Men's Health Journal. 2021; 5(1): e4

ORIGINAL RESEARCH

Comparing the Effect of Vitamin E and N-Acetylcysteine on Prevention of Contrast-Induced Nephropathy in Diabetic Patients under Coronary Angiography

Mehdi Pishgahi[1]*, Mahtab Niroomand[2], Omolbanin Taziki[3], Sepideh Shahi[1], Kimia Karimi Toudeshki[1], Mina Mirzaei Pirloo[1]†

1. Cardiology Department, Shohada-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
2. Endocrinology Department, Shohada-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
3. Nephrology Department, Shohada-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Received: June 2020; Accepted: August 2020; Published online: September 2020

Abstract: **Introduction:** Considering the incidence of contrast induced nephropathy (CIN) as well as its complications and costs, prevention and reducing the risk of CIN is an essential issue. The present study aimed to evaluate the efficacy of vitamin E and N-acetylcysteine (NAC) on the prevention of CIN in diabetic patients undergoing coronary angiography. **Methods:** 360 patients with diabetes who required angiography, including patients with stable angina susceptible to acute myocardial infarction and patients with acute coronary syndrome were included and randomized into three groups . Group 1 received serum therapy (Normal Saline) plus NAC and placebo of vitamin E, group 2 received serum therapy plus vitamin E and placebo of NAC, and group 3 only received serum therapy with two placebos of NAC and vitamin E. The groups were compared considering CIN after angiography. **Results:** A total of 93 patients were studied in group 1, 94 in group 2, and 113 in group 3. CIN occurred in 4 patients (4.3%), 4 patients (4.3%), and 8 patients (7.1%) in groups 1, 2, and 3, respectively (P=0.58). There was a significant difference in mean difference of creatinine levels before and after study in groups 1 and 2 (both P<0.001). In the subgroup of patients with chronic kidney disease, NAC significantly reduced CIN (P=0.03). **Conclusion:** The results suggested efficacy of both interventions, considering reduction of mean Serum creatinine (Scr) after the study, while lack of significant difference in the incidence of CIN could be because of the low number of CIN in our study. The second important finding of this study, probably the reduced risk of CIN in diabetic patients with chronic kidney disease receiving NAC, recommends the use of NAC for prevention of CIN, especially in this subgroup of patients undergoing angiography.

Keywords: Acetylcysteine; Angiography; Diabetes Mellitus; Kidney Diseases; Vitamin E

Cite this article as: Pishgahi M, Niroomand M, Taziki O, Shahi S, Karimi Toudeshki K, Mirzaei Pirloo M. Comparing the Effect of Vitamin E and N-Acetylcysteine on Prevention of Contrast-Induced Nephropathy in Diabetic Patients under Coronary Angiography. Mens Health J. 2021; 5(1): e4.

1. Introduction

Contrast induced nephropathy (CIN), also known as contrast-induced acute kidney injury (AKI), which refers to the deterioration of renal function because of iodine contrast media (ICM), is the third most common cause of hospital acquired acute renal injury (1) that can increase the length of hospitalization, costs, and patients' morbidity and/or mortality (2). The exact mechanism of CIN is not completely understood, while it has been suggested to be related to the renal vasoconstriction or direct cytotoxic effects, induced by ICM, resulting in hypoxic injury to the renal tubules (3). However, ICM is essential to many diagnostic and therapeutic procedures, such as angiography and cardiac interventions (4).

The most commonly used method for assessing CIN is >0.5 mg/dL or 25% increase in serum creatinine (Scr) levels from

*Corresponding Author: Mehdi Pishgahi; Address: Shohada-e-Tajrish Hospital, Qods Sq., Tajrish, Tehran, Iran. Email: mpishgahi.cr@gmail.com, Phone: (+98)2125719

