

Comparison of N-acetylcysteine, ascorbic acid, and normal saline effect in prevention of contrast-induced nephropathy

Arsalan Khaledifar⁽¹⁾, Ali Momeni⁽²⁾, Amrollah Ebrahimi⁽³⁾, Soleiman Kheiri⁽⁴⁾, Ali Mokhtari⁽⁵⁾

Original Article

Abstract

BACKGROUND: Considering the crucial role of appropriate preventative strategies in reducing the rate of contrast-induced nephropathy (CIN) occurrence and its related morbidity and mortality, the effect of N-acetylcysteine (NAC), ascorbic acid (AA), and normal saline (NS) was investigated in the patient's undergone coronary angiography.

METHODS: In this clinical trial, 120 patients scheduled for elective coronary angiography with serum creatinine (Cr) level > 1.5 mg/dl or glomerular filtration rate (GFR) \geq 60 selected by convenience method. Selected patients were allocated in three treatment groups randomly to receive oral NAC (600 mg/twice daily) plus NS (100 ml/hour) (Group A), oral AA (250 mg/twice daily) plus NS (100 ml/hour) (Group B) and NS (100 ml/hour) (Group C), respectively. The occurrence of CIN was evaluated based on serum Cr and GFR in three studied groups, before and after angiography procedure. The analysis of variance and paired t-test were used for data analysis by SPSS.

RESULTS: The serum Cr increased and GFR decreased significantly during the intervention in three groups ($P < 0.010$). However, the amounts of these changes were equal between groups ($P > 0.050$).

CONCLUSION: The study showed that nor the addition of NAC neither the addition of AA to sodium chloride infusion has more beneficial effect than hydration with sodium chloride, in the prevention of CIN.

Keywords: Contrast Media, N-Acetylcysteine, Ascorbic Acid, Sodium Chloride Solution

Date of submission: 19 Jan 2014, *Date of acceptance:* 27 Jun 2015

Introduction

In accordance with increasing cardiovascular disease and development of effective diagnostic and interventional procedures, the rate of their related complications such as contrast induced nephropathy (CIN) has been increased.^{1,2} CIN is defined as serum creatinine (Cr) rising in patients using intravenous contrast for diagnostic or therapeutic procedure.³ The incidence rate of CIN in the general population has reported about 2%, but is higher in high-risk population with estimate rate of 12-50%.⁴ Though CIN has a benign course and in almost all of the cases its related renal impairment is transient but it considered as the third leading cause of acute renal failure in hospitalized patients and is associated with

increased risk of morbidity, mortality, and medical care costs.^{5,6} The exact mechanism of CIN and its related renal impairment has not understood yet. Some evidences suggested that factors such as increasing level of adenosine, endothelin, and free radicals and decreasing level of prostaglandins and nitric oxide after using contrast media may result in renal hemodynamics impairment, renal tubular cells toxicity and consequently renal failure.⁷⁻⁹ Several preventative strategies including using calcium-channel antagonists, atrial natriuretic peptide, adenosine antagonists, and dopamine have been investigated in this regard, and different controversial results have been reported.^{10,11} Pre-procedural hydration like an infusion of sodium chloride or half saline, considered as one of the

1- Assistant Professor, Department of Internal Medicine, School of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran

2- Associate Professor, Department of Internal Medicine, School of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran

3- Internist, Department of Internal Medicine, School of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran

4- Associate Professor, Clinical Biochemistry Research Center AND Department of Biostatic, School of Health, Shahrekord University of Medical Sciences, Shahrekord, Iran

5- General Practitioner, Department of Internal Medicine, School of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran

Correspondence to: Ali Momeni, Email: ali.momenydr@gmail.com

most effective strategies for prevention of CIN.¹² Moreover, regarding the fact that one of the reported factors in the pathogenesis of CIN are oxygen free radical, the concept of using antioxidant agents such as N-acetylcysteine (NAC) or ascorbic acid (AA) have been developed in the treatment of CIN. However, the effectiveness of mentioned antioxidants is controversial.^{13,14} Previous studies demonstrated that combination therapy of NAC and AA had not any additive effect in preventing CIN probably due to their similar mechanism of oxygen free radical scavenging.¹⁵

