

# Evaluation the Effects of Alpha-tocopherol in Comparison with N-acetylcystein for Prevention of Contrast Induced Nephropathy (CIN) in CKD Patients

Katayoon Samadi,<sup>1</sup> Massih Naghibi,<sup>1</sup> Mahmood Shabestari,<sup>2</sup> Farzaneh Sharifipour,<sup>1</sup> Mohammad Khajeh dalooee,<sup>3</sup> Vajehallah Raeesi,<sup>4</sup> Sara Moosavi Nik,<sup>5</sup> Mohammad Samadi<sup>5</sup>

<sup>1</sup>Kidney Transplantation Complications Research Center, Department of Internal Medicine, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, Iran

<sup>2</sup>Cardiology Department, Imam Reza Hospital, School of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

<sup>3</sup>Social Medicine Department, School of Medicine, Mashhad University Of Medical Sciences, Mashhad, Iran

<sup>4</sup>Mashhad University of Medical Sciences, Mashhad, Iran

<sup>5</sup>Mashhad, Iran

**Keywords.** contrast induced nephropathy, chronic kidney disease, alpha tocopherol

**Introduction.** Contrast induced nephropathy (CIN), a well-known complication of using radio contrast media, dramatically increases the likelihood of patient morbidity and mortality following coronary angiography. As there is no specific treatment for CIN, prevention could be the best strategy to address this issue. Since now, the only approved preventing strategy was hydration with normal saline while antioxidant agents as a new yet unapproved remedy for this purpose could be applied. The present study was conducted to examine the effect of alpha tocopherol in CIN prevention.

**Methods.** This prospective controlled trial was carried out on 201 patients with chronic kidney disease (eGFR < 60 cc/min) underwent coronary angiography. We assigned three groups of CKD patients: 72 patients who received prophylaxis administration with isotonic saline (Group A), 66 patients with isotonic saline plus N-acetylcysteine (1200mg twice a day) for 2 days (Group B) and 63 patients who received isotonic saline plus daily alpha tocopherol (600 IU once daily from one day before till 2 days after angiography) for 4 days (Group C). The contrast media in all three groups was nonionic iso-osmolal agent, Visipaque.

**Results.** Even though CIN didn't developed in any of the three aforementioned groups but there was statistically significant reduction in eGFR from baseline in all three groups ( $P < .001$ ). Moreover, We found no statistically significant difference in GFR reduction between three studied groups.

**Conclusion.** Administration of alpha tocopherol has no additive beneficial effect over isotonic saline in CIN prevention in CKD patients.

IJKD 2020;14:26-30  
www.ijkd.org

## INTRODUCTION

Chronic Kidney Disease (CKD) is an important global health problem. Statistics show a growing incidence and prevalence of kidney failure with poor prognosis which takes its toll<sup>1</sup> and according to new studies, roughly 26 million US citizens over 20 y/o suffer from CKD.<sup>2</sup>

Cardiovascular diseases are prevalent among CKD patients. Thus there should be an evaluation for this likely complication in patients to administer optimal treatment in order to reduce their morbidity and mortality.<sup>3</sup> There are evidences that patients CKD are associated with increased cardiovascular diseases risk apart from degree of their renal

impairment<sup>4</sup> while coronary angiography itself is one of the most usual methods of cardiovascular diseases diagnosis in which the contrast media is applied. Administration of radiocontrast media can cause a type of acute kidney injury named contrast induced nephropathy (CIN) that is usually reversible but increases morbidity and mortality following coronary angiography in CKD patients.

CIN is generally defined as serum creatinine concentration elevation of 0.5 mg/dL or 25% above baseline within 48-72 hours after procedures that apply contrast media. It is estimated that the prevalence of CIN is approximately 1% to 6% in patients who are hospitalized.<sup>5</sup> As there is no known specific treatment for CIN, the best approach would be prevention meanwhile there is no optimal strategy for preventing CIN yet.<sup>4</sup> While hydration with isotonic saline before and after exposure to contrast agents is the standard practice, a considerable proportion of at-risk patients do not response well. Beside hydration with isotonic saline, some medications are used to tackle with this issue. Antioxidants are one of these medications however studies reveal conflicting results regarding using them in preventing CIN.

