Original Article

Impact of Supplementation with Omega-3 in the Prevention of Contrast-Induced Nephropathy Following Elective Percutaneous Coronary Intervention in Patients with Chronic Kidney Disease: A Randomized Placebo-Controlled Trial

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Abstract

Background: Anti-oxidants were investigated in several studies as a preventive strategy for prevention of contrast-induced nephropathy (CIN). Omega-3 polyunsaturated fatty acids have antioxidant properties; however, their role in the prevention of CIN is still unknown. Therefore, in this study, we aimed to evaluate the efficacy of omega-3 supplementation in the prevention of contrast-induced nephropathy following elective percutaneous coronary intervention in patients with chronic kidney disease. **Methods:** This is a double-blinded and randomized clinical trial. Eighty eligible patients with glomerular filtration rate of 30-60 mL/min/1.73 m^2, scheduled to undergo elective PCI, were randomly divided into omega-3 (a single dose of 2500 mg omega-3 12 hours before PCI plus hydration therapy) or control (placebo plus hydration therapy) groups. Blood specimens for measuring serum creatinine and cystatin C were collected from each patient at baseline and 24 h after PCI. **Results:** Omega-3 did not show any significant effect on post-PCI serum creatinine and cystatin C compared to the controls. In addition, serum creatinine analysis showed that CIN occurred in 6 (16.2%) patients of the omega-3 and 4 (9.3%) patients of the control group (P = 0.50). **Conclusions:** Our results could not support the protective effect of a single dose of omega-3 in decreasing serum creatinine, serum cystatin C, and the incidence of CIN in patients with CKD undergoing PCI. To better evaluate the effect of omega-3, future studies with higher and/or multiple doses of omega-3 are highly recommended.

Keywords: *Chronic, contrast-induced nephropathy, creatinine, cystatin C, fatty acids, omega-3, renal insufficiency*

Introduction

Contrast-induced nephropathy (CIN) is a major complication in patients who have undergone cardiovascular procedures such as percutaneous coronary intervention (PCI) and coronary angiography. Despite advances in preventive methods, the adverse effects of contrast agents can seriously influence human health. Contrast agents are the third leading reason for hospital-acquired acute kidney injury (AKI) and it is the cause of about 10% of all in-hospital nephropathies. In addition, this complication may prolong the duration of hospitalization and cost of care.[1]

The risk for CIN is low (0.6-2.3%) in the general population, however; some groups of patients are at high-risk (up to 20%) such as patients with diabetes mellitus, anemia, cardiovascular disease, age more than 75 years, hypertension, heart failure, volume-depleted conditions, consumption of nephrotoxic drugs or contrast medium with high osmolality and volume, and especially those with chronic kidney disease (CKD).[2,3] The incidence of CIN in patients with CKD was reported to be 11-44%.[4]

The most common definition of CIN is an absolute rise of ≥0.5 mg/dL or a relative increase of ≥25% in serum creatinine concentration within 48–72 hours following contrast medium exposure.[5] Currently, there is no sensitive and specific laboratory test for the diagnosis of kidney injury during CIN. A dynamic change of serum creatinine within 48–72 hours after administration of contrast agent is the most common marker in the diagnosis of CIN.[6] In addition to renal factors, a range of non-renal factors

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such as age, sex, ethnicity, muscle mass, diet, and drugs could affect creatinine level. Moreover, the concentration of creatinine might not change in early stages of CIN (before 50% decline in the kidney function); therefore, it lacks sensitivity in the diagnosis of CIN. Because of creatinine limitations, an alternative marker, cystatin C, has been recently used for the diagnosis of CIN.[7]

Currently, several different preventive strategies have been implemented in order to reduce the incidence of CIN in post- PCI patients. Decreasing contact with contrast agents, alkalization of tubular fluid, high consumption of fluids, and administration of anti-oxidant agents such as N-acetyl cysteine are some of these preventive strategies but the role of these strategies is still argumentative.[6] The efficacy of pretreatment with atorvastatin, ascorbic acid, N-acetyl cysteine, and alprostadil in the prevention of CIN in patients undergoing PCI was previously evaluated showing a relatively acceptable protection.[8-10]

Omega-3 fatty acids are a group of polyunsaturated fatty acids (PUFAs). The positive effects of omega-3 in the treatment of different renal diseases such as diabetic nephropathy and cyclosporine nephrotoxicity have been previously mentioned.[11] Accordingly, the present study aimed to investigate the efficacy of omega-3 supplementationin prevention of CIN in patients with CKD undergoing coronary stenting. To the best of our knowledge and available databases, this trial is the first on this topic.

Methods

Study design and participants

This is a prospective, double-blinded, and randomized clinical trial (IRCT2016031320441N3) performed between January 2015 and March 2016 in the cardiac catheterization laboratory of two tertiary care cardiac centers affiliated to Shiraz University of Medical Sciences (SUMS), Shiraz, Iran.

Eighty-six eligible patients were assigned to control and omega-3 groups, using simple randomization method. For this, patients were randomized through the use of random number tables, tossing a coin. Patients, investigator and analyzer were blind. The control group received placebo plus routine hydration therapy for the prevention of CIN (normal saline or dextrose saline) before PCI. Patients in the omega-3 group were administered a single 2500 mg dose of omega-3 (2 pearls) as well as routine hydration therapy within 12 hours before PCI.

The inclusion criteria were age over 18 years and less than 80 years, an estimated glomeration filtration rate (eGFR) between 30 and 60 mL/min/1. 73 m during recent 3 months, and candidates for elective PCI. Patients with a history of heart bypass surgery in the last 3 months, need for emergency PCI, allergy to drugs including aspirin, clopidogrel, and omega-3, failed PCI, signs of active bleeding, platelet count less than 70×10^9/L, and previous treatment with N-acetylcysteine or vitamin C during recent month were excluded.

CKD was confirmed with the results of laboratory tests and physician reports. In order to identify patients with CKD, eGFR was calculated by Cockcroft-Gault equation. Creatinine was obtained at the nearest time before the PCI.

Procedures and outcomes evaluation

Single or multiple drug-eluting stents were used for various lesions for all investigated patients by standard techniques. Two non-ionic contrast agents, omnipaque and visipaque, were used for patients during PCI.

Nutralab's Omega-3 pearls (SUPER NATURAL®; NUTRALAB, Canada) were used in this study [1250 mg poly-unsaturated fatty acids, 600 mg eicosapentaenoic acid (EPA) and 300 mg docosahexaenoic acid (DHA), in each pearl].

Based on institutional protocol, pre-procedural therapy are clopidogrel (a loading dose of 600 mg) and aspirin (a loading dose of 325 mg) 12 h before catheterization as well as weight-adjusted intravenous heparin (target activated clotting time of 250–350 seconds) before PCI, followed by a daily dose of 75 mg/dayclopidogrel for at least one year post-PCI and 80 mg/day aspirin for the rest of life.

The differences in post-PCI serum creatinine and cystatin C between the study arms were measured as the primary endpoints. Blood samples were collected from each patient at baseline (before consumption of omega-3 in the treatment group) and 24 h after PCI to measure serum creatinine and cystatin C levels. The serum creatinine was assessed