Protection of Radiocontrast Induced Nephropathy by Vitamin E (Alpha Tocopherol): A Randomized Controlled Pilot Study

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Background: *Contrast-induced nephropathy (CIN) increases the likelihood of patient morbidity and mortality following coronary procedures. Contrast agents cause an acute deterioration in renal function via the generation of reactive oxygen species. The present study was designed to evaluate the administration of antioxidant vitamin E (alpha tocopherol) as a means of preventing CIN in these patients.*
Material and Method: *The authors conducted a prospective, double-blind, randomized and placebo-controlled trial in 103 patients with serum creatinine (SCr) levels $\geq$ 1.2 mg/dL, baseline creatinine clearance levels $\leq$ 60 mL/min, and who had undergone coronary procedures. Alpha tocopherol (525 IU) or a placebo compound was administered orally at 48 hr, 24 hr, and in the morning prior to coronary procedures.*
Results: *CIN developed in 3 of 51 patients (5.88%) in the alpha tocopherol group and 12 of 52 patients (23.08%) in the placebo group (odds ratio [OR], 0.21; 95% confidence interval [CI], 0.05 to 0.79; p = 0.02). The mean SCr increased significantly in the placebo group (from 1.67 $\pm$ 0.53 to 1.9 $\pm$ 0.87 mg/dL, p = 0.02) but not in the alpha tocopherol group (from 1.62 $\pm$ 0.44 to 1.64 $\pm$ 0.59 mg/dL, p = 0.74). Patients with diabetes, anemia, or with contrast agent dosages greater than 120 ml exhibited significantly lower incidences of CIN development in the alpha tocopherol group than the placebo group (p < 0.05).*
Conclusion: *Prophylactic oral administration of alpha tocopherol is capable of protecting against CIN in patients with chronic kidney disease undergoing elective coronary procedures.*

Keywords: *Alpha-Tocopherol, Vitamin E, Contrast induced nephropathy (CIN), Coronary procedures*

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Contrast-induced nephropathy (CIN) is a major cause of acute renal function deterioration, particularly among chronic kidney disease (CKD) patients, and contributes to prolonged hospitalizations and increased mortality and morbidity[1]. CIN occurs in 12% - 26% of patients with CKD or diabetes mellitus but is relatively rare in patients with normal renal function[2]. Risk factors for the development of CIN include pre-existing CKD, diabetes mellitus, a reduced effective circulatory volume arising from dehydration or congestive heart failure, high-dose administration of contrast agents, and the concomitant use of medication which impairs renal function[2,3].

The development of CIN probably is related to the ability of contrast agents to induce renal vasoconstriction causing ischemic injury. Hypoxia can promote further renal injury through the release of reactive oxygen species (ROS). Organ injury occurs when tissue hypoperfusion generates ROS that exceed the patient's antioxidant reserves[4]. Contrast agents also result in direct tubular toxicity. Many types of

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prophylaxis have been used in an attempt to prevent CIN. While hydration with isotonic saline or half saline before and after exposure to contrast agents is the standard practice in the prevention of CIN, however a substantial proportion of patients at risk continue to have CIN[5,6]. Other agents such as dopamine, captopril, theophylline, atrial natriuretic peptide, and calcium channel blockers are also ineffective[6,7]. Preliminary studies on the antioxidant N-acetylcysteine (NAC) as a preventative measure for CIN have yielded conflicting results[5-7].

Vitamin E is the name given to a family of eight molecules. They consist of two groups, tocopherols and tocotrienols, which contain saturated or unsaturated side chains, respectively. Vitamin E, particularly in the form of alpha tocopherol, has been proposed for the prevention or treatment of numerous health problems[8], which is primarily due to its antioxidant and anti-inflammatory properties[9,10]. Vitamin E is an antioxidant which may be effective in the treatment of CIN by scavenging oxygen free radicals that are generated as a result of renal tubular toxic damage.

In the present study, the authors conducted a prospective, randomized, double-blind placebo-controlled trial to evaluate the effects of oral vitamin E (alpha tocopherol) administration and routine intravenous isotonic saline hydration on the biochemical markers of renal function, and on the clinical development of CIN in CKD patients undergoing coronary procedures.

