Original Article

Intravenous Vitamin C to Prevent Contrast-Induced Nephropathy in Patients Undergoing Percutaneous Coronary Intervention

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ABSTRACT

Background: This retrospective cohort study aimed to evaluate the effects of the intravenous administration of vitamin C before and after exposure to the contrast medium for the prophylaxis of contrast-induced nephropathy (CIN) in patients undergoing coronary angiography.

Methods: Data on 210 patients with chronic kidney disease (CKD) (defined as an estimated glomerular filtration rate ≤ 60 mL/min/1.73m^2) were obtained through medical chart reviews and electronic data in 3 different groups: 1) no vitamin C administered, 2) vitamin C administered 30 minutes before angiography, and 3) vitamin C administered 30 minutes after angiography. Each group consisted of 70 patients, and vitamin C was administered intravenously. CIN incidence in all the groups was defined as an increase of 0.5 mg/dL or 25% in serum creatinine levels.

Results: Overall, CIN incidence was significantly lower in patients who received intravenous vitamin C before ($P \leq 0.05$) and after ($P \leq 0.05$) angiography than in patients with no prophylaxis. The post-angiography administration of vitamin C was very effective in diminishing creatinine rise and preventing CIN. CIN occurred in 7.1% of the patients in the pre-administered and post-administered groups.

Conclusions: The intravenous administration of vitamin C before and after angiography could effectively decrease CIN incidence in patients undergoing percutaneous coronary intervention. The post-angiography administration of vitamin C is more effective to decrease serum creatinine levels. *(Iranian Heart Journal 2022; 23(1): 149-159)*

KEYWORDS: Contrast-induced nephropathy, Chronic kidney disease, Coronary angiography, Vitamin C, Antioxidant

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Contrast-induced nephropathy (CIN) is a relatively common complication of percutaneous coronary intervention (PCI) and is associated with high rates of mortality and cardiovascular events. CIN is defined as either a 25% increase in serum creatinine (sCr) from the baseline or an equal to or greater than 0.5 mg/dL increase in the absolute value of Cr within 48 to 72 hours following contrast administration and may rise for up to 3 to 5 days after exposure. [1,2] The underlying mechanisms of CIN are still poorly understood. Evidence indicates that multiple factors such as increased levels of free radicals, endothelins, and adenosine, besides decreased levels of prostaglandins and nitric oxide, after contrast medium exposure may lead to tubular cell toxicity and renal hemodynamic impairment, resulting in renal failure. [3] In recent years, various medications and fluid management approaches have been investigated to clarify the optimal preventive strategy for CIN in patients undergoing PCI. Nonetheless, as a consequence of the heterogeneity of available data on the etiology and associated mechanisms of CIN, the efficacy of some preventive strategies in this field is still a matter of debate. [4] To date antioxidant supplementation is an attractive approach to reducing CIN in patients needing PCI. [5] The protective roles of several antioxidants such as vitamin E, vitamin C, α-lipoic acid, and N-acetyl cysteine to prevent CIN have been studied previously. [6] These antioxidants have well-known cytoprotective effects by scavenging oxygen-free radicals (ROS), which can reduce pro-inflammatory mediators such as tumor necrosis factor-α (TNFα) and interleukin-10 and eventually attenuate renal impairment. Vitamin C is a water-soluble vitamin with anti-oxidative and anti-inflammatory effects and is widely used as a dietary supplement. [7] Strong evidence shows that vitamin C scavenges excess ROS (which can cause damage to DNA and cell proteins), regenerates other antioxidants, and reduces renal injury caused by other insults like post-ischemic oxidative stress. [8] As oxidative stress is known as a crucial factor in the etiology of CIN, [9] the prophylactic use of vitamin C in patients undergoing catheterization could serve as a potentially safe and readily available preventive medication. Nevertheless, previous studies have discussed that the maintenance time and bioavailability of intravenous and oral administrations of vitamin C could be different. [10] Indeed, the contradictory conclusions reported by comparative trials have made it difficult to ascertain the optimum approach to CIN prevention in clinical practice. Accordingly, in the present retrospective cohort study, we sought to determine the potential efficacy of the intravenous administration of vitamin C before and after coronary angiography in reducing the incidence of CIN.