The role of normal saline (NS) is evaluated in several studies and mentioned as a standard strategy for prevention of CIN. Additional drugs were added to NS for increasing effect of prevention strategy; however, results of these studies are different and controversial, so it seems that additional investigations are needed for detection of the best preventive method. Therefore, the aim of this study was the evaluation and comparison of the effects of two antioxidant agents, including NAC and AA plus NS with the traditional approach (NS) in preventing of CIN in the patients undergone coronary angiography.

Materials and Methods

In a randomized clinical trial, 120 patients who scheduled for elective coronary angiography were enrolled. This study was done in Hajar Hospital, Shahrekord, Iran. The study protocol was approved by Regional Bioethics Committee of Shahrekord University of Medical Sciences (Research project number; 934). Iranian registration clinical trial (IRCT) number is "IRCT 2015050722134N1." Written informed consent was obtained from all selected patients. We prospectively selected 120 patients with baseline Cr level of > 1.5 mg/dl or glomerular filtration rate (GFR) ≤ 60 . Patients with oliguria (< 400 cc/24 hours), severe heart failure with left ventricular ejection fraction $< 35\%$, contrast-agent hypersensitivity, pregnancy, lactation, acute renal failure, IV use of contrast medium within previous week, vitamin C supplements use within previous week were excluded. Selected patients were allocated in three treatment groups randomly to receive oral NAC plus NS, (Group A), oral ascorbic acid plus NS (Group B) and intravenous NS (Group C). Patients of Group A received NAC (600 mg) bid (from 24 hours before to 24 hours after the procedure) plus NS (100 ml/hour from

12 hours before to 12 hours after the procedure). For Group B patients AA 500 mg (250 mg 12 hours before and 12 hours after the procedure) plus NS (100 ml/hour, 12 hours before to 12 hours after the procedure) prescribed. Group C patients received only NS (100 ml/hour, 12 hours before to 12 hours after the procedure). The occurrence of CIN and mean of Cr and GFR in three studied groups, before and 72 hours after the procedure was evaluated and compared.

CIN defined as increase ≥ 0.5 mg/dl in serum Cr or decrease $\geq 25\%$ of GFR after 72 hours. Serum Cr was measured using Pars Azmoon Diagnostic Kits (Tehran-Iran) by BT 3000 equipment. GFR was measured using the Cockcroft-Gault equation $[(140 - \text{age}) \times \text{Body Weight} / 72 \times \text{Cr}]$.¹⁶

Data were shown as means \pm standard deviation. Because the sample size was moderately high in each group, so the parametric analysis of variance (ANOVA) was used to comparing the variables between groups. Paired t-test was used for comparing the change of variables during the study. Statistical analysis was done by SPSS software (version 17, SPSS Inc., Chicago, IL, USA) and $P < 0.050$ were determined as statistically significant.

Results

In this clinical trial 120 patients, including 80 (66.7%) male and 40 (33.3%) female were randomly entered in three groups, each one including 40 patients. There were 26, 27, and 26 males in the Group A (oral NAC plus NS), Group B (oral AA plus NS) and Group C (intravenous NS) respectively. The chi-square test did not show any significant difference between the distribution of sex in the groups ($P = 0.313$). The overall age of patients was from 38 to 81 years with the mean of 67.6 ± 8.1 years. The mean age of patients in the Groups of A, B, and C was 67.5 ± 7.5 , 67.8 ± 6.8 and 67.6 ± 8.1 years respectively. The ANOVA test did not show any significant difference between the age of patients in the three groups ($P = 0.127$).