Vitamin E, especially alpha tocopherol, has been suggested to prevent or treat a great number of health problems because of vitamin's lipophilic antioxidant and anti-inflammatory effects.<sup>6,7</sup> The protective effects of vitamin E against CIN is reported as well.<sup>8</sup>

In this study, as the first specifically relevant attempt in Iran, the effect of alpha tocopherol in preventing CIN was evaluated in detail in which we compared alpha-tocopherol, N-Acetylcysteine and isotonic saline effects in prevention of contrast-induced nephropathy (CIN).

## MATERIALS AND METHODS

In this prospective clinical trial, 201 CKD patients who were referred for coronary angiography were evaluated. The patients were randomly divided into three groups. Among them, 72 patients were assigned to prophylaxis administration with isotonic saline infusions 1 cc/kg from 12 hours before angiography till 12 hours after it (group A), 66 patients received isotonic saline plus N-acetylcysteine (1200 mg / twice a day) from 24 hours before angiography to the day of angiography (group B) and the remaining 63 patients received

isotonic saline plus alpha tocopherol (600 IU once daily) from a day before till 2 days after angiography for total 4days (group C). Patients' eGFR (calculated by MDRD formula) were compared before and 72 hours after coronary angiography.

In order to analysis the data, we used the IBM SPSS Statistics version 16 (Copyright IBM corporation and others 1989-2012) and the confidence interval in all statistical analysis considered 95%.

Inclusion criteria were the CKD patients with GFR less than 60cc/ min for at least three months.

Exclusion criteria were the followings: CKD stage 5, allergy to the contrast, mechanical ventilation, CHF, cardiogenic shock, urgent angiography and patients who received: mannitol, theophylline, dopamine, ascorbic acid or contrast media within 14 days before angiography as well as history of taking daily alpha tocopherol during the week prior to the study.

Having done coronary angiography, GFR was calculated based on serum creatinine 72 hours later and results were compared in three groups.

## RESULTS

Mean age of 201 patients was  $62.98 \pm 9.2$  years, including 127 females (63.2%) and 74 male patients (36.8%), randomly divided into three groups.

As mentioned above, 72 patients were assigned to isotonic saline (group A) while 66 patients to isotonic saline and NAC (Group B) and 66 remaining patients to isotonic saline plus alpha tocopherol Group (group B).

Out of total number of patients, 101 patients (50.2%) were diagnosed with diabetes mellitus. Other demographic characteristics of patients before angiography are shown in detail in Table.

We found no significant statistically difference between the initial level of creatinine and GFR among three mentioned groups.

According to paired Wilcoxon Signed Ranks Test in the three groups, eGFR after coronary angiography showed significant decline compared with the baseline eGFR ( $P < .001$ ). It is noteworthy that there were no statistically remarkable differences between three studied groups. ( $P > 0.05$ ) (Figure 1).

We also performed an extra analysis between three groups according to the diabetes status.

According to Wilcoxon matched paired signed rank test, although, GFR reduction was significant

Evaluation Matching Demographic and Clinical Characteristics Between 3 Groups

Variables	Groups of Study			P
	Isotonic Saline	Isotonic Saline & Alpha-Tocopherol	Isotonic Saline & NAC	
Sex				
Female	39 (54.2%)	42 (66.7%)	46 (69.7%)	> .05*
Male	33 (45.8%)	21 (33.3%)	20 (30.3%)	
Diabetes Mellitus				
Positive	51 (70.8%)	12 (20%)	34 (51.5%)	< .001*
Negative	21 (29.2%)	48 (80%)	32 (48.5%)	
Hypertension				
Positive	24 (33.3%)	21 (35%)	18 (27.3%)	> .05*
Negative	48 (66.7%)	39 (65%)	48 (72.7%)	
Age				
≤ 75	63 (91.3%)	51 (81%)	60 (90.9%)	> .05*
> 75	6 (8.7%)	12 (19%)	6 (9.1%)	
Creatinine	1.31 (0.33)	1.32 (0.46)	1.21 (0.18)	> .05 <sup>§</sup>
GFR	51.19 (7.55)	50.52 (10.21)	51.84 (6.15)	> .05 <sup>§</sup>

in diabetic patients too, there was no significant difference between three studied groups in diabetic patients ( $P > .05$ ) (Figure 2).