†Corresponding Author: Mina Mirzaei Pirloo; Address: Shohada-e-Tajrish Hospital, Qods Sq., Tajrish, Tehran, Iran. Email: Minamirzai29@yahoo.com, Phone: (+98)2125719

baseline level within 48 hours; according to this definition, the incidence of CIN is reported in about <1% to 50% of the general population, varying according to the presence of (one or combination of) risk factors in the patients (1). The most important risk factors of CIN include advanced age, baseline chronic renal failure (CRF), congestive heart failure, and diabetes mellitus (DM), and other risk factors include anemia, left ventricular dysfunction and hypotension, renal transplant, low serum albumin, and concomitant use of nephrotoxins (5). DM is considered an important risk factor due to the susceptibility of diabetic kidney to intensified hypoxic and oxidative stress (6). Accordingly, special attention should be paid to patients with risk factors when the patient is scheduled for an intervention with injection of ICM (7). Preventive measures, such as reducing the modifiable risk factors, pre-procedural hydration, and adjusting the volume and type of ICM based on patient's conditions have been suggested to reduce the risk of CIN (8). Additionally, several pharmacologic agents have been investigated, with special attention on vitamins and other antioxidant agents (9). Vitamin E (α- and γ-tocopherol) has been suggested as a new strategy of CIN prevention (10, 11). N-acetylcysteine (NAC), a thiol-containing antioxidant, has been suggested to reduce the risk of CIN; nevertheless, the results of comparing its efficacy with hydration are controversial: two meta-analyses showed significant efficacy of NAC on CIN prevention, compared to hydration (12, 13), while another study with meta-analysis showed no significant efficacy of intravenous NAC with a large heterogeneity among the results of studies in this regard (14). Another meta-analysis concluded that NAC can prevent CIN in patients undergoing coronary, but not peripheral angiography (15).

According to the controversial results, the limitations of previous studies, and considering the high incidence of CIN after coronary angiography (CA) or angioplasty (about 12%) in Iranian patients (16), as well as the important of DM as risk factor of CIN (6) and high prevalence of DM in Iran (17), in the present study, we selected a sample of Iranian patients undergoing diagnostic CA, and aimed to evaluate the efficacy of vitamin E and NAC on prevention of CIN in diabetic patients undergoing diagnostic CA in a randomized placebo-controlled clinical trial.

2. Materials and Methods

2.1. Study design

The protocol of this study is registered in the Iranian Registry of Clinical Trials (IRCT) with the code IRCT20200417047114N1. Adult diabetic patients who referred to Shahid Modarres and Shahid Rajaei hospitals in Tehran, Iran, from June 2019 to May 2020 for diagnostic CA were considered as the study population of the present randomized placebo-controlled double-blind clinical trial. All patients with DM type I and II, according to the medical records, were included. Diagnostic CA was indicated at these centers for patients with stable angina susceptible to acute myocardial infarction and patients with acute coronary syndrome. Any patient with sensitivity to ICM, cardiogenic shock, acute myocardial infarction, pulmonary edema, acute renal failure (ARF), , pregnancy, and patients on nutine hemodialysis and patients with acute coronary syndrome, who underwent CA or angioplasty or injected any other ICM in the past 5 days were not included into the study. Patients with chronic kidney disease (CKD), who had glomerular filtration rate (GRF) of <30 mL/min were not included into the study. the research team referred to the patients, explained the objectives, the study protocol and steps, and risks and benefits of the administered drugs, etc. and asked them to read and sign the written informed consent form.

The recruited patients were randomized by randomization table into three equal groups, each group comprising 120 participants. The randomization was generated by an analyst, not involved in other study steps, who provided 360 coded envelopes to the nurses. Neither the nurses/physicians who prescribed the drugs to the patients, nor the patients were aware of the allocations. In all patients on metformin, drug hold from 72 h before intervention.

Group 1 received serum therapy (Normal Saline) plus NAC and placebo of vitamin E, group 2 received serum therapy plus vitamin E and placebo of NAC, and group 3 only received serum therapy with two placebos of NAC and vitamin E. The drugs were prepared by ZAHRAVI Pharmaceutical Company. The serum therapy included infusion of 1 cc/kg/hr 0.9% sodium chloride serum, from 12 hours before until 12 hours after CA. NAC tablets (1200mg) were given to the patients 2 hours before and 4 hours after the CA; 600mg vitamin E was given to the patients 2 hours before and 40 mg 4 hours after CA.

Demographic characteristics of the participants, including age, sex, BMI, and risk factors, such as hypertension, dyslipidemia, smoking status, history of bypass cardiac surgery, type of DM, CKD, and the drugs the patients used were recorded by taking patients' medical history. On the day of admission, the ward's nurse measured the patients' height, weight, and vital signs, including systolic and diastolic blood pressure (measure in sitting position from the left hand) and recorded the patients' heart rate (HR) based on the electrocardiogram results and ejection fraction (EF) based on the results of echocardiography, performed on admission day. One 8-hour fasting venous blood sample was taken from all participants 8 hours before CA and another 48 hours after CA., and sent to the laboratory for measurement of the baseline serum values of white blood cell (WBC), platelet, hemoglobin (Hb), fasting and non-fasting blood sugar, very

low, low, and high density lipoprotein (VLDL, LDL, and HDL), total cholesterol (TC), triglyceride (TG), blood urea nitrogen (BUN) and Cr , sodium (Na), and potassium (K) were recorded. The exact value of ICM was also recorded for each patient.