The results of serum Cr and GFR in the three groups before and after the study was shown in table 1. The amount of serum Cr ($P = 0.661$) and GFR ($P = 0.785$) were equal in the three groups of patients at the beginning of the study. The serum Cr increased, and GFR decreased significantly during the intervention in three groups (Table 1). However, the amounts of these changes were equal between groups (Table 1).

Table 1. Comparison the mean of serum creatinine (Cr) and glomerular filtration rate (GFR) in the three groups before and after the study

	Group A (n = 40)	Group B (n = 40)	Group C (n = 40)	P*
Cr				
Before intervention	1.68 ± 0.28	1.61 ± 0.36	1.66 ± 0.35	0.661
After intervention	1.74 ± 0.37	1.69 ± 0.34	1.75 ± 0.36	0.771
Change	0.06 ± 0.12	0.08 ± 0.14	0.09 ± 0.13	0.716
P** (before-after)	0.002	0.001	0.001	-
GFR				
Before intervention	54.80 ± 7.00	55.70 ± 6.00	55.30 ± 5.60	0.785
After intervention	53.60 ± 7.50	52.90 ± 5.70	52.90 ± 6.70	0.876
Change	-1.22 ± 2.42	-2.75 ± 2.83	-2.45 ± 2.83	0.074
P** (before-after)	0.003	0.001	0.001	-

* Based on ANOVA test; ** Based on paired t-test; Cr: Creatinine; GFR: Glomerular filtration rate; ANOVA: Analysis of variance

Discussion

This study showed that adding of NAC and AA have not any significant superior effect than traditionally used NS for preventing of CIN. Though several studies performed in this field, but differences in study designs such as patient selection, protocol of prophylaxis including dose of drugs and its administration form make the determination of an optimal approach for the prevention of CIN as a challenging issue in this field. In this study, the outcome of all three administrated regimens was similar. NAC and AA as antioxidant agents have not more advantages than sodium chloride in preventing CIN. The nephroprotective effect of NAC has been reported in many studies.^{17,18} Accordingly the mentioned protective effect of NAC is mostly reported in patients with higher risk of nephropathy.¹⁹ However, there are controversies regarding the effectiveness of NAC in reducing the occurrence of CIN in its different doses and type of administration. There were also studies which failed to confirm the protective effect of NAC in CIN.^{20,21} The influence of orally administrated NAC (600 mg/twice daily) for CIN prevention first time was investigated by Tepel et al.²² They reported that administration of oral NAC plus hydration was more effective than hydration alone for prevention CIN in patients with chronic renal failure using a low-osmolality contrast agent. A.C.T investigators²³ in their recent meta-analysis have announced that reports regarding the effectiveness of NAC belong to smaller clinical trials with an inappropriate methodology which tended to overestimate the role of NAC in this regard. Similar our results, Ozcan et al. have indicated that oral NAC plus hydration therapy have not any additional effect than hydration with sodium chloride alone.²⁴

The efficacy of AA for prevention of CIN, have been studied both in animal and human studies, for example Spargias et al.¹⁴ have studied the effect of high dose of AA, in 231 patients with a serum Cr ≥ 1.2 mg/dl. The mean increase in serum Cr level was significantly higher in the placebo group than AA group. They concluded that prophylactic orally administrated AA may have a protective effect for CIN in high-risk patients undergoing the coronary procedure. Similarly, in a recent study in Slovenia, Dvorsak et al.²⁵ reported that AA could have a protective role for CIN in patients with mild renal function impairment not in those with chronic renal failure.