Material and Method

Patients

The patients had undergone clinically-driven elective coronary angiography and/or intervention at Thammasat Chalerm Prakiat Hospital during the period from January 2006 to June 2007. Approval was obtained from the Ethics Committee of the Faculty of Medicine at Thammasat University. All patients provided written, informed consent to participate in the present study. Those with serum creatinine levels $\geq$ 1.2 mg/dL and baseline creatinine clearance levels $\leq$ 60 mL/min (as measured in their most recent sample, drawn within 2 months prior to the beginning of the protocol) were included in the present study. However, patients with acute renal failure, end stage renal disease (requiring dialysis) or unstable renal function (as evidenced by a change in serum creatinine of $\geq$ 0.5 mg/dL, or $\geq$ 25%, within 14 days prior to the study) were excluded from further participation. Subjects were also excluded if they had a known allergy to any of the contrast agents, or were receiving mechanical ventilation, or suffered from congestive heart failure, cardiogenic shock or emergent angiography. Furthermore, those receiving NAC, mannitol, diuretics, theophylline, dopamine, or contrast agents within 14 days before the present study commencement were not included, as were those who used alpha tocopherol supplements on a daily basis during the week prior to the present study.

Study protocol

The present study was a prospective, randomized, double-blind, placebo-controlled trial. The patients were randomly assigned to receive either oral alpha tocopherol (525 IU) or a placebo at 48 hrs, 24 hrs and in the morning before the coronary procedures. The yellow-flavored capsule of vitamin E was purchased from Pharma-Nord, Thailand. An identical capsule was added to the placebo and patients returned all of the empty envelopes at the end of the present study to prove compliance. All subjects received isotonic (0.9%) saline at the rate of 1 mL/kg per hour for 12 hours before and 12 hours after elective coronary procedures. Variation in the hydration rates allowed for adjustments according to the clinical heart failure of individual patients. Hospital procedures mandated accurate, hourly recording of all in-hospital volume inputs for patients undergoing elective coronary interventions. All patients were encouraged to drink if they were thirsty.

Coronary intervention was performed in standard fashion, through either the radial or femoral approach by the attending interventional cardiologist. When therapeutic coronary interventions were required, the procedure was performed immediately following angiography and according to the recommendations by the attending interventional cardiologist. All procedures were performed using low-osmolar, non-ionic contrast media agent (Iopromide, Schering AG, Germany).

Venous blood samples were obtained for the measurement of complete blood count, serum blood urea nitrogen (BUN) and serum creatinine (SCr) baseline levels at 12-24 hrs prior to intervention, and then again at 48 hrs after the procedure. Creatinine clearance (CrCl) was calculated using the Cockroft-Gault equation, where CrCl = ([140 - age] x weight (kg)/ SCr (mg/dL) x 72). CrCl in women was adjusted by further multiplication by a factor of 0.85. All measurements were performed in a single, hospital-based laboratory using standard methods.

The primary end-point of this present study was the development of CIN, which was defined as an absolute increase in SCr of $\geq$ 0.5 mg/dL or a relative increase of $\geq$ 25% in SCr at 48 hrs after the coronary procedure, as compared to baseline measurements. Secondary end-points included changes in BUN, SCr and CrCl at 48 hrs after the coronary procedure, as compared to baseline levels, but also included the side effects of study medication, the requirement for dialysis, and others.

Statistical methods

Data were expressed as mean $\pm$ SD for continuous variables and as percentages for discrete variables. Demographic clinical outcome characteristics of the study groups were analyzed by the Student's t-test for continuous measurements and the X2 statistic for categorical measurements. For categorical variables with expected values less than 5, the Fisher exact test was used. Logistic regression was performed with the primary end-point of CIN as the dependent variable and the study treatment assignment as the independent variable. The influence of contrast agents on the change in BUN, SCr, and CrCl at 48 hrs after the coronary procedure in each treatment group was evaluated by means of univariate analyses of variance. Differences in BUN, SCr, and CrCl before (baseline) and 48 hrs after the coronary procedure were analyzed with the paired t-test. The effects of other significant covariates on the development of CIN in the treatment groups such as diabetes mellitus, hypertension, contrast agent dosage, age, baseline CrCl, anemia, and gender were evaluated by means of stepwise logistic regression. Secondary analyses included comparison of the absolute change in BUN, SCr and CrCl among the present study groups and of the mean baseline and follow-up BUN, SCr and CrCl within each group. All statistical tests were two-sided. Statistical analyses were performed with SPSS software (version 15.0, SPSS, Inc) and significance was assigned when p-values of $\leq$ 0.05 were obtained.

Results

Initially, 110 patients were enrolled in the present study. Five patients declined the invitation to attend, whereas another two patients experienced acute congestive heart failure overnight before coronary angiography and were excluded from the present study. Thus, a total of 103 patients (76 men and 27 women) participated. After 103 patients were randomized, 52 patients received placebo doses while the remaining 51 patients received alpha tocopherol. There were no significant differences between the alpha tocopherol group and the placebo group with respect to their clinical characteristics, underlying disease, concomitant medications, and contrast agent and intravenous volumes (Tables 1). Furthermore, baseline serum BUN, SCr and CrCl levels were not significantly different between the two groups (Table 2).