The primary outcome of the study was considered as the incidence of CIN, defined as >0.5 mg/dL or 25% increase in serum creatinine (Scr) levels from baseline level within 48 hours; the secondary outcome was considered as the Scr levels and GFR before and after the intervention. The patients' GFR was calculated. Visipaque contract agent was used for all patients.

2.2. Statistical analysis

Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. Categorical variables were compared using chi-square test or Fisher's exact test. One–sample Kolmogorov–Smirnov test was used to determine the normal distribution of data and Levene's test was used to test the equality of variances. Continuous variables were compared using one way ANOVA or Kruskal-Wallis H test, whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. For the statistical analysis, the statistical software IBM SPSS Statistics for Windows version 21.0 (IBM Corp. 2012. Armonk, NY: IBM Corp.) was used. P values of 0.05 or less were considered statistically significant.

3. Results

A total of 300 patients completed the study; 93 patients in group 1, 94 patients in group 2, and 113 patients in group 3 (Figure 1). The demographic characteristics (age, sex, BMI) of the three study groups and the frequency of hypertension, dyslipidemia, smoking status, history of bypass cardiac surgery, type of DM, and CKD, baseline values of systolic and diastolic blood pressure, number of heart rate (HR), ejection fraction (EF), and the drugs the patients used were not different among the groups (P>0.05; table 1).

Comparing the results of baseline serum parameters showed significant differences among the three study groups in mean values of LDL, VLDL, and TC (P=0.018, 0.033, and 0.04, respectively), while other serum parameters were not different (P>0.05; table 2).

Mean ±SD of ICM was 40± 23 cc , 42±12 cc , and 45±13 cc in groups 1, 2, and 3, respectively (P=0.43). The frequency of CIN was 4.3% (N=4), 4.3% (N=4), and 7.1% (N=8) in groups 1, 2, and 3, respectively (P=0.58), as the results of chi square test showed. Pairwise comparison between the groups using Fisher's exact test showed no difference between groups 1 and 2 (P=1), 1 and 3 (P=0.55), and 2 and 3 (P=0.55).

Mean ±SD of Scr levels of the participants before and after the intervention are shown in table 3. As demonstrated, there was a significant difference in mean Scr levels after the intervention among the three groups (P=0.043) with significant difference between groups 1 and 2 (P=0.04). The mean difference of Scr (after intervention vs. before intervention) was also different among the three study groups (P=0.001) with significant difference between groups 1 and 3 and between groups 2 and 3 (both P<0.001). Although the difference in mean Scr was not clinically significant.

4. Discussion

The results of the present study showed a prevalence of 5.3% in diabetic patients without severe CKD who underwent diagnostic CA, which is much higher than the rate reported in a previous study on Iranian patients undergoing CA or angioplasty (12%) (16). It is well known that the incidence of CIN depends on the presence of risk factors and the two most important risk factors of CIN includes CKD and DM (18). It has been suggested that the defective diabetic kidneys have a higher vulnerability to renal damage, hypoxia, and oxidative stress, induced by ICM (6) that results in about increase in the risk of CIN in diabetic patients with normal GFR (19). In a previous study on 155 diabetic patients, undergoing CA or angioplasty, CIN occurred in about 26% of diabetic patients (20). Also, in another study on 114 diabetic patients who underwent percutaneous coronary intervention (PCI), CIN was observed in 18.4% of the patients (21). The incidence of CIN in the above-mentioned studies (20, 21) are higher than that of the present study, which determines the effectiveness of the interventions used in the present study. Furthermore, the discrepancy in the results of studies can be due to the baseline renal function of the study subjects, which play a significant role in the susceptibility to CIN (19, 22). In this study, we included patients with GFR >30 ml/min and did not include patients with ARF to minimize the effect of this confounder on the study results. In another study on diabetic patients undergoing elective cardiac catheterization or PCI, the results reported the CIN rate at 5.2% (22), which is close to the results of the present study.

