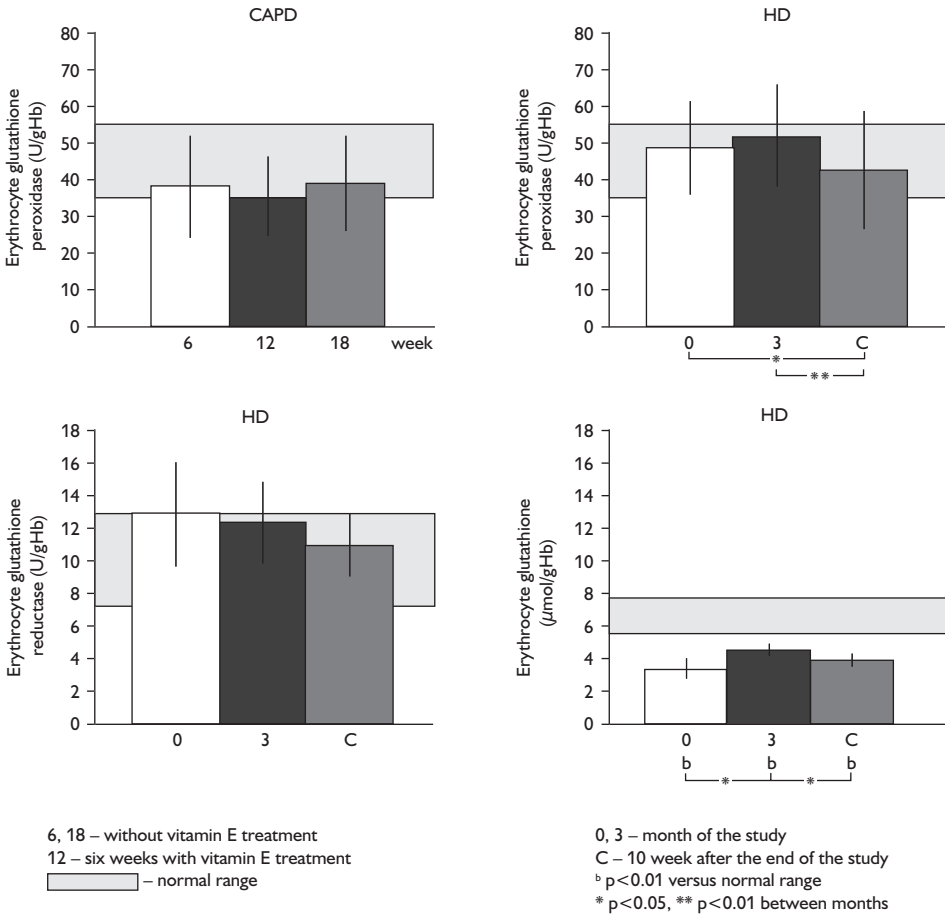


Figure 2 – Erythrocyte glutathione peroxidase in CAPD and haemodialysis patients, erythrocyte glutathione reductase and glutathione in haemodialysis patients.

Discussion

In this study we investigated the effect of orally administered vitamin E in CAPD patients and of the use of vitamin E-coated dialyzer in HD patients on the markers of oxidative stress and of antioxidative system. The activity of erythrocyte SOD in our CAPD and HD patients were in the lower margin or under the lower margin of normal range. These findings are in the agreement with the data of Zima et al [27], of Bonnefont-Rousselot et al [28], of Paul et al. [5]. Some authors reported that activity of erythrocyte GPX in CAPD patients was decreased [27, 29, 30], other increased [31] or in normal range [28]. These discrepancies in the published data about the activity of erythrocyte enzymes could be caused by: different methods used for their determination, length of CAPD and HD treatment, age of patients, use of EPO treatment [32] and other causes. In the investigated groups of patients we found the activity of erythrocyte GPX, GR and CAT within or in the lower margin of normal range, and neither oral vitamin E nor the vitamin E-coated dialyzer influenced those parameters. Albumin and GPX are the parameters of the nutritional status in patients with chronic renal failure. This fact was indirectly confirmed by the direct relationships between erythrocyte GPX and serum albumin in both groups of patients at the beginning of our studies.