METHODS

The present study was a retrospective cohort study performed in Rajaie Cardiovascular Medical and Research Center, Tehran, Iran. Data on 210 patients who underwent PCI between October 2016 and May 2018 and met our inclusion criteria were obtained using medical chart reviews and electronic data. Three groups of patients (70 patients per group) were studied: 1) patients who did not receive vitamin C, 2) patients who received vitamin C (1 g) intravenously before angiography, and 3) patients who received vitamin C (1 g) intravenously 30 minutes after angiography. Vitamin C solution was added to normal saline and was infused intravenously for the patients.

Inclusion criteria were as follows: minimum age of 18 years, an estimated glomerular filtration rate (eGFR) below 60 mL/min/1.73m^2 on the day of angiography (determined by the Modification of Diet in

Renal Disease equation), and a minimum Mehran CIN-Risk score of 10.

A dose of 0.5–2 mL/kg of iodixanol (VISIPAQUE, GE Healthcare; 320 mg iodine/mL), a nonionic iso-osmolar contrast medium, was used for the patients.

Ethics Statement

The present study was approved by the Ethics Committee of Rajaie Cardiovascular Medical and Research Center (ID: IR.RHC.REC.1397.058). Informed consent was not required by the ethics committee of the hospital because of the retrospective design of the study.

Data Collection

The primary independent variable was the intravenous administration of vitamin C before and 30 minutes after angiography. Other variables included the values of sCr before and 72 hours after angiography and GFR, which was calculated using sCr values and age. Information regarding age, sex, and clinical characteristics (eg, heart failure, diabetes mellitus, hypertension, prophylactic medications, the dose and type of intravenous contrast medium, and hemoglobin values) was gathered. Our institution's standard protocol for the prophylactic treatment of patients at risk of CIN at the time of the study was the intravenous injection of 1 mL/kg/h of normal saline (adjusted to the ejection fraction) for 12 hours before and after the contrast medium infusion. The patients received 1200 mg of oral N-acetylcysteine twice a day on the day before and on the day of angiography.

Primary and Secondary Outcomes

The primary outcome was the effectiveness of vitamin C prophylactic therapy in preventing CIN in the patients who received it before or after angiography compared with the patients who did not receive it. The secondary outcomes were the incidence of CIN, defined as an increase equal to or greater than 0.5 mg/dL from the baseline sCr concentration, and changes in eGFR levels within 72 hours after contrast medium exposure.

Statistical Analysis

Statistical analysis was performed with the SPSS software, version 20 (IBM Corporation). Categorical variables were compared between the groups using the Pearson χ^2 test or the Fisher exact test. Between-group analyses of continuous variables were conducted using the one-way analysis of variance (ANOVA) test, followed by the post hoc Tukey test. Within-group comparisons were analyzed using the paired Student t test. The data were expressed as numbers (percentages) and the mean ± the standard error of the mean (SEM). Two-sided P values were reported, and P values less than 0.05 were considered statistically significant.

RESULTS

The patients' characteristics, baseline clinical, and laboratory data are presented in Table 1. The χ^2 analysis revealed no significant differences between the sex distribution of the 3 experimental groups, and 52.3% of the patients were male. The mean age of all the patients was 64±0.85 years, and the between-group analysis demonstrated no significant differences between all the study groups in this regard. The baseline Mehran CIN-Risk score was calculated for all the patients and compared between the 3 groups. The results showed no significant differences between the groups (Table 1). The baseline and postprocedural values of sCr and eGFR in the 3 study groups are presented in Table 2. The mean baseline sCr for all the patients was 1.9±0.09 mg/dL, and the mean eGFR was 39.23±1.5 mL/min/1.73m^2, indicating no statistically