Hydration has been suggested as an important component for CIN prevention, recommended to be used in all patients receiving ICM, especially those with risk factors (23). However, hydration does not eliminate this risk and CIN is still observed in 13-28% of patients undergoing CA, despite sufficient hydration (24). Accordingly, complementary interventions are suggested. The results of our study showed that administration of NAC or vitamin E plus hydration resulted in 4.3% CIN, while hydration alone resulted in 7.1% CIN without statistically significant difference among the study groups; however, the authors suggest that the lack of statis-

tical significant in the incidence of CIN is because of the low frequency of CIN, as we have observed a significant difference in the before-after difference in Scr levels among the study groups: Scr levels increased in the control group after the study, while it decreased in the two intervention groups with statistically significant difference, compared to the control group. This finding shows the significant efficacy of both of the interventions, namely NAC and vitamin E on renal function of diabetic patients. The results of previous studies on the preventive effect of NAC are controversial. Sar and colleagues evaluated the efficacy of addition of 1200mg NAC to hydration with saline in patients with type II DM and showed that it resulted in reduction of Scr from 0.83 to 0.79 (mean values), while Scr increased in the control group (25). These results are consistent with the results of the present study. In the study by Berwanger et al, evaluation of 1395 diabetic patients undergoing coronary and peripheral angiography showed that administration of 1200 mg oral NAC (once before and once after angiography) could not reduce the incidence of CIN (14.7% in NAC group vs. 13.8% in the control group) (26), which confirms the results of the present study, although the CIN rates were much higher in their study, compared to that reported in the current study.

One of the most important risk factors of CIN is CKD and several studies have investigated the efficacy of agents reducing the risk of CIN in these subgroup of patients (13, 15). The results of subgroup analysis in the present study showed that NAC could significantly reduce the risk of CIN in subgroup of patients with CKD, compared to the control group, which is consistent with the results of the study by Carbonell et al., suggesting the incidence of CIN at 5.1% in the group receiving NAC, vs. 23.8% in the control group (27), although they have not focused on diabetic patients. On the other hand, other studies suggest no efficacy for 600 mg oral NAC twice a day (28) or intravenous injection of 600 mg NAC (29) on prevention of CIN, compared to hydration of patients by normal saline in high-risk patients (with baseline Scr >1.5 mg/dL) undergoing elective CA. This discrepancy in the results of the studies could be due to the difference in the frequency of other risk factors that confound the results. One of the important influential factors is the volume of ICM and the results of our study showed that the three groups had no significant difference in mean ICM. Also, our results showed the similarity of the study groups in terms of other influential factors suggested, such as mean arterial blood pressure, and the use of medications, like diuretics and vasoactive agents (30).

The results of our study also showed the significant reduction of Scr in the group receiving vitamin E, compared to the control group. But, we could not find any other study investigating the effect of vitamin E on prevention of CIN in diabetic patients and previous studies have only considered CKD patients. In the subgroup of patients with CKD in the present study, we did not observe significant difference in the incidence of CIN. These results are consistent with the results of the study by Kitzler et al., which showed no difference in the incidence of CIN in CKD patients receiving vitamin E, compared to hydration with sodium chloride (31). This is while, other studies on patients with CKD have shown significant effect of vitamin E (α- and γ-tocopherol) on reduction of CIN rates (10, 11, 32), confirmed by the meta-analysis on the four studies (33). The discrepancy in the results of studies could be due to the fact that they have not focused on diabetic patients. One of the limitations of the present study was the variability of the ICM volume that could be a confounder. Furthermore, we enrolled the patients into the study by non-randomized method and from one city (Tehran, center of Iran), which increased the risk of bias in the study results. It has to be mentioned that we did not follow the patients, as the study objectives was centered on ARF, while studying the long-term follow-up outcomes of patients can conclude different results.

5. Conclusion

In conclusion, the results of the present study suggested the efficacy of both interventions, considering the reduction of mean Scr after the study. Although, none of them could reduce the incidence of CIN clinically, which could be due to the low number of CIN in our study. The second important finding of this study, the reduced risk of CIN rise of Cr in diabetic patients with CKD receiving NAC, although the difference was not clinically significant, recommends the use of NAC for prevention of CIN, especially in this subgroup of patients undergoing angiography. Considering the fact that several risk factors can affect the incidence of CIN, further studies are required to examine the exact effect of these supplements on different subgroups of diabetic patients.

