Original Article

Ascorbic acid effect on CIN incidence in diabetic patient after coronary angiography

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Abstract

Background: This study aims to investigate the antioxidant effect of vitamin C in preventing contrast-induced nephropathy (CIN) in diabetic patients after catheterization.

Materials and Methods: In a double blinded, randomized controlled trial, 90 diabetic patients who were referred for cardiac catheterization were randomly allocated into two arms of vitamin C (A) and placebo (B). The treatment arm (A) received 2 g of vitamin C orally 2 h before catheterization and the control group (B) received 2 g of oral placebo. Six hours before catheterization, patients received fluid resuscitation with normal saline (CIN was considered as a 25% rise in creatinine (Cr) level or an increase of 0.5 mg/dL in earlier creatinine). CIN was compared between groups. Before andthree days after catheterization. Serum Bun – Cr was measured and GFR were calculated. The results were compared between the two groups. Six hours before catheterization, patients received fluid resuscitation with normal saline CIN was compare between arms.

Results: Mean GFR in group (A) before procedure was respectively 69.82±19.26 and after the treatment was 81.51±27.40 (P=0.001). But in group (B) it was 74.18±24.41 and 75.20±29.65 (P=0.747). Contrast-induced nephropathy was observed in 10 patients (12.3%) including 3 patients (7.7%) in group (A) and (16.7%, 7 patients) in group (B) (P=0.315).

Conclusion: Ascorbic acid intake in diabetic patients prior to use of contrast agents can be effective in maintaining GFR, but the incidence of contrast-induced nephropathy is not associated with the consumption of ascorbic acid.

Key Words: Contrast induced nephropathy, diabetes, Vitamin C

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INTRODUCTION

Contrast-induced nephropathy (CIN) is one of the known complications after coronary catheterization and is the third leading cause of acute renal failure requiring hospitalization. Its incidence in the general population is less than 3% but in high-risk patients such as those with renal failure or diabetes reaches up to 50%.[1]

Although contrast-induced nephropathy is reversible in most cases, even a transient increase in serum creatinine leads to longer admission period.[2,3] Sometimes these patients require dialysis, which also causes increased hospital length of stay, increased

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healthcare costs and an increase in hospital mortality rate to 12%–37%.[4] There are several risk factors for contrast-induced nephropathy of which diabetes is one of the most important and common ones.

A variety of measures are suggested to prevent and reduce the incidence of contrast-induced nephropathy, including adequate hydration of patients before, during and after treatment, discontinuation of nephrotoxic drugs before treatment and prescribing sodium bicarbonate and some antioxidants such as ascorbic acid N. Acetylcysteine (NAC).[5] Possible effects of antioxidants in the prevention of contrast-induced nephropathy are inhibiting the direct toxic influence from contrast-induced on renal epithelial cells. Renal epithelial cell damage was induced by free radicals reducing their uptake, and results in lipid peroxidation damage to kidney cells which are vascuolization of epithelial cells inflammatory interstitial cells and cell necrosis.

The effect of antioxidant drugs has not been proven yet[5] Vit C as an inexpensive and available and feasible administrate antioxidant drug that is orally taken by patients had been proposed for the prevention of CIN. Ascorbic acid is an antioxidant that is easily absorbed by the digestive system and reaches the required serum level in a short period of time (2 h). It has liver metabolism and it is excreted through the kidneys. Maximum permissible dose is 2 g per day.[6,7] Therefore, considering the specific features of ascorbic acid, it has been proposed as an appropriate medication for the prevention of CIN, but enough research has not been done yet in this area and various results have been reported in previous studies. This study aims to investigate the effect of vitamin C on the prevention of CIN in diabetic patients.

MATERIALS AND METHODS

In this double-blinded randomized controlled trial, 90 patients with diabetes who were referred to Afshar Hospital and undertook coronary angiography for catheterization were randomly divided into two arms of Vit C (A) and placebo (B). Patients with acute and chronic renal failure, patients treated with mannitol or the ophyline and vitamin C that underwent re-catheterization over the past 5 days were excluded.

Details are given contain patients' demographic data, duration of diabetes, medications, heart condition (patient's EF by echocardiography or angiography), BUN-Cr (urea - creatinine) before treatment, BUN-Cr 2-3 days after treatment, and the volume and type of contrast agent used for each patient were given in registration form. Subsequent follow-up was performed on all patients by telephone. For some patients who needed prolonged hospitalization due to heart surgery, if possible, necessary test was requested before the next procedure. According to their previous heart condition, all patients underwent rehydration with 0.5–1 cc/kg normal saline serum from 6 h before to 12 h after treatment. Furosemide and metformin was stopped 24 h before the treatment and restarted after that, depending on the patient's condition.[8] About 2 hours before catheterization, group A received 2 g of oral vitamin C and group (B) received 2 g of oral placebo (choice of dose and time of administration was based on pharmacokinetic properties of vitamin C). Bun-Cr was measured before and 3 days after catheterization. Afterwards, GFR was calculated according to the following formula and the results were compared (GFR formula = [weight × (140-age)] ÷ (72 × Cr), for women the result was multiplied by 0.85).