significant differences between the groups. The mean values of sCr and eGFR within the first 72 postprocedural hours were evaluated in the entire study population. In the group of patients who did not receive vitamin C, a significant increase in sCr concentration (2.3±0.081 vs 1.8±0.09; *P*<0.001) and a significant decrease in eGFR (35.8±1.68 vs 42.41±1.61; *P*<0.01) occurred within 72 hours following the intervention compared with the baseline values (Table 2, Fig. 1 & Fig. 2). In the group of patients who received vitamin C before catheterization, a significant fall in sCr concentration (1.83±0.089 vs 2.3±0.081; *P*<0.001) and a significant rise in eGFR (37.5± 1.6 vs 35.8± 1.68; *P*<0.01) were seen following the intervention compared with the control group (Table 2, Fig. 1 & Fig. 2). The within-group analysis showed that the pre-administration of vitamin C led to improvements in renal function, a significant decrease in sCr, and a significant increase in

eGFR compared with the baseline levels (Table 2, Fig. 1 & Fig. 2).

The administration of vitamin C 30 minutes after catheterization significantly and more potently than pre-administration decreased sCr concentration (1.7±0.08 vs 2.3±0.081; *P*<0.001) and increased eGFR (44.85± 2.07 vs 35.8± 1.68; *P*<0.01) (Table 2, Fig. 1 & Fig. 2). The within-group analysis showed that the post-administration of vitamin C significantly decreased sCr and increased eGFR compared with the baseline levels (Table 2, Fig. 1 Fig. 2).

The incidence of CIN was significantly higher in the control group (18.5%) than in the groups that received vitamin C before and after catheterization (7.1%; *P*=0.04) (Table 3). There was no significant difference in CIN incidence between the patients who received vitamin C before catheterization and those who received vitamin C after catheterization.

Table 1. Baseline characteristics of the study population

Characteristics	Control Group (n=70)	Vit C Group (pre-CAT) (n=70)	Vit C Group (post-CAT) (n=70)	*P* value
Clinical Characteristics				
Age (y)	63.71±1.1	64±1.4	65.3±2.5	0.8
Male sex	39 (55.7)	36 (51.4)	35 (50)	0.7
Hypertension	55 (78.5)	58 (82.8)	60 (85.7)	0.5
Diabetes mellitus	32 (45.7)	35 (50)	42 (60)	0.2
Heart failure	15 (21.4)	9 (12.8)	11 (15.7)	0.3
LVEF (%)	48±1.1	50±1	51±1.01	0.7
Mehran CIN-Risk score	11.2±0.4	11.1±0.47	12.8±0.8	0.07
Medication				
Diuretics	28 (40)	22 (31.4)	16 (22.8)	0.09
ACE inhibitor	25 (35.7)	36 (51.4)	41 (58.5)	0.02
ARB	47 (67.1)	40 (57.14)	50 (71.4)	0.09
Procedural Characteristics				
Multivessel disease	47 (67.1)	40 (57.1)	50 (71.4)	0.1
NSTE-ACS	15 (21.4)	20 (28.5)	17 (24.2)	0.5
Contrast volume (mL/kg of body weight)	0.5–2	0.5–2	0.5–2	---
Serum Biochemistry				
BUN (mg/dL)	29.4±1.5	30.65±1.60	37.52±3.9	0.06
Hemoglobin (mg/dL)	12.39±0.2	12.43±0.2	11.66±0.4	0.3

Values are expressed as the mean ± the SEM or numbers (%).

Vit C, Vitamin C; CAT, Catheterization; LVEF, Left ventricular ejection fraction; ACE inhibitor, Angiotensin-converting enzyme inhibitor; ARB, Angiotensin receptor blocker; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; BUN, Blood urea nitrogen

Table 2. Values of sCr and eGFR in the study groups before and after procedures

		Control Group (n=70)	Vit C Group (pre-CAT) (n=70)	Vit C Group (post-CAT) (n=70)
sCr	Before	1.8±0.099	1.83±0.089	2.1±0.12
	After	2.3±0.081	1.57±0.078	1.7±0.08
	P value	*P*=0.0001	*P*=0.01	*P*=0.002
eGFR	Before	42.41± 1.61	37.5± 1.6	37.78± 1.59
	After	35.8± 1.68	43.71± 1.6	44.85± 2.07
	P value	*P*=0.005	*P*=0.004	*P*=0.005