6. Limitations

In this study, according to the formula, were to get included near to 500 patients, but due to lack of sufficient time and exiting condition, 360 patients were included.

7. Appendix

7.1. Acknowledgements

None.

7.2. Author contribution

All authors have equally contributed in the study, data analysis and writing the manuscript.

7.3. Funding/Support

None.

7.4. Conflict of interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

References

1. Mohammed NM, Mahfouz A, Achkar K, Rafie IM, Hajar R. Contrast-induced nephropathy. Heart views: the official journal of the Gulf Heart Association. 2013;14(3):106.
2. Aubry P, Brillet G, Catella L, Schmidt A, Bénard S. Outcomes, risk factors and health burden of contrast-induced acute kidney injury: an observational study of one million hospitalizations with image-guided cardiovascular procedures. BMC nephrology. 2016;17(1):167.
3. Seeliger E, Sendeski M, Rihal CS, Persson PB. Contrast-induced kidney injury: mechanisms, risk factors, and prevention. European heart journal. 2012;33(16):2007-15.
4. Sudarsky D, Nikolsky E. Contrast-induced nephropathy in interventional cardiology. International journal of nephrology and renovascular disease. 2011;4:85.
5. Evola S, Lunetta M, Macaione F, Fonte G, Milana G, Corrado E, et al. Risk factors for contrast induced nephropathy: A study among Italian patients. Indian heart journal. 2012;64(5):484-91.
6. Heyman SN, Rosenberger C, Rosen S, Khamaisi M. Why is diabetes mellitus a risk factor for contrast-induced nephropathy? BioMed Research International. 2013;2013.
7. Maliborski A, Żukowski P, Nowicki G, Bogusławska R. Contrast-induced nephropathy–a review of current literature and guidelines. Medical science monitor: international medical journal of experimental and clinical research. 2011;17(9):RA199.
8. Faggioni M, Mehran R. Preventing contrast-induced renal failure: a guide. Interventional Cardiology Review. 2016;11(2):98.
9. Ali-Hasan-Al-Saegh S, Mirhosseini SJ, Ghodratipour Z, Sarafan-Chaharsoughi Z, Dehghan AM, Rahimizadeh E, et al. Protective effects of anti-oxidant supplementations on contrast-induced nephropathy after coronary angiography: an updated and comprehensive meta-analysis and systematic review. Kardiologia Polska (Polish Heart Journal). 2016;74(7):610-26.
10. Tasanarong A, Vohakiat A, Hutayanon P, Piyayotai D. New strategy of α-and γ-tocopherol to prevent contrast-induced acute kidney injury in chronic kidney disease patients undergoing elective coronary procedures. Nephrology Dialysis Transplantation. 2013;28(2):337-44.
11. Cho MH, Kim SN, Park HW, Chung S, Kim KS. Could vitamin E prevent contrast-induced acute kidney injury? A systematic review and meta-analysis. Journal of Korean medical science. 2017;32(9):1468-73.
12. Su X, Xie X, Liu L, Lv J, Song F, Perkovic V, et al. Comparative effectiveness of 12 treatment strategies for preventing contrast-induced acute kidney injury: a systematic review and Bayesian network meta-analysis. American Journal of Kidney Diseases. 2017;69(1):69-77.
13. Ali-Hassan-Sayegh S, Mirhosseini SJ, Ghodratipour Z, Sarrafan-Chaharsoughi Z, Rahimizadeh E, Karimi-Bondarabadi AA, et al. Strategies preventing contrast-induced nephropathy after coronary angiography: a comprehensive meta-analysis and systematic review of 125 randomized controlled trials. Angiology. 2017;68(5):389-413.
14. Sun Z, Fu Q, Cao L, Jin W, Cheng L, Li Z. Intravenous N-acetylcysteine for prevention of contrast-induced nephropathy: a meta-analysis of randomized, controlled trials. PloS one. 2013;8(1):e55124.
15. Xu R, Tao A, Bai Y, Deng Y, Chen G. Effectiveness of N-Acetylcysteine for the Prevention of Contrast-Induced Nephropathy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Journal of the American Heart Association. 2016;5(9):e003968.
16. Nough H, Eghbal F, Soltani M, Nejafi F, Falahzadeh H, Fazel H, et al. Incidence and main determinants of contrast-induced nephropathy following coronary angiography or subsequent balloon angioplasty. Cardiorenal medicine. 2013;3(2):128-35.
17. Mirzaei M, Rahmaninan M, Mirzaei M, Nadjarzadeh A. Epidemiology of diabetes mellitus, pre-diabetes, undiagnosed and uncontrolled diabetes in Central Iran: results from Yazd health study. BMC Public Health. 2020;20(1):166.
18. Calvin AD, Misra S, Pflueger A. Contrast-induced acute kidney injury and diabetic nephropathy. Nature Reviews Nephrology. 2010;6(11):679-88.
19. Golshahi J, Nasri H, Gharipour M. Contrast-induced nephropathy; A literature review. Journal of nephropathology. 2014;3(2):51.
20. Rahman M, Haque H, Banerjee S, Ahsan S, Rahman M, Mahmood M, et al. Contrast induced nephropathy in diabetic and non-diabetic patients during coronary angiogram and angioplasty. Mymensingh medical journal: MMJ. 2010;19(3):372-6.
21. Xue-chao W, Xiang-hua F, Yan-bo W, Xin-wei J, Wei-li W, Xin-shun G, et al. Prediction of contrast-induced nephropathy in diabetics undergoing elective percutaneous coronary intervention: role of the ratio of contrast medium volume to estimated glomerular filtration rate. Chinese medical journal. 2011;124(6):892-6.
22. Worasuwannarak S, Pornratanarangsi S. Prediction of contrast-induced nephropathy in diabetic patients undergoing elective cardiac catheterization or PCI: role