Primary end point: incidence of contrast agent-induced nephropathy (CIN)

Based on the definition of CIN outlined in the present study, CIN developed in 15 of the 103 patients overall (14.56%), with 3 of the 51 patients (5.88%) belonging to the alpha tocopherol group and 12 of the 52 patients (23.08%) in the placebo group. When compared with the placebo group, the alpha tocopherol group contained significantly lower incidences of CIN ($p = 0.02$) with a corresponding odds ratio (OR) of 0.21 (95% CI 0.05-0.79) (Table 3).

CIN developed in 23.26% of diabetic patients and 8.33% in non-diabetics. Within the diabetic subgroup, alpha tocopherol was found to significantly reduce occurrences of CIN when compared to the placebo group, from 38.09% to 9.09% ($p = 0.03$) with a corresponding OR of 0.16 (95% CI 0.03-0.89) (Table 3).

In patients who met the criteria of anemia, CIN developed in 15.38%. This condition was observed in 27.03% of these patients receiving a placebo, while only 4.88% in the alpha tocopherol group. Outstandingly, comparison with the placebo group showed that alpha tocopherol significantly reduced the incidence of CIN in anemia patients ($p = 0.01$) with a corresponding OR of 0.14 (95% CI 0.03-0.68) (Table 3).

When contrast agent dosages exceeded 120 ml, CIN occurred in 16.67% of these patients. The frequency of the occurrence was 29.63% in these patients receiving a placebo, but just 3.7% receiving alpha tocopherol group developed the condition. This reduction by alpha tocopherol was significant ($p = 0.02$) and a corresponding OR of 0.09 (95% CI 0.01-0.58) (Table 3).

In female patients, CIN occurred in 22.22% and in the hypertension subgroup contained 14.12% of patients who developed CIN. Moreover, in all patients aged over 60 years, the occurrence of CIN was 15.38%. However, there were no statistics significantly different in the incidence of CIN in these patients' subgroups between patients who received an alpha tocopherol or placebo (Table 3).

Table 1. Clinical characteristics of patients included in the present study

Characteristic	Placebo (n = 52)	Vitamin E (n = 51)	p-value
Age (yr)	65 ± 11	68 ± 9	0.06
Men: women	36:16	40:11	0.14
Systolic blood pressure (mmHg)	143 ± 29	141 ± 21	0.72
Diastolic blood pressure (mmHg)	77 ± 14	76 ± 12	0.70
Height (cm)	161 ± 10	160 ± 8	0.80
Weight (kg)	64 ± 14	66 ± 11	0.43
Body mass index (kg/m2)	25 ± 4	26 ± 4	0.17
Diabetes mellitus (%)	21 (40)	22 (43)	0.94
Hypertension (%)	40 (77)	45 (88)	0.14
Hypercholesterolemia (%)	29 (56)	28 (55)	0.93
ACEI, n (%)	15 (29)	14 (27)	0.87
ATRA, n (%)	8 (15)	9 (18)	0.76
Beta blocker, n (%)	34 (65)	27 (53)	0.20
Calcium channel blocker, n (%)	14 (27)	20 (39)	0.19
Diuretic, n (%)	13 (25)	9 (18)	0.37
Aspirin, n (%)	37 (71)	29 (57)	0.13
Statin, n (%)	24 (46)	23 (45)	0.92
Nitrate, n (%)	18 (35)	24 (47)	0.20
Contrast volume (mL)	132 ± 58	150 ± 83	0.19
IV volume (mL)	1,483 ± 453	1,591 ± 260	0.14
Hematocrit (%)	35 ± 4	35 ± 5	0.65

Table 2. Baseline, follow-up and absolute changes (from baseline) for BUN, creatinine, and creatinine clearances, and the incidence of CIN in each study groups

Characteristic	Placebo (n = 52)	Vitamin E (n = 51)	p-value
BUN (mg/dL)			
Baseline	26 ± 13	22 ± 10	0.13
Follow-up (48 hr after)	27 ± 13	22 ± 9	
Absolute change	1.66 ± 10.77	-0.69 ± 6.38	0.98
Serum creatinine (mg/dL)			
Baseline	1.67 ± 0.53	1.62 ± 0.44	0.60
Follow-up (48 hr after)	1.90 ± 0.87	1.64 ± 0.59	
Absolute change	0.23 ± 0.71	0.02 ± 0.33	0.05
Creatinine clearance (mL/min)			
Baseline	41 ± 21	42 ± 14	0.84
Follow-up (48 hr after)	40 ± 24	43 ± 16	
Absolute change	-1.03 ± 9.40	1.11 ± 7.50	0.20
Incidence of CIN (%)	12 (23.08)	3 (5.88)	0.02