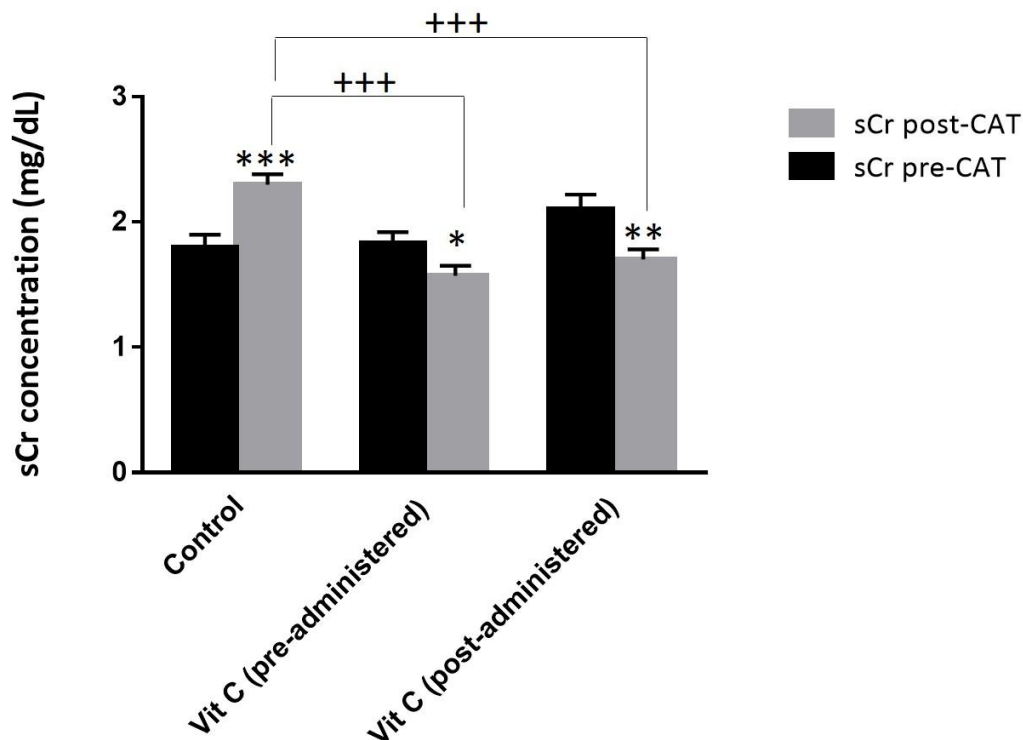Values are expressed as the mean ± the SEM (the paired *t* test).

Vit C, Vitamin C; sCr, Serum creatinine; eGFR, Estimated glomerular filtration rate; CAT, Catheterization

Table 3. CIN incidence, defined as a rise in sCr ≥0.5 mg/dL and eGFR

	Control Group (n=70)	Vit C Group (pre-CAT) (n=70)	Vit C Group (post-CAT) (n=70)	*P* value
sCr increase by ≥0.5 mg/dL	13 (18.5)	5 (7.1)	5 (7.1)	Control vs pre-CAT= 0.04 Control vs post-CAT= 0.04
eGFR decrease by ≥25%	13 (18.5)	4 (5.7)	5 (7.1)	Control vs pre-CAT= 0.01 Control vs post-CAT= 0.04

Values are expressed as numbers (%).