of volume-to-creatinine clearance ratio and iodine dose-to-creatinine clearance ratio. J Med Assoc Thai. 2010;93(Suppl 1):S29-S34.
23. Schilp J, de Blok C, Langelaan M, Spreeuwenberg P, Wagner C. Guideline adherence for identification and hydration of high-risk hospital patients for contrast-induced nephropathy. BMC nephrology. 2014;15(1):2.
24. Burchardt P, Guzik P, Tabaczewski P, Synowiec T, Bogdan M, Faner P, et al. Early renal dysfunction after contrast media administration despite prophylactic hydration. The international journal of cardiovascular imaging. 2013;29(5):959-66.
25. Sar F, Saler T, Ecebay A, Saglam ZA, Ozturk S, Kazancioglu R. The efficacy of n-acetylcysteine in preventing contrast-induced nephropathy in type 2 diabetic patients without nephropathy. JN journal of nephrology. 2010;23(4):478.
26. Berwanger O, Cavalcanti AB, Sousa AM, Buehler A, Castello-Júnior HJ, Cantarelli MJ, et al. Acetylcysteine for the prevention of renal outcomes in patients with diabetes mellitus undergoing coronary and peripheral vascular angiography: a substudy of the acetylcysteine for contrast-induced nephropathy trial. Circulation: Cardiovascular Interventions. 2013;6(2):139-45.
27. Carbonell N, Sanjuán R, Blasco M, Jordá Á, Miguel A. N-acetylcysteine: short-term clinical benefits after coronary angiography in high-risk renal patients. Revista Española de Cardiología (English Edition). 2010;63(1):12-9.
28. 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 atherosclerosis. 2015;11(4):228.
29. Boedeker R-H, Scheibelhut C, Boening A. 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.
30. Hoste EA, Doom S, De Waele J, Delrue LJ, Defreyne L, Benoit DD, et al. Epidemiology of contrast-associated acute kidney injury in ICU patients: a retrospective cohort analysis. Intensive care medicine. 2011;37(12):1921-31.
31. Kitzler TM, Jaberi A, Sendlhofer G, Rehak P, Binder C, Petnehazy E, et al. Efficacy of vitamin E and N-acetylcysteine in the prevention of contrast induced kidney injury in patients with chronic kidney disease: a double blind, randomized controlled trial. Wiener klinische Wochenschrift. 2012;124(9-10):312-9.
32. Rezaei Y, Khademvatani K, Rahimi B, Khoshfetrat M, Arjmand N, Seyyed-Mohammadzad MH. 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. 2016;5(3):e002919.
33. Monami M, Cignarelli A, Pinto S, D'Onofrio L, Milluzzo A, Miccoli R, et al. Alpha-Tocopherol and contrast-induced nephropathy: A meta-analysis of randomized controlled trials. International Journal for Vitamin and Nutrition Research. 2019.