Some similar studies have evaluated the effectiveness of our studied agents (NAC and AA) in preventing CIN among patients undergone coronary angiography, and different results have reported in this regard. Brueck et al.²⁶ in a prospective randomized double-blind placebo controlled trial have investigated the effect of NAC (600 mg, IV) or AA (500 mg, IV) versus placebo to prevent contrast-induced acute kidney injury in chronic kidney disease patients (serum Cr ≥ 1.3) undergoing elective cardiac catheterization. They concluded that standard doses of NAC and AA did not prevent CIN in the high-risk patients with non-ionic, low-osmolality contrast agent. Briguori et al.²⁷ in the North American synchrophasor initiative (NASPI) study, found that NAC was more effective than AA in CIN prevention, however, the current study did not find the same results. As mentioned above there are controversy in the results of studies because the different protocol of prevention, the dose of drugs, studied population and type of drug administration. It seems that prophylactic effect of AA is higher in patients with renal insufficiency than normal renal function. Regarding the inappropriate

preventative effect of AA, factors such as its dose which was lower than previous studies or the administration form (oral) may explain the controversy in findings. Regarding the amount of administered contrast media, as our study was single center and there were not any cases with repeated contrast media administration, so the effect of the amount of contrast agent was similar in all studied groups. In this study, we represented a single-center experience among a small sample size of patients, which considered the limitation of this study.

Conclusion

The current study showed that adding of NAC or AA to NS infusion had not more beneficial effect. Further studies are warranted to evaluate the optimal pre-procedural volume repletion or appropriate dose of preventative NAC and AA. In addition, it is recommended to use more accurate laboratory methods such as neutrophil gelatinase-associated lipocalin or cystatin C in addition to serum Cr for early detection of CIN.

Acknowledgments

We acknowledge all staff of Hajar Angiography and CCU Centers for their cooperation in this study.

Conflict of Interests

Authors have no conflict of interests.

References

- Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, Best PJ, et al. Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. *Circulation* 2002; 105(19): 2259-64.
- Davidson CJ, Hlatky M, Morris KG, Pieper K, Skelton TN, Schwab SJ, et al. Cardiovascular and renal toxicity of a nonionic radiographic contrast agent after cardiac catheterization. A prospective trial. *Ann Intern Med* 1989; 110(2): 119-24.
- Mehran R, Nikolsky E. Contrast-induced nephropathy: definition, epidemiology, and patients at risk. *Kidney Int Suppl* 2006; (100): S11-S15.
- Berg KJ. Nephrotoxicity related to contrast media. *Scand J Urol Nephrol* 2000; 34(5): 317-22.
- Bagshaw SM, Culleton BF. Contrast-induced nephropathy: epidemiology and prevention. *Minerva Cardioangiol* 2006; 54(1): 109-29.
- Cavusoglu E, Chhabra S, Marmur JD, Kini A, Sharma SK. The prevention of contrast-induced nephropathy in patients undergoing percutaneous coronary intervention. *Minerva Cardioangiol* 2004; 52(5): 419-32.
- Murphy SW, Barrett BJ, Parfrey PS. Contrast nephropathy. *J Am Soc Nephrol* 2000; 11(1): 177-82.
- Pannu N, Tonelli M. Strategies to reduce the risk of contrast nephropathy: an evidence-based approach. *Curr Opin Nephrol Hypertens* 2006; 15(3): 285-90.
- Katholi RE, Woods WT, Taylor GJ, Deitrick CL, Womack KA, Katholi CR, et al. Oxygen free radicals and contrast nephropathy. *Am J Kidney Dis* 1998; 32(1): 64-71.
- Kurnik BR, Allgren RL, Genter FC, Solomon RJ, Bates ER, Weisberg LS. Prospective study of atrial natriuretic peptide for the prevention of radiocontrast-induced nephropathy. *Am J Kidney Dis* 1998; 31(4): 674-80.
- 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(6A): 59K-77K.
- 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(3): 329-36.
- Koc F, Ozdemir K, Kaya MG, Dogdu O, Vatankulu MA, Ayhan S, et al. Intravenous N-acetylcysteine plus high-dose hydration versus high-dose hydration and standard hydration for the prevention of contrast-induced nephropathy: CASIS--a multicenter prospective controlled trial. *Int J Cardiol* 2012; 155(3): 418-23.
- Spargias K, Alexopoulos E, Kyrzopoulos S, Iokovis P, Greenwood DC, Manginas A, et al. Ascorbic acid prevents contrast-mediated nephropathy in patients with renal dysfunction undergoing coronary angiography or intervention. *Circulation* 2004; 110(18): 2837-42.
- Briguori C, Airolidi F, D'Andrea D, Bonizzoni E, Morici N, Focaccio A, et al. Renal Insufficiency Following Contrast Media Administration Trial (REMEDIAL): a randomized comparison of 3 preventive strategies. *Circulation* 2007; 115(10): 1211-7.
- Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16(1): 31-41.
- Kelly AM, Dwamena B, Cronin P, Bernstein SJ, Carlos RC. Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. *Ann Intern Med* 2008; 148(4): 284-94.
- Shyu KG, Cheng JJ, Kuan P. Acetylcysteine protects against acute renal damage in patients with abnormal renal function undergoing a coronary procedure. *J Am Coll Cardiol* 2002; 40(8): 1383-8.
- Moist L, Sontrop JM, Gallo K, Mainra R, Cutler M,