Moreover, relying on Wilcoxon Signed Rank Test, GFR reduction was statistically significant after coronary angiography in non-diabetic patients. According to the modified Bonferroni

post hoc test based on the Mann-Whitney test ( $\alpha = 0.016$ ).

GFR reduction in group B (Isotonic Saline & NAC) was statistically less than group C (alpha-tocopherol & isotonic saline) as well as group A (isotonic saline) ( $P < .05$  and  $P < .05$ , respectively; Figure 3).

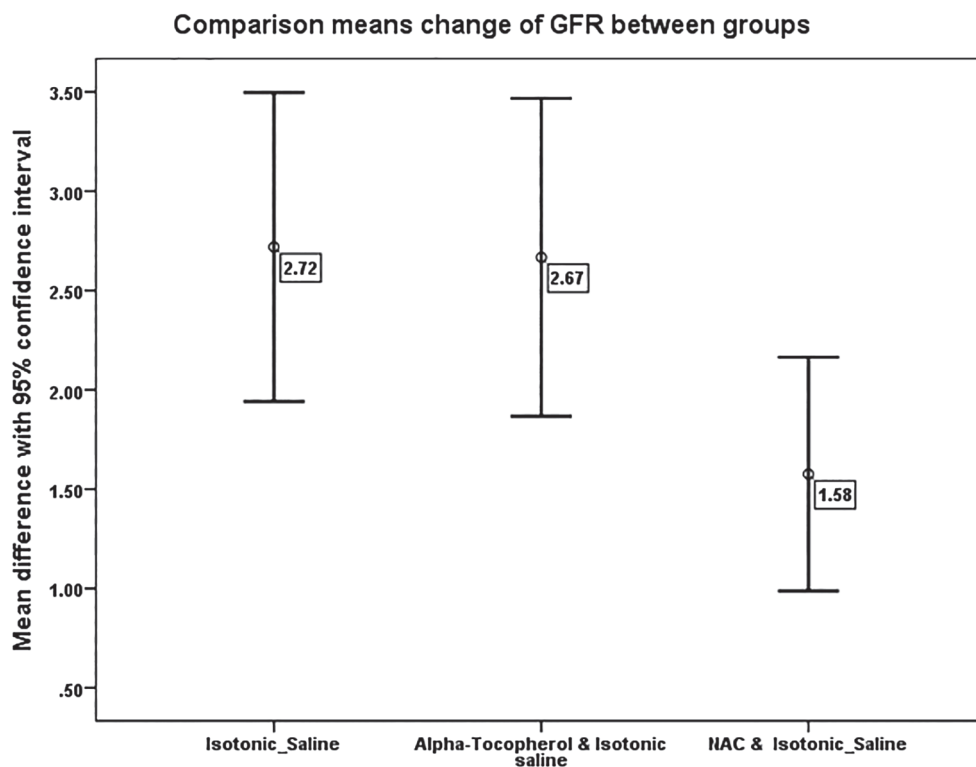