Table 1: Comparing the demographic and clinical characteristics among the three study groups.

Variable	Categories	Group 1 (N=93)	Group 2 (N=94)	Group 3 (N=113)	p-value
Age (years),	mean ±SD	65± 8.9	65± 9.3	64± 7.4	0.58*
Sex, No. (%)	Male	72(77.4)	66(70.2)	78(69)	0.37†
	Female	21(22.6)	28(29.8)	35(31)	
Weight (kg),	mean ±SD	78±11	78±12	78±12	0.86*
Height (m),	mean ±SD	167±7.9	166±9.3	166±12	0.75*
BMI (kg/m2),	mean ±SD	27±13	28±30	28±28	0.68*
Hypertension,	No. (%)	64(68.8)	63(67)	60(53.1)	0.071
Systolic blood pressure (mmHg),	mean ±SD	125±12	126±14	127±11	0.50*
Diastolic blood pressure (mmHg),	mean ±SD	77±7.1	78±7.8	77±6.6	0.87*
Heart rate (/min),	mean ±SD	72±10	72±10	73±10	0.52*
Dyslipidemia,	No. (%)	44(47.3)	43(45.7)	55(48.7)	0.91†
Smoker,	No. (%)	34(36.6)	42(44.7)	48(42.5)	0.50†
Positive history of bypass cardiac surgery,	No. (%)	19(20.4)	13(13.8)	21(18.6)	0.47†
Ejection fraction (%),	mean ±SD	48±4.8	47±4.6	50±4.4	0.74*
Chronic kidney disease,	No. (%)	4(4.2)	3(3.1)	5(4.4)	0.21†
Diabetes type I,	No. (%)	47(50.5)	50(53.2)	60(53.1)	0.91†
Diabetes type II,	No. (%)	46(49.5)	44(46.8)	53(46.9)	
Drug history,	Aspirin/Plavix	87(93.5)	87(92.6)	103(93.8)	0.93†
No. (%)	Atorvastatin	88(94.6)	85(90.4)	105(93.8)	0.49†
	Captopril	24(25.5)	23(24.7)	25(22.1)	0.73†
	Losartan	45(47.87)	45(47.3)	47(41.59)	0.94†
	metformin	60±32.3	58±45.3	65±42.4	0.76

*The results of one way ANOVA; †The results of chi square test; p-values <0.05 are considered significant.

Table 2: Comparing the results of serum parameters before intervention among the three study groups.

Serum Parameter	Group 1 (N=93)	Group 2 (N=94)	Group 3 (N=113)	p-value*
White blood cell	7963±1877	9269±1084	9267±1143	0.53
Platelet count	232819±64697	214223±55754	227415±62499	0.10
Hemoglobin (mg/dL)	13.8±1.6	14±1.7	14±1.7	0.23
Fasting blood sugar (mg/dL)	129±56	137±58	127±58	0.48
Non-fasting blood sugar (mg/dL)	196±103	178±93	178±94	0.33
Total cholesterol (mg/dL)	136±48	154±49	150±57	0.04
LDL (mg/dL)	67±18	74±16	74±20	0.018
HDL (mg/dL)	41±9.2	40±1.1	43±1.3	0.23
VLDL (mg/dL)	50±21	53±15	57±17	0.033
Triglyceride (mg/dL)	192±61	208±63	200±71	0.27
Blood urea nitrogen (mg/dL)	19±8.6	18±6.3	17±5.9	0.13
Sodium (meq/dL)	135±18	136±13	138±2.7	0.33
Potassium (meq/dL)	4±0.5	4±2.6	4±2.7	0.41
Cr (mg/dl)	1.37±0.20	1.38±0.22	1.31±0.16	0.18

*The results of one way ANOVA; all values are reported as mean ±SD p-values <0.05 are considered significant.
LDL: Low Density Lipoprotein; HDL: High Density Lipoprotein; VLDL: Very Low Density Lipoprotein

Table 3: Comparing the results of serum creatinine levels before and after intervention among the three study groups.