- Freeman D, et al. Effect of N-acetylcysteine on serum creatinine and kidney function: results of a randomized controlled trial. *Am J Kidney Dis* 2010; 56(4): 643-50.
20. Kshirsagar AV, Poole C, Mottl A, Shoham D, Franceschini N, Tudor G, et al. N-acetylcysteine for the prevention of radiocontrast induced nephropathy: a meta-analysis of prospective controlled trials. *J Am Soc Nephrol* 2004; 15(3): 761-9.
 21. Thiele H, Hildebrand L, Schirdewahn C, Eitel I, Adams V, Fuernau G, et al. Impact of high-dose N-acetylcysteine versus placebo on contrast-induced nephropathy and myocardial reperfusion injury in unselected patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. The LIPSIA-N-ACC (Prospective, Single-Blind, Placebo-Controlled, Randomized Leipzig Immediate Percutaneous Coronary Intervention Acute Myocardial Infarction N-ACC) Trial. *J Am Coll Cardiol* 2010; 55(20): 2201-9.
 22. 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.
 23. Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography: main results from the randomized Acetylcysteine for Contrast-induced nephropathy Trial (ACT). *Circulation* 2011; 124(11): 1250-9.
 24. Ozcan EE, Guneri S, Akdeniz B, Akyildiz IZ, Senaslan O, Baris N, et al. Sodium bicarbonate, N-acetylcysteine, and saline for prevention of radiocontrast-induced nephropathy. A comparison of 3 regimens for protecting contrast-induced nephropathy in patients undergoing coronary procedures. A single-center prospective controlled trial. *Am Heart J* 2007; 154(3): 539-44.
 25. Dvorsak B, Kanic V, Ekart R, Bevc S, Hojs R. Ascorbic Acid for the prevention of contrast-induced nephropathy after coronary angiography in patients with chronic renal impairment: a randomized controlled trial. *Ther Apher Dial* 2013; 17(4): 384-90.
 26. Brueck M, Cengiz H, Hoeltgen R, Wiczorek M, Boedeker RH, Scheibelhut C, et al. Usefulness of N-acetylcysteine or ascorbic acid versus placebo to prevent contrast-induced acute kidney injury in patients undergoing elective cardiac catheterization: a single-center, prospective, randomized, double-blind, placebo-controlled trial. *J Invasive Cardiol* 2013; 25(6): 276-83.
 27. Briguori C, Manganelli F, Scarpato P, Elia PP, Golia B, Riviezzo G, et al. Acetylcysteine and contrast agent-associated nephrotoxicity. *J Am Coll Cardiol* 2002; 40(2): 298-303.

How to cite this article: Khaledifar A, Momeni A, Ebrahimi A, Kheiri S, Mokhtari A. **Comparison of N-acetylcysteine, ascorbic acid, and normal saline effect in prevention of contrast-induced nephropathy.** *ARYA Atheroscler* 2015; 11(4): 228-32.