Figure 1. comparison of mean eGFR between three studied groups

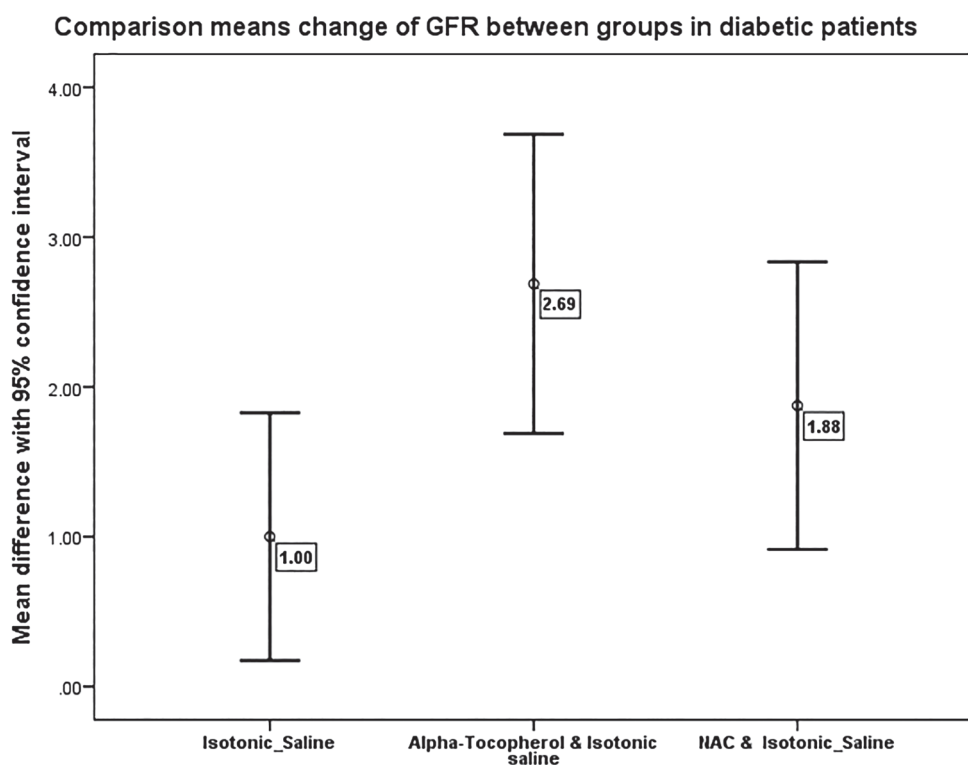


Figure 2. comparison of GFR changes in diabetic patients

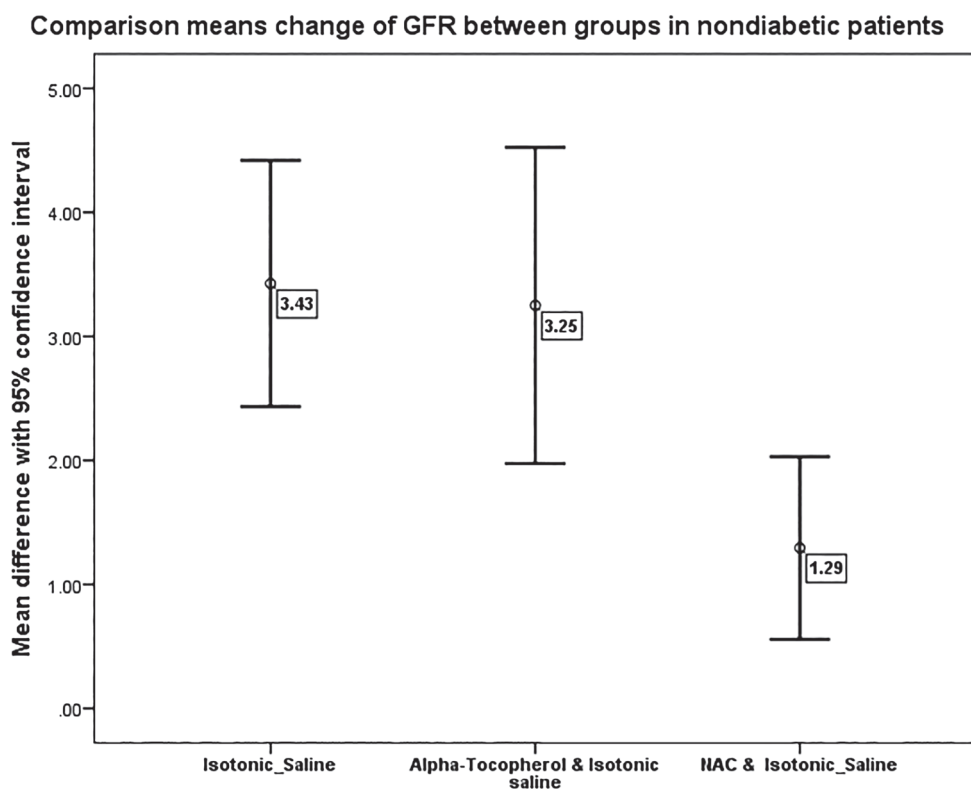


Figure 3. comparison of GFR changes in non-diabetic patients

## DISCUSSION

Contrast-induced nephropathy (CIN) is a major factor of increasing morbidity and mortality among patients after coronary angiography. A known preventing way to address this problem is volume expansion with isotonic saline while antioxidant prophylaxis is controversial yet.<sup>9</sup>