Secondary end-point: change in SCr, CrCl, and other

At 48 hours following coronary procedures, serum BUN, SCr and CrCl were measured in all 103 patients. SCr levels increased significantly at this time within the placebo group (an increase from 1.67 ± 0.53 mg/dl to 1.9 ± 0.87 mg/dl; p = 0.02) (Table 2, Fig. 1A) but this was not observed for the alpha tocopherol group (a slight increase from 1.62 ± 0.44 mg/dl to 1.64 ± 0.59 mg/dl respectively, p = 0.74) (Table 2, Fig. 1B). There were no significant changes in serum BUN 48 hrs after the coronary procedure, as compared to baseline levels. In the placebo group, the mean serum BUN was 26 ± 13 mg/dl at baseline and 27 ± 13 mg/dl 48 hours later (p = 0.27). In the alpha tocopherol group, the

Table 3. Odds ratio for contrast-induced nephropathy. Each subgroup analysis shows benefit of alpha tocopherol therapy in different patient subsets

Variable	Incidence of CIN (%)		OR	95% CI	p-value
	Placebo	Vitamin E			
Chronic kidney disease	23.08	5.88	0.21	0.05-0.79	0.02
Diabetes mellitus	38.09	9.09	0.16	0.03-0.89	0.03
Hypertension	23.08	6.52	0.23	0.06-0.93	0.05
Contrast agent > 120 ml	29.63	3.70	0.09	0.01-0.58	0.02
Age > 60 yr	24.32	7.32	0.23	0.06-0.86	0.05
Age > 75 yr	40.00	13.33	0.23	0.02-2.37	0.25
Female gender	31.25	9.09	0.17	0.02-1.45	0.17
Anemia	27.03	4.88	0.14	0.03-0.68	0.01

CrCl = creatinine clearance; CIN = contrast induced nephropathy; OR = odds ratio

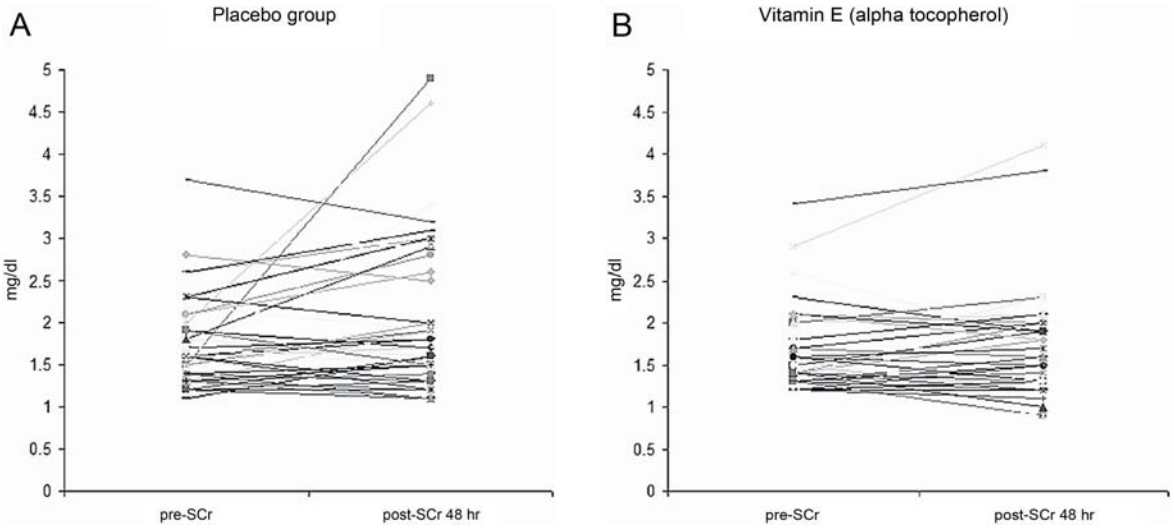

Fig. 1 Serum creatinine concentrations prior to, and 48 hr after, coronary procedures in placebo (A) and vitamin E (alpha tocopherol) (B) groups

mean serum BUN was unchanged between the two time-points (22 ± 10 mg/dl at baseline to 22 ± 9 mg/dl; p = 0.45) (Table 2). Similarly, there were no significant changes in CrCl levels at 48 hrs after the coronary procedure. In the placebo group, the mean CrCl was 41 ± 21 mL/min at baseline and 40 ± 24 mg/dl at 48 hrs (p = 0.43). The alpha tocopherol group produced mean CrCl levels of 42 ± 14 mg/dl at baseline and 43 ± 16 mg/dl at 48 hrs (p = 0.3) (Table 2).