The concentration of plasma MDA as a marker of lipid peroxidation in our CAPD and HD patients was increased in comparison with the normal range, oral administration of vitamin E and the use of vitamin E-coated dialyzer led to the significant decrease of MDA. The decrease of plasma MDA in CAPD patients continued in the last period without administration of oral vitamin E, probably as a result of the late effect of that vitamin. Ten-week interruption of the use of the

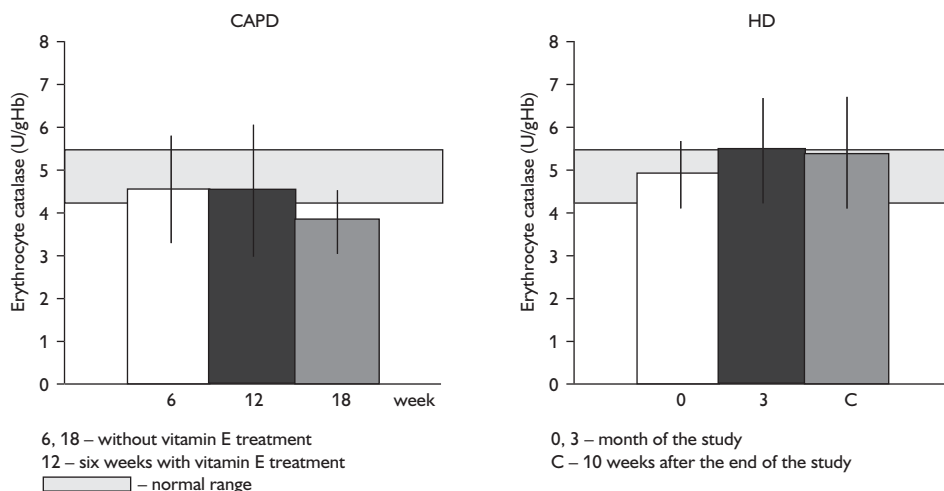


Figure 3 – Erythrocyte catalase in CAPD and in haemodialysis patients.

vitamin E-coated dialyzer led to the significant increase of plasma MDA in HD patients. Levels of GSH, which is a major cellular antioxidant, were very low in HD patients [6, 9, 10, 11, 12]. Three-month use of the vitamin E-coated dialyzer led to the gradual significant increase of erythrocyte GSH but not to normalization of its value. Our finding is similar to the data of Galli et al. [12]. Six-week short term oral administration of vitamin E to CAPD patients did not lead to the increase of

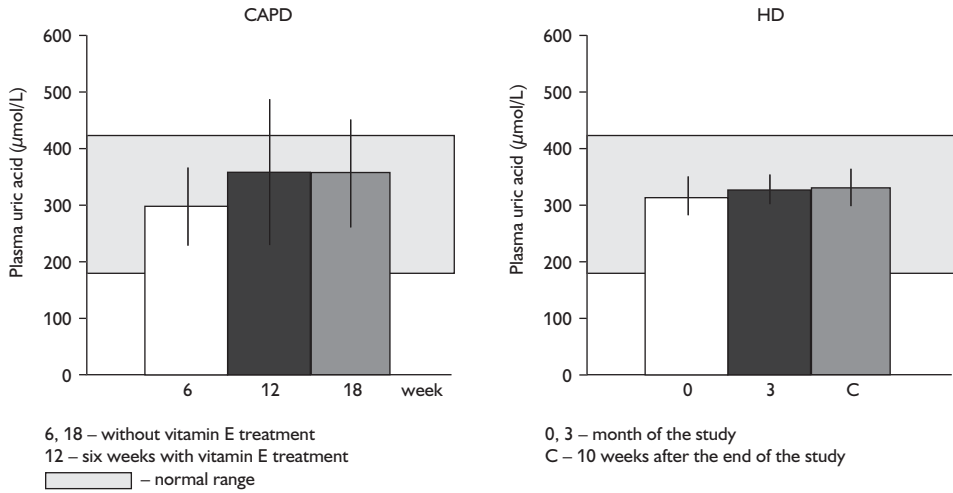


Figure 4 – Plasma uric acid in CAPD and haemodialysis patients.

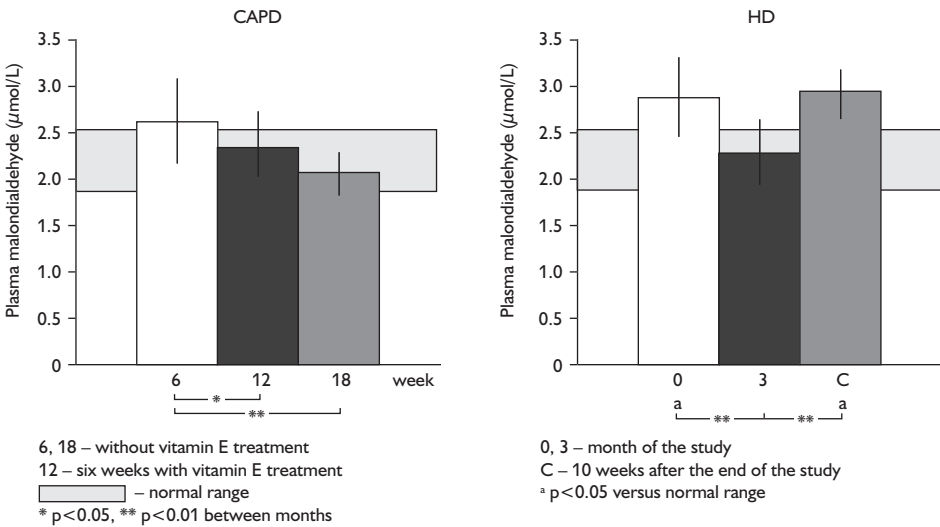


Figure 5 – Plasma malondialdehyde in CAPD and in haemodialysis patients.