Drug and placebo were supplied by Osveh pharmaceutical company based on a specific order, which were prepared in two separate packages labeled A and B in the same color and same shape pills. During the study, neither the patient nor the person who gave the drug was aware of the content of the packet. After collecting the data, the information in the questionnaires were coded and entered into SPSS software table (CIN was considered as a 25% rise in creatinine level or an increase of 0.5 mg/dl in earlier creatinine.

RESULTS

In this study, three patients in group A (7.7%) and seven patients in group B (16.7%) had CIN which was tested using Fisher's Exact Test. The mean Cr before and after treatment in group (A) was 1.16 ± 0.32 and 1.03 ± 0.43, P = 0.006 and in group B it was respectively 1.11 ± 0.2 and 1.15 ± 0.49. P=0.661.

In group A those who were hypertensive, before treatment GFR was 65.38±19.38 and after treatment GFR was 76.28 ± 29.37 (P = 0.003). In group B who were hypertensive, before treatment GFR was 69.56 ± 21.7 and after treatment GFR was 71.34 ± 26.23 (P = 0.644). The mean GFR in Group A who were taking ACEI was 66.69 ± 19.45 before treatment and 79.55 ± 28.78 after treatment with (P = 0.003). In this group, those who were taking nephrotoxic drugs (containing NSAID and aminoglycoside,…) mean GFR was 62.49 ± 20.26 before treatment and 98.25 ± 23.27 after treatment (P = 0.066) [Table 1]. In the same

group in those who were taking metformin, mean GFR was 68.13±8.81 before treatment and 80.20 ± 27.16 after treatment (P = 0.001).

With ACEI use in group B, the mean GFR before and after treatment was respectively 77.86 ± 26.47 and 77.77 ± 31.70 (P = 0.982).

With nephrotoxic use in group B, the mean GFR before and after treatment was 86.25 ± 33.89 and 92.63 ± 49.05 (P = 0.465).

With metformin use in group B, the mean GFR before and after treatment was 74.18 ± 24.41 and 75.20 ± 29.25 (P = 0.747) [Table 2].

Apart from some variables such as received contrast agent, drugs, patients' EF, previous renal function, age and gender, there was no significant difference between two groups in terms of the incidence of CIN and only in cases group the mean GFR and Cr before and after treatment were significantly different.

DISCUSSION

In this study, only three patients in group A (7.7%) and seven patients in group B (16.7%) had CIN (P=0.315). A study on 326 patients in Italy in 2007 to investigate the effect of vitamin C on CIN demonstrated that there was no significant difference in the incidence of CIN between the three groups of VitC, VitC+ NAC, and VitC + bicarbonate recipient.[9]

According to our findings the mean serum creatinine in group A decreased 3 days after catheterization significantly (P=0.006) and also mean GFR increased significantly (69.82 ± 19.26 and 81.51 ± 27.40, P = 0.001). But the difference between GFR and Cr in Group B before and after treatment was not significant.

Our study showed that improvement in mean GFR and Cr induced by vit C administrated was independent to history of hypertention, ACEI, metformine and nephrotoxic agent NSAID, Aminoglycozide intake.

One study showed failure of ascorbic acid in prevention of CIN.[10,11]

In our study, the mean GFR significantly increased with vit C only in visipaque contrast agent usage.

In a study of CIN incidence in terms of contrast agent, there was no significant difference between contrast groups (P=0.348) and in a review study in 2005 by Solomon R. on 17 previous studies, at least in case of contrast agents with osmolarity ≤ 800 mos/kg (i.e., isoosmolar or lowosmolarity) factors other than osmolarity are involved in creating CIN.[9] The result of our study is similar to the first study [Table 3].

The mean GFR increased in vit C group only in doses that received the amount of less than 120 cc contrast agent (P=0.002), however, in the group that received an amount of >120 cc and also in placebo group there was no significant difference [Table 4].