None of the patients who developed CIN required renal replacement therapy. Two patients in the alpha tocopherol group experienced minor side effects (nausea, vomiting and abdominal discomfort) as in the placebo group on the initial day of prescription.

Discussion

The present study stands as the first clinical trial in a human population demonstrating the remarkable capability of the antioxidant vitamin E (alpha tocopherol) of assisting in the prevention of CIN. The important findings of the present study are based on prospective, double-blind, randomized, placebo-controlled trials. They provide evidence for the beneficial role (s) of prophylactic oral administration

of alpha tocopherol in reducing the incidence of CIN when used in conjunction with 0.9% saline hydration in CKD patients undergoing coronary procedures. Additionally, these advantages were observed in patients suffering from diabetes mellitus, anemia, and those receiving contrast agent dosages greater than 120 ml.

CIN pathogenesis studies have revealed that the nephropathy which follows contrast agent administration is caused by a combination of renal ischemia and direct TEC toxicity[4]. The hypoperfusion of renal tissues promote the generation of ROS to levels which exceed kidney antioxidant reserves[11]. Both increased production of ROS and reduced anti-oxidant defenses have been observed in CKD, ESRD and hemodialysis patients[12,13]. Hence, hypoxia, ROS, and inflammatory stimulation processes induce the expression of many cytokines and chemokines leading to acute kidney injuries[14]. In addition, direct toxic effect of contrast agents on renal TECs is substantiated by the histopathological changes that arise, such as TEC vacuolization with necrosis[15].

Hydration with normal saline has been found to be beneficial in preventing CIN in patients diagnosed with renal insufficiency[16]. An excellent study demonstrated that periprocedural with isotonic 0.9% saline are superior to 0.45% saline in preventing the development of CIN[17]. These evidences support using 0.9% saline to be the standard hydration in the present study. Currently, the antioxidant NAC has been implemented for the prevention of CIN following coronary procedures and evaluated using several clinical trials[18,19]. However, various studies further remind a significant heterogeneity in the NAC effect across trials[20,21]. So, controversy remains as to the definitive conclusions of such work and need a large placebo, control trial to resolve this question.

In the present study, the authors tried to explore the benefit of alternative antioxidant vitamin E to prevent CIN. Vitamin E comprises 8 different forms, namely α-, β-, γ-, and □-tocopherol and α-, β-, γ-, and □-tocotrienol[22] and is different in the bio-availability and bio-equivalence which can lead to varying effects. Alpha tocopherol possesses both antioxidant and anti-inflammatory properties, and in fact its antioxidant activity is more potent than other tocopherols due to its increased capacity to donate phenolic hydrogen electrons to lipid radicals[23].

In healthy volunteers, alpha tocopherol concentrations in plasma are approximately 22.3 μmol/L, which increased to a maximal level of 33.3 μmol/L, at approximately 12 hrs following dosage and returned to baseline levels 72 hrs after administration[24]. Besides the well-known antioxidant effects of alpha tocopherol, physiological concentrations establish as 10 μmol/L of the compound also suppresses smooth muscle cell proliferation via inhibition of protein kinase C activity, and this effect is further enhanced significantly at higher concentrations[25]. According to CKD patients, elevation of oxidative stress level has been reported in many studies and correlated with the level of renal dysfunction[26,27]. Like a mirror, increasing of vitamin E metabolites has been demonstrated from many reports in CKD patients and had some correlation with renal function[28,29]. Tocopherol administration in CKD patients particularly in ESRD result markedly increasing serum vitamin E metabolite concentration[30] and can decrease oxidative stress in dialysis patients[31]. These findings may help to support that the oral alpha tocopherol administration protocol employed in the present study could be sufficient to elevate serum alpha tocopherol metabolite concentration required for the prevention of CIN.

In diabetic patients, hyperglycemia can lead to EC dysfunction via increased oxidative stress[32,33]. As observed in hypertensive patients, there is also a reduction in the antioxidant activity[34]. Findings from many studies reported higher oxidative stress levels causing in anemia patients[35,36], but vitamin E can inhibit this process[37]. Clinical studies have reviewed that patients with underlying diabetes mellitus, hypertension, and anemia are the independent risk factor for CIN in CKD patients[7,38]. Patients with CKD who are at particular risk can reduce the incidence of CIN by antioxidant NAC administration with hydration. The same as in the present study, alpha tocopherol does significantly decrease the incidence of CIN in similar patients. This suggests that alpha tocopherol could have an equivalent antioxidant effect like NAC and may prevent CIN in CKD patients such as those included in the present study.