The present study is the first one to compare alpha-tocopherol, N-acetylcysteine and isotonic saline impacts on CIN prevention in Iran. We studied 201 CKD patients with GFR less than 60 cc/min (calculated by MDRD equation) who were candidate for coronary angiography. They were divided in three groups and received isotonic saline, isotonic saline plus NAC and isotonic saline plus alpha-tocopherol for CIN prophylaxis. CIN did not develop in any patients. This might be due to the fact that the studied patients didn't have very low GFR (the average eGFR was more than 50 cc/min in all three studied groups). It means that all this patients suffer from mild CKD and as a result the risk of CIN development was not remarkable.

Although, we found no CIN in any of the three studied groups, statistical analysis revealed that reduction in eGFR was significant after coronary angiography in all three studied groups and eGFR changes shows no statistical significant difference between three studied groups.

In addition, we found that in non-diabetic patients, eGFR reduction in Group B (NAC & isotonic saline) was statistically less than group C (alpha-tocopherol & isotonic saline) and group A (isotonic saline) ( $P < .05$  and  $P < .05$ , respectively).

## CONCLUSION

As the first specifically related study in Iran, we compared the prophylactic effects of alpha tocopherol and NAC in CIN patients. According to statistical analysis of this controlled trial data, administration of alpha tocopherol has no significant additive beneficial effect to isotonic saline in prevention of CIN in CKD patients. In other words, our study showed no superiority of alpha tocopherol plus isotonic saline over isotonic saline alone in prevention of CNI among CKD patients. Moreover, we found that administration of NAC have beneficial effect in CIN prevention in non-diabetic patients.

## ACKNOWLEDGEMENT

This article was based on the results of thesis to receive subspecialty degree that has been accepted by MUMS Research Council (number 931212).

## REFERENCES

1. McCullough PA, Wolyn R, Rocher LL et al. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *AM J Med* 1997; 103: 368–375
2. Marenzi G, Lauri G, Assanelli E et al. Contrast-induced nephropathy in patients undergoing primary angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 2004; 44: 1780–1785.
3. Rihal CS, Textor SC, Grill DE et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 2002; 105: 2259–2264.
4. Nikolsky E, Mehran R, Turcot D et al. Impact of chronic kidney disease on prognosis of patients with diabetes mellitus treated with percutaneous coronary intervention. *Am J Cardiol* 2004; 94: 300–305.
5. Tepel M, van der Giet M, 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(3): 180–4.
6. Marenzi G, Assanelli E, Marana I, Lauri G, Campodonico J, Grazi M, De Metrio M, Galli S, Fabbicchi F, Montorsi P, Veglia F, Bartorelli AL. "N-acetylcysteine and contrast-induced nephropathy in primary angioplasty". *N. Engl. J. Med.*(2006) 354(26): 2773–82.
7. Y. Rezaei, K. Khademvatani, B. Rahimi, M. Khoshfetrat, N. Arjmand, and M.-H. Seyyed-Mohammadzad, "Short-term high-dose vitamin e to prevent contrast medium-induced acute kidney injury in patients with chronic kidney disease undergoing elective coronary angiography: a randomized placebo-controlled trial," *Journal of the American Heart Association*, vol. 5, no. 3, Article ID e002919, 2016.
8. Tasanarong A, Piyayotai D, Thitiarchakul S. Protection of radioccontrast induced nephropathy by vitamin E (alpha tocopherol): a randomized controlled pilot study. *J Med Assoc Thai*. 2009;92:1273–1281.
9. Tasanarong A, Vohakiat A, Hutayanon P, Piyayotai D. New strategy of  $\alpha$ - and  $\gamma$ -tocopherol to prevent contrast-induced acute kidney injury in chronic kidney disease patients undergoing elective coronary procedures. *Nephrol Dial Transplant*(2013) 28: 337–344.

Correspondence to:

Farzaneh Sharifipour, MD

Kidney Transplantation Complications Research Center,  
Department of Internal Medicine, Imam Reza Hospital, School of  
Medicine, Mashhad University of Medical Sciences, Mashhad,  
Iran

Tel: 0098 5138 5988 18

E-mail: sharifipourF@mums.ac.ir

Received May 2019

Revised August 2019

Accepted November 2019