In a study in 2004 by Mehran *et al*., the amount of contrast agent with (P<0.0001) was recognized as an independent risk factor in the incidence of CIN,[12] however, Warren reported that,[9] the incidence of CIN

Table 1: Baseline characteristics of the patients

Variable	ArmB *N* (%)	ArmA* *N* (%)	*P* value
Age (year)	60.22±11.7	11.7±59.2	0.679
Sex (male)	24 (53.3)	24 (53.3)	1.000
Hypertension	32 (86.5)	31 (81.6)	0.754
EF ≤45%) HF)	17 (37.8)	22 (48.9)	0.395
GFR <60) RF)	17 (37.8)	12 (26.7)	0.367
Contrast agent volume ≥120 cc	40 (88.9)	37 (82.2)	0.550
ACEI use	32 (71.1)	36 (80)	0.462
NSAID use	(11.1)	5 (11.1)	1.000
Insulin use	4 (8.9)	2 (4.4)	0.677
Ant glycemic drug	43 (95.6)	40 (88.9)	0.434

EF: Ejection fraction, HF: Heart failure, RF: Renal failure, GRF: Glomerular filtration rate

Table 2: Mean GFR and Cr before and after treatment in arms A and B

Variable	Group A	Group B
Mean (mg/dl) cr		
Before treatment	1.11±0.20	1.16±0.32
After treatment	1.15±0.49	1.03±0.43
P value	0.661	0.006
Mean GFR		
Before treatment	74.18±24.41	69.82±19.26
After treatment	75.20±29.65	81.51±27.40
P value	0.747	0.001

Mean creatinin and mean GFR significantly improved after vit C treatment. GFR: Glomerular filtration rate

Table 3: The mean GFR before and after treatment in terms of the type of contrast agent in groups A and B

Contrast agent	GFR (before)	GFR (after)	*P* value
A			
OmniPaque	71.70±20.41	86.60±25.21	0.109*
VisiPaque	70.16±17.17	82.60±27.25	0.005**
Ulteravist	58.75±22.91	69.65±31.89	0.397*
B			
OmniPaque	76.74±26.40	77.96±31.99	0.757**
VisiPaque	69.11±24.36	71.36±29.25	0.209*
Ulteravist	71.35±19.68	73.37±26.10	1.000*

*Base on paired T-Test, **Base on Wilcoxon signed test, In group A those who received VisiPaque, GFR significantly increased. This difference was not significant in the other groups

Table 4: The mean GFR before and after intervention in terms of the amount of contrast agent used in groups A and B

Variable	GFR (before)	GFR (after)	*P* value
A			
120^{cc} ≥	69.97±20.01	80.37±27.44	0.002*
120^{cc} <	68.18±15.75	74.51±30.42	0.176**
B			
120^{cc} ≥	74.11±24.35	74.51±30.42	0.909*
120^{cc} <	72.54±24.08	72.54±28.22	0.961**

Based on paired T T*, Based on Wilcoxon signed test**. According to the above table and mentioned *P* value, there was only a significant difference in mean GFR before and after treatment in group A that received contrast material ≥120^{cc} . This difference was not significant in other groups

was not significantly associated with the amount of contrast agent used, similar to our result.

In the comparison of the mean GFR before and after treatment based on the presence or absence of early kidney failure, only in group A with early GFR ≥ 60 with no early kidney failure, the differences were significant but the difference was not significant in other groups.

In many studies, including studies in 2004 in New York,[12] 2007 in America,[13] and 2002 in Australia,[3] chronic renal disease was considered as an independent risk factor in the incidence of CIN. In a study in 2010 in the Heart Center of Yazd Afshar Hospital,[14] CRF was recognized as an independent risk factor for CIN (P = 0.026). In our study, perhaps due to the low number of samples, especially in the group consisting of patients with GFR <60, this difference was not significant in other groups. In group A, in those with hypertension, there was a significant difference in mean GFR before and after treatment (P=0.003) but this difference was not significant in group B.

Hypertension was proposed as an independent factor in the incidence of CIN (P = 0.02). In a study conducted in Switzerland, hypertension with P = 0.016 was considered as an independent risk factor. In our study this difference was not significant in group B because generally in this group the mean GFR before and after treatment did not change independent of other risk factors. Studying the effect of nephrotoxic drugs, there was a significant difference between GFR before and after treatment in Vit C patients who were taking metformin and ACEI (P = 0.001 and P = 0.003 respectively). But also in those in the group B and in those who were taking NSAID in both groups, this difference was not significant.

Nephrotoxic drugs with P = 0.03 had a significant relationship with the incidence of CIN and was proposed as an independent risk factor. This difference was not significant in our study in the NSAID group because sample size was low.

CONCLUSION

Oral vitamin C before angiography and angioplasty can be a protector of GFR of diabetic patients who receive angiographic contrast agent. This is significant in patients with left ventricular function of less than 40% or patients who take more than 120 cc of contrast agent.

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