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

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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) ≥ 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

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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

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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 ≥ 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-age) × Body Weight/72 × Cr].[16]

Data were shown as means ± 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 investigators[23] 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 administrated 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.

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Conflict of Interests

Authors have no conflict of interests.

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