By the time acute kidney injury (AKI) in CIN is detected by using a SCr level, it may not be correlated with CrCl in many conditions, as in the present study. Many reports demonstrated that a SCr level is too insensitive to be useful as an indicator in clinical studies evaluating nephrotoxicity and ischemic injury. So, the authors will require a novel biomarker for detection AKI for specifics in early diagnosis and follow-up.

In conclusion, the present study has been the first exploration of the advantage of new

alternative treatment to prevent CIN. Prophylactic oral administration of the antioxidant vitamin E (alpha tocopherol) at a dose of 525 IU at 48 hrs, 24 hrs, and in the morning before coronary procedures, combined with 0.9% saline hydration, assists in the prevention CIN in CKD patients. The authors, however, still require large randomized studies to prove the superiority of alpha tocopherol in the future.

References

1. Gruberg L, Mintz GS, Mehran R, Gangas G, Lansky AJ, Kent KM, et al. The prognostic implications of further renal function deterioration within 48 h of interventional coronary procedures in patients with pre-existent chronic renal insufficiency. J Am Coll Cardiol 2000; 36: 1542-8.
2. Goldenberg I, Matetzky S. Nephropathy induced by contrast media: pathogenesis, risk factors and preventive strategies. CMAJ 2005; 172: 1461-71.
3. Barrett BJ, Parfrey PS. Clinical practice. Preventing nephropathy induced by contrast medium. N Engl J Med 2006; 354: 379-86.
4. Tumlin J, Stacul F, Adam A, Becker CR, Davidson C, Lameire N, et al. Pathophysiology of contrast-induced nephropathy. Am J Cardiol 2006; 98: 14K-20K.
5. Wong GT, Irwin MG. Contrast-induced nephropathy. Br J Anaesth 2007; 99: 474-83.
6. Stacul F, Adam A, Becker CR, Davidson C, Lameire N, McCullough PA, et al. Strategies to reduce the risk of contrast-induced nephropathy. Am J Cardiol 2006; 98: 59K-77K.
7. Pannu N, Wiebe N, Tonelli M. Prophylaxis strategies for contrast-induced nephropathy. JAMA 2006; 295: 2765-79.
8. Tucker JM, Townsend DM. Alpha-tocopherol: roles in prevention and therapy of human disease. Biomed Pharmacother 2005; 59: 380-7.
9. Singh U, Devaraj S, Jialal I. Vitamin E, oxidative stress, and inflammation. Annu Rev Nutr 2005; 25: 151-74.
10. Singh U, Jialal I. Anti-inflammatory effects of alpha-tocopherol. Ann N Y Acad Sci 2004; 1031: 195-203.
11. Persson PB, Hansell P, Liss P. Pathophysiology of contrast medium-induced nephropathy. Kidney Int 2005; 68: 14-22.
12. Andreoli SP. Reactive oxygen molecules, oxidant injury and renal disease. Pediatr Nephrol 1991; 5: 733-42.
13. Stratta P, Canavese C, Dogliani M, Mazzucco G, Monga G, Vercellone A. The role of free radicals in the progression of renal disease. Am J Kidney Dis 1991; 17: 33-7.
14. Sung FL, Zhu TY, Au-Yeung KK, Siow YL, O K. Enhanced MCP-1 expression during ischemia/reperfusion injury is mediated by oxidative stress and NF-kappaB. Kidney Int 2002; 62: 1160-70.
15. Moreau JF, Noel LH, Droz D. Proximal renal tubular vacuolization induced by iodinated contrast media, or so-called "osmotic nephrosis". Invest Radiol 1993; 28: 187-90.
16. Solomon R, Werner C, Mann D, D'Elia J, Silva P. Effects of saline, mannitol, and furosemide to prevent acute decreases in renal function induced by radiocontrast agents. N Engl J Med 1994; 331: 1416-20.
17. Mueller C, Buerkle G, Buettner HJ, Petersen J, Perruchoud AP, Eriksson U, et al. Prevention of contrast media-associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. Arch Intern Med 2002; 162: 329-36.
18. Kay J, Chow WH, Chan TM, Lo SK, Kwok OH, Yip A, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. JAMA 2003; 289: 553-8.
19. Tepel M, van der GM, Schwarzfeld C, Laufer U, Liermann D, Zidek W. Prevention of radiographic-contrast-agent-induced reductions in renal function by acetylcysteine. N Engl J Med 2000; 343: 180-4.
20. Pannu N, Manns B, Lee H, Tonelli M. Systematic review of the impact of N-acetylcysteine on contrast nephropathy. Kidney Int 2004; 65: 1366-74.
21. Bagshaw SM, Ghali WA. Acetylcysteine for prevention of contrast-induced nephropathy after intravascular angiography: a systematic review and meta-analysis. BMC Med 2004; 2: 38.
22. Kasparek S. Chemistry of tocopherols and tocotrienols. In: Machlin LJ, editor. Vitamin E: a comprehensive treasure. New York: Marcel Dekker; 1980: 7-65.
23. Kamal-Eldin A, Appelqvist LA. The chemistry and antioxidant properties of tocopherols and tocotrienols. Lipids 1996; 31: 671-701.
24. Radosavac D, Graf P, Polidori MC, Sies H, Stahl W. Tocopherol metabolites 2, 5, 7, 8-tetramethyl-2-(2'-carboxyethyl)-6-hydroxychroman (alpha-CEHC) and 2, 7, 8-trimethyl-2-(2'-carboxyethyl)-6-hydroxychroman (gamma-CEHC) in human serum