Vit C, Vitamin C; sCr, Serum creatinine; eGFR, Estimated glomerular filtration rate; CAT, Catheterization

Figure 1. The image depicts the serum concentration of creatinine in all the study groups before and after catheterization. The data are shown as the mean ± the SEM.
* *P* ≤0.05, ** *P*≤0.01, and *** *P*≤0.001 (the within-group analysis); +++ *P*≤0.001 (the between-group analysis)
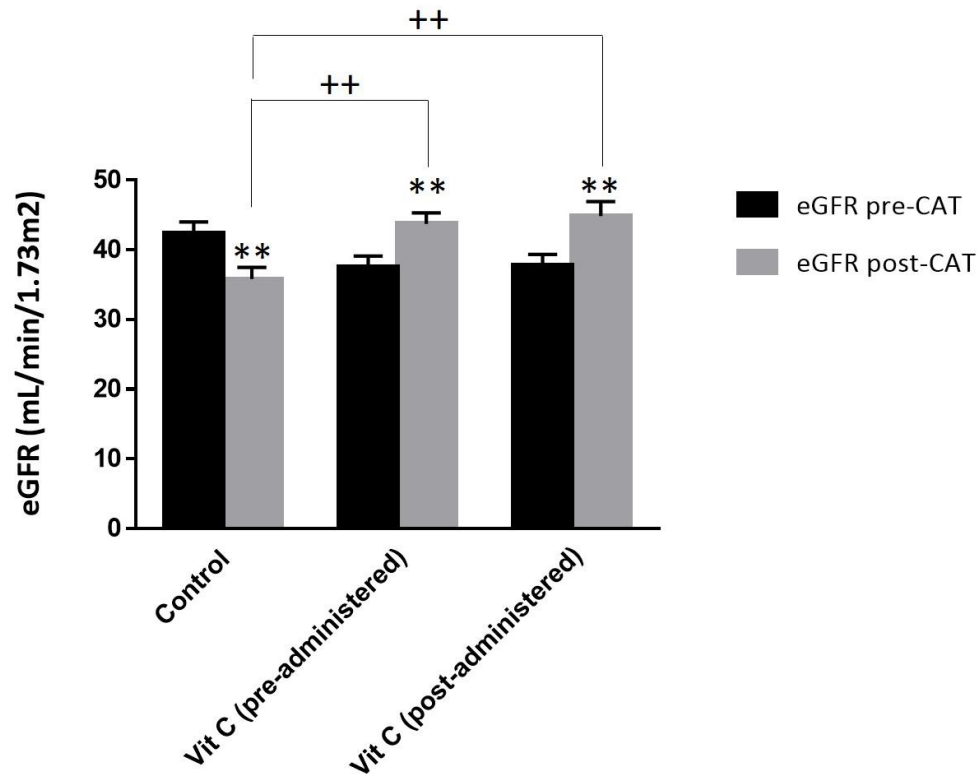sCr, Serum creatinine; CAT, Catheterization; Vit C, Vitamin C

Figure 2. The image illustrates the estimated glomerular filtration rate in all the study groups before and after catheterization. The data are shown as the mean ± the SEM.
** $P \le 0.01$ (the within-group analysis); ++ $P \le 0.01$ (the between-group analysis)
eGFR, Estimated glomerular filtration rate; CAT, Catheterization; Vit C, Vitamin C

DISCUSSION

The present retrospective cohort study enrolled patients at risk of CIN based on the Mehran CIN-Risk score and eGFR who underwent PCI. Clinical data were obtained from 210 patients in 3 separate groups: 1) patients who received intravenous vitamin C (1 g) before angiography, 2) patients who received intravenous vitamin C (1 g) 30 minutes after angiography, and 3) patients with no prophylaxis supplementation. Based on the key findings of the study, prophylactic intravenous infusions of 1 g of vitamin C, combined with the hydration of 0.9% normal saline infusion (1 mL/kg/h), 12 hours before to 12 hours after angiography, decreased CIN incidence in patients at risk compared with normal saline alone. The primary index considered for the diagnosis