enzymatic and non enzymatic markers of antioxidant defence system, with the exception of vitamin E. The erythrocyte vitamin E level was decreased in HD patients [12, 14, 16, 33], in contrast to the results of Paul et al. [5], who found its value in normal range. According to Nenov et al. [33] the long-term treatment of EPO in HD patients led to the increase of erythrocyte vitamin E level to the normal range. We were not able to confirm that finding because our HD patients were treated simultaneously with EPO, their haematocrit values and haemoglobin

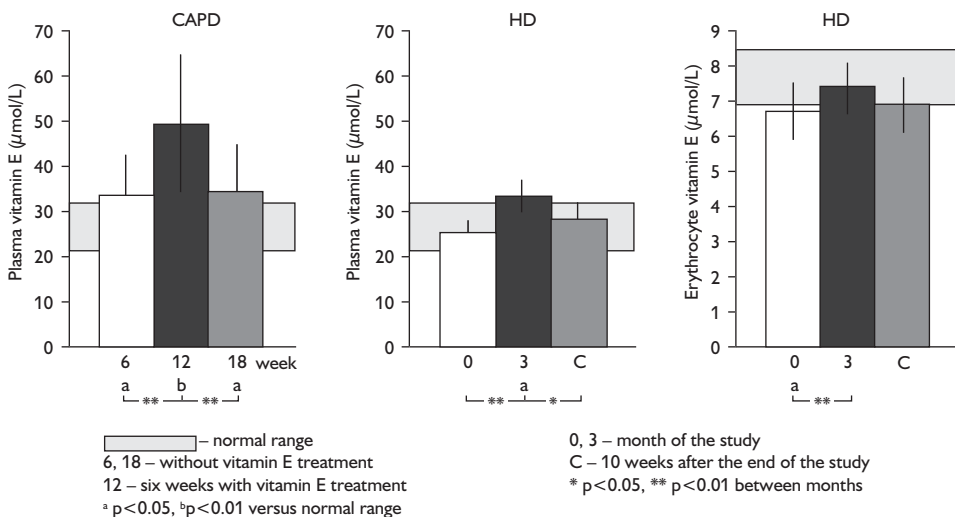


Figure 6 – Plasma vitamin E in CAPD and in haemodialysis patients, erythrocyte vitamin E in haemodialysis patients.

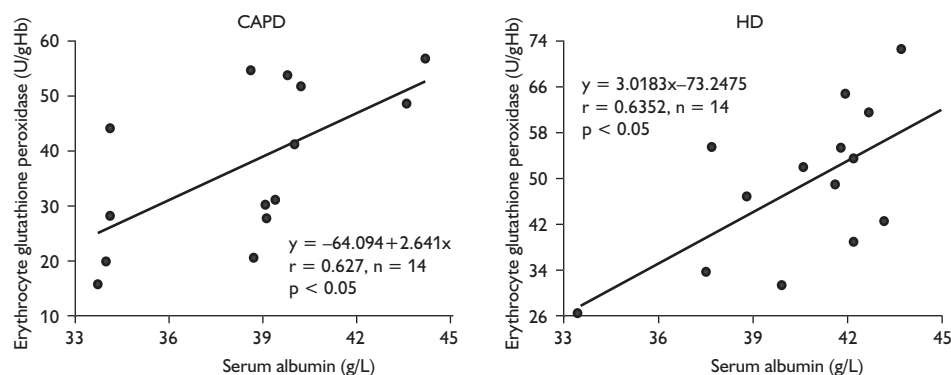


Figure 7 – Direct relationships between erythrocyte glutathione peroxidase and serum albumin in CAPD and haemodialysis patients at the beginning of the study.

concentrations reached target values and despite that the erythrocyte vitamin E was decreased significantly. Normalization of erythrocyte vitamin E was observed only after the treatment with vitamin E-coated dialyzer. The concentration of plasma and erythrocyte vitamin E increased during the use of vitamin E-coated dialyzer in HD patients, which was probably caused by in situ interaction of vitamin E with the other antioxidants present in blood or there is a partially release of the bound vitamin E into the blood during HD. The results from our study showed that orally administered vitamin E is a very important antioxidant agent for CAPD patients and also suggest the beneficial effect of vitamin E-coated dialyzer against oxidative stress in HD patients or its positive influence, at least partially, to reduce HD-related oxidative stress [12, 13, 16, 18, 34, 35, 36, 37, 38].

According to our results, supplementation by oral vitamin E (400 mg/day) or the use of vitamin E-coated dialyzer in all chronic renal failure patients during renal replacement therapy can be recommended.

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