after a single dose of natural vitamin E. Eur J Nutr 2002; 41: 119-24.
25. □zer NK, Taha S, Stocker A, Azzi A. Effects of high cholesterol, vitamin E and probucol on protein kinase C activity and proliferation of smooth muscle cells. In: Packer L, Hiramatsu M, Yoshikawa T, editors. Antioxidant food supplements and human health. London: Academic Press; 1999: 73-86.
26. Pawlak K, Mysliwiec M, Pawlak D. Oxidative stress, phosphate and creatinine levels are independently associated with vascular endothelial growth factor levels in patients with chronic renal failure. Cytokine 2008; 43: 98-101.
27. Terawaki H, Yoshimura K, Hasegawa T, Matsuyama Y, Negawa T, Yamada K, et al. Oxidative stress is enhanced in correlation with renal dysfunction: examination with the redox state of albumin. Kidney Int 2004; 66: 1988-93.
28. Stein G, Richter G, Funfstuck R, Sperschneider H, Gunther K. Serum vitamin E levels in patients with chronic renal failure. Int J Artif Organs 1983; 6: 285-7.
29. Galli F, Floridi AG, Floridi A, Buoncristiani U. Accumulation of vitamin E metabolites in the blood of renal failure patients. Clin Nutr 2004; 23: 205-12.
30. Himmelfarb J, Kane J, McMonagle E, Zaltas E, Bobzin S, Boddupalli S, et al. Alpha and gamma tocopherol metabolism in healthy subjects and patients with end-stage renal disease. Kidney Int 2003; 64: 978-91.
31. Islam KN, O'Byrne D, Devaraj S, Palmer B, Grundy SM, Jialal I. Alpha-tocopherol supplementation decreases the oxidative susceptibility of LDL in renal failure patients on dialysis therapy. Atherosclerosis 2000; 150: 217-24.
32. Baynes JW, Thorpe SR. Role of oxidative stress in diabetic complications: a new perspective on an old paradigm. Diabetes 1999; 48: 1-9.
33. Giugliano D, Ceriello A, Paolisso G. Oxidative stress and diabetic vascular complications. Diabetes Care 1996; 19: 257-67.
34. Redon J, Oliva MR, Tormos C, Giner V, Chaves J, Iradi A, et al. Antioxidant activities and oxidative stress byproducts in human hypertension. Hypertension 2003; 41: 1096-101.
35. Chaves MA, Leonart MS, do Nascimento AJ. Oxidative process in erythrocytes of individuals with hemoglobin S. Hematology 2008; 13: 187-92.
36. Pavlova LE, Savov VM, Petkov HG, Charova IP. Oxidative stress in patients with beta-thalassemia major. Prilozi 2007; 28: 145-54.
37. Claro LM, Leonart MS, Comar SR, do Nascimento AJ. Effect of vitamins C and E on oxidative processes in human erythrocytes. Cell Biochem Funct 2006; 24: 531-5.
38. Toprak O, Cirit M. Risk factors for contrast-induced nephropathy. Kidney Blood Press Res 2006; 29: 84-93.