of CIN was the sCr level. Routinely, changes in sCr within 48 to 72 hours following contrast medium exposure are used to define CIN. In the present study, we considered sCr concentration measured at the baseline and within 72 hours after angiography; then, we defined CIN as a 25% relative increase or a minimum of 0.5 mg/dL absolute increase in the baseline creatinine level after angiography. The majority of studies in this area have reported the peak sCr level within 2 to 3 days after contrast exposure. [11] Generally, a nonionic iso-osmolar contrast medium (290 mOsm/kg water) is tolerated well; however, it can cause CIN in patients at risk, especially those with chronic kidney disease. Nowadays, an increase in the number of cardiac interventions performed has resulted

in a rise in CIN incidence and various related complications that could increase in-hospital mortality in patients exposed to the contrast medium. [12] Several risk factors are associated with the incidence of CIN. Knowing these risk factors could help predict the risk of CIN preprocedurally in cardiac patients undergoing PCI. The most important risk factors are a decreased eGFR, a high baseline sCr level, and the volume and type of contrast medium. [13] The Mehran CIN-Risk score is a useful calculator for the risk assessment of CIN based on 8 factors: chronic kidney disease, hypotension, having intra-aortic balloon pumps, diabetes, congestive heart failure, anemia, age above 75 years, and the volume of the contrast medium. [14] Patients with high blood glucose levels are at higher risk of CIN than nondiabetic subjects. [15] The important biomarkers that indicate glycemic status are blood sugar, fasting blood glucose, and hemoglobin A1c. Among patients undergoing PCI in a previous investigation, increased baseline hemoglobin A1c levels were associated with a higher risk of CIN in nondiabetic patients. [16] Another study demonstrated that elevated preprocedural blood glucose levels were associated with an increased risk for CIN in nondiabetic patients undergoing coronary angiography. [17] In line with these results, we also found that the risk of CIN was significantly higher in patients who had elevated preprocedural fasting blood glucose and those with diabetes mellitus. (The data are not included.) This finding chimes in with previous studies on the etiology of CIN. [18] Since we performed this study retrospectively, we did not have data regarding other markers indicating nephropathy in diabetic patients such as albuminuria and hemoglobin A1c, which are correlated with the risk of CIN in patients with diabetes. [19,20] Notably, in this study, the use of nephrotoxic medications such as

metformin, nonsteroidal anti-inflammatory drugs, angiotensin receptor blockers, and angiotensin-converting-enzyme inhibitors was limited. Additionally, an adjusted dose of Lasix was administered for patients with heart failure. Our findings showed that the administration of vitamin C 30 minutes after angiography reduced the risk of CIN more effectively than its pre-administration. In other words, the administration of vitamin C after angiography is more effective in elevating the necessary ascorbate concentration to prevent CIN than its pre-administration. Some studies have reported that the half-life for vitamin C at high concentrations is about 30 minutes, but controversies surrounding this topic still abound. [21] Recent studies have confirmed that concentrations of vitamin C in the plasma could vary with the administration route, and only intravenous administration is effective in killing cancer cells. [22,23] The limitation of the current studies is that the pharmacokinetics of the intravenous administration of high doses of vitamin C are poorly investigated; hence, the efficacy of vitamin C in preventing CIN cannot be judged from investigations that evaluate only oral administration. A recently published meta-analysis that evaluated results from 9 randomized clinical trials comparing vitamin C with other treatments demonstrated that CIN risk in patients treated with vitamin C was 33% lower than that in patients receiving other interventions. Nonetheless, another recent systematic review revealed that vitamin C could not act as effectively as N-acetylcysteine for prophylaxis against CIN, and changing the dose, duration, and timing of administration did not improve the results. [24] Another systematic review and network meta-analysis investigated the efficacy of some medications for the prevention of CIN such as ascorbic acid, N-acetylcysteine, probucol, prostaglandins, sodium bicarbonate, statins,