Serum Creatinine level	Group 1 (N=93)	Group 2 (N=94)	Group 3 (N=113)	p-value*
Before intervention	1.37±0.20	1.38±0.22	1.31±0.16	0.18
After intervention	1.29±0.28	1.32±0.30	1.39±0.30	0.043
After vs. before intervention	-0.086±0.26	-0.06±0.27	0.08±0.23	0.001

*The results of one way ANOVA; all values are reported as mean ±SD; p-values <0.05 are considered significant.
Pairwise comparison by posthoc test showed significant difference in serum creatinine levels after intervention between groups 1 and 2 (P=0.04) and in mean difference between groups 1 and 3 and between groups 2 and 3 (both P<0.001).

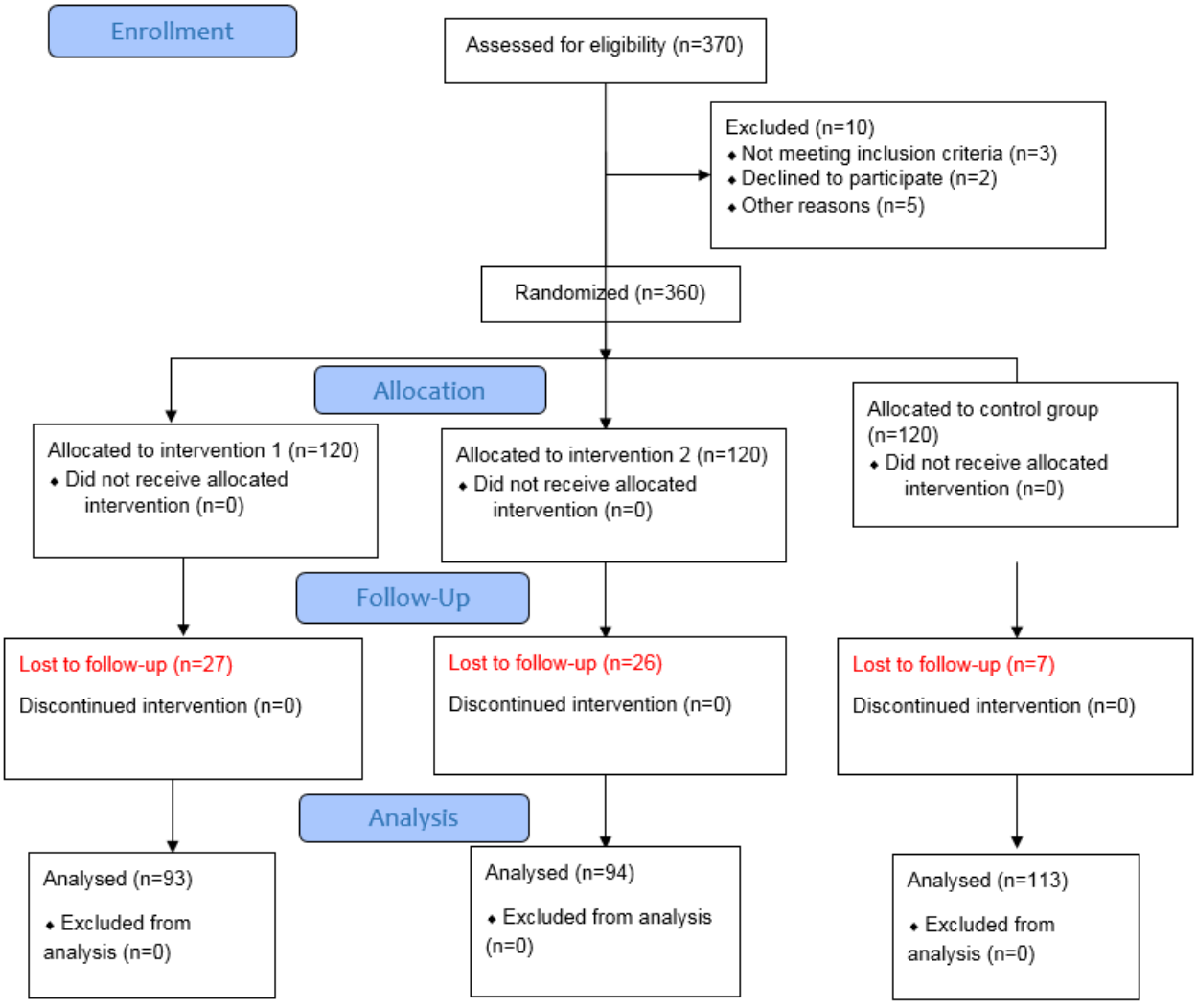

Figure 1: Flow diagram for participant screening and enrollment for this study.