การป้องกันภาวะเสื่อมหน้าที่ของไตอย่างฉับพลันที่เกิดขึ้นจากการได้รับสารทึบรังสีโดยวิตามิน อี (แอลฟา โทโคฟีรอล): การศึกษาเบื้องต้นโดยการควบคุมแบบสุ่ม

อดิศว์ ทัศณรงค์, ดิลก ภิยโยทัย, ศุภชัย ฐิติอาชากุล

ภูมิหลัง: *ภาวะเสื่อมหน้าที่ของไตอย่างฉับพลันที่เกิดขึ้นจากการได้รับสารทึบรังสีนำมาซึ่ง การเพิ่มขึ้นของอัตราการบาดเจ็บ และอัตราการเสียชีวิตในผู้ป่วยที่ได้รับการฉีดสารทึบรังสีเพื่อดูหลอดเลือดหัวใจ สารทึบรังสีนี้ทำให้เกิดการเสื่อมหน้าที่ของไตอย่างฉับพลัน โดยการกระตุ้นให้เกิดการสร้าง reactive oxygen species เพิ่มมากขึ้น ดังนั้น การศึกษานี้ จึงออกแบบมาเพื่อทำการพิสูจน์ผลของการให้วิตามิน อี (แอลฟา โทโคฟีรอล) เพื่อป้องกันการเสื่อมหน้าที่ของไตอย่างฉับพลันในผู้ป่วยที่ได้รับสารทึบรังสีเหล่านี้*

วัสดุและวิธีการ: *คณะผู้นิพนธ์ได้ออกแบบการศึกษาแบบไปข้างหน้าโดยการควบคุมแบบสุ่มในการให้วิตามิน อี และยาหลอก ในผู้ป่วยจำนวน 103 ราย ที่มีระดับซีรัมครีเอตินินมากกว่าหรือเท่ากับ 1.2 มก./ดล. หน้าที่การทำงานของไตต่ำกว่าหรือเท่ากับ 60 มล./นาที/1.73 $ม^2$ และมีความจำเป็นจะต้องได้รับการฉีดสารทึบรังสีเพื่อดูหลอดเลือดหัวใจ ผู้ป่วยทั้งหมดได้รับการแบ่งออกเป็น 2 กลุ่ม เพื่อที่จะได้รับ วิตามิน อี (แอลฟา โทโคฟีรอล) 525 IU หรือยาหลอก โดยการรับประทานที่ 48 ชั่วโมง, 24 ชั่วโมง และในตอนเช้าของวันที่จะได้รับการฉีดสารทึบรังสีเพื่อดูหลอดเลือดหัวใจ*

ผลการศึกษา: *พบผู้ป่วยที่มีการเสื่อมหน้าที่ของไตอย่างฉับพลันจากการได้รับสารทึบรังสีในผู้ป่วยกลุ่ม ที่ได้รับวิตามิน อี ร้อยละ 5.88 (3 รายใน 51 ราย) และร้อยละ 23.08 (12 รายใน 52 ราย) ในผู้ป่วยกลุ่มที่ได้รับยาหลอก (odds ratio [OR], 0.21; 95% confidence interval [CI], 0.05 to 0.79; p = 0.02) ระดับซีรัมครีเอตินินเพิ่มขึ้นอย่างมีนัยสำคัญ ทางสถิติในผู้ป่วยกลุ่มที่ได้รับยาหลอกโดยเพิ่มขึ้นจาก 1.67 $\pm$ 0.53 เป็น 1.9 $\pm$ 0.87 มก./ดล. (p = 0.02) แต่ไม่พบการเปลี่ยนแปลงในผู้ป่วยกลุ่มที่ได้รับวิตามิน อี โดยมีค่าเท่ากับ 1.62 $\pm$ 0.44 เป็น 1.64 $\pm$ 0.59 มก./ดล. (p = 0.74) รวมทั้งผู้ป่วยที่เป็นเบาหวาน, ภาวะซีด, หรือได้รับสารทึบรังสีปริมาณมากกว่า 120 มล. พบว่าผู้ป่วยในกลุ่มที่ได้รับวิตามิน อี มีอัตราการเกิดไตเสื่อมอย่างฉับพลัน ภายหลังการได้รับสารทึบรังสี ต่ำกว่ากลุ่มที่ได้รับยาหลอกอย่างมีนัยสำคัญทางสถิติ (p < 0.05)*

สรุป: *การให้วิตามิน อี (แอลฟา โทโคฟีรอล) สามารถป้องกันการเกิดภาวะไตเสื่อมอย่างฉับพลันในผู้ป่วยไตวายเรื้อรังที่มีความจำเป็นที่จะต้องได้รับการตรวจโดยการฉีดสารทึบรังสีเพื่อดูหลอดเลือดหัวใจ*