methylxanthines, and trimetazidine and demonstrated that vasodilator agents like prostaglandins, methylxanthines, and trimetazidine could significantly decrease the incidence of CIN compared with standard protocols such as saline or N-acetylcysteine, whereas other medications such as ascorbic acid, sodium bicarbonate, or furosemide had no preventive effects. [25] In a randomized clinical trial conducted by Spargias et al [8] on 231 patients, the effects of the oral administration of 3 g of vitamin C 2 hours before angiography and 2 g of vitamin C on the night and morning after angiography were evaluated and compared with a placebo. Hydration with 0.9% NaCl (50–125 mL/h) was done for all the patients until 6 hours after the procedure. The incidence rates of CIN were 9% and 20% in the vitamin C and placebo groups, respectively ($P \leq 0.05$). Palli et al [26] evaluated the effects of the intravenous administration of vitamin C (2 g) and N-acetylcysteine (1200 mg) dissolved in 100 mL of normal saline on patients with a normal renal function who underwent contrast-enhanced computed tomography. They showed that the administration of both vitamin C and N-acetylcysteine 2 hours before and 10 and 18 hours after the contrast infusion failed to reduce the incidence of CIN. Kota Komiyama et al [27] administered intravenous ascorbic acid, combined with 20 mEq of sodium bicarbonate, for the prevention of CIN in patients with chronic kidney disease undergoing catheterization. They used 3 doses of ascorbic acid: 3 g before catheterization, 2 g following the procedure, and 2 g after 12 hours. Their results showed that the incidence of CIN 72 hours after contrast medium administration in the combination-treated group decreased significantly (2.8%) compared with the control group (8.7%). This effectiveness might be related to the synergistic activity of ascorbic acid and sodium bicarbonate

against CIN. Because of the antioxidant effects of vitamin C, its efficacy in the prevention of oxidative stress-induced diseases has been extensively studied. Oxidative stress, inflammation, osmotic overloading, tubular damage, and hypoxia in the medulla have a significant role in the pathogenesis of CIN. [28] The novel preventive strategies are mostly focused on the involved pathophysiological mechanisms in CIN. Following exposure to the contrast medium, the urine flow rate decreases due to an increase in tubular viscosity; consequently, the activation of the renin–angiotensin system leads to GFR decline. Within 2 to 4 hours after the injection of a contrast medium, the renal blood flow decreases by 30% to 45%, followed by the occurrence of medullary hypoxia, which could have deleterious effects on renal function. [29] Furthermore, contrast agents promote the mitochondrial production of ROS, which may cause vasoconstriction [30] and hypoperfusion in the medulla. [31] It has been demonstrated that hydration therapy is the main preventive strategy for CIN by enhancing the tubular urine flow and consequently decreasing the viscosity of tubular lumens and contrast medium concentration. [32] Accordingly, the administration of common antioxidants such as vitamin C, N-acetylcysteine, and vitamin E could be considered an effective strategy to attenuate radiocontrast-induced oxidative stress and prevent CIN by acting through different signaling pathways. Vitamin C inhibits oxidative damage through direct effects on hydrogen peroxide and hydroxyl radicals to attenuate lipid peroxidation. The antioxidant activity of vitamin E is mediated by the inhibition of ROS generation and oxidative damage via the stabilization of cell membranes and the scavenging of lipid peroxyl radicals. [33] N-acetylcysteine, which is a glutathione precursor, can detoxify hydroxyl groups by enhancing intracellular

glutathione levels. [34] Considering these various mechanisms of the actions of antioxidants, more studies are required to reach a more accurate conclusion regarding their efficacy in CIN prevention.

Our study has several limitations. Firstly, it was designed as a retrospective study, and due to the lack of randomization, some baseline characteristics were different between the groups. Secondly, sCr was considered for the definition of CIN, whereas 24-hour urine collection or inulin clearance can be a more accurate index of renal function. Unfortunately, these assessments were not feasible in this retrospective study.

CONCLUSIONS

The findings of the present study revealed that the administration of 1 g of vitamin C is a safe, efficacious, and well-tolerated supplementation to prevent CIN incidence in patients undergoing coronary angiography. In our patients who received intravenous vitamin C, the level of sCr was significantly lower and eGFR was significantly higher following angiography compared with controls. Further large randomized clinical trials are warranted to evaluate the optimal time for the intravenous administration of vitamin C to increase its efficiency in the prevention of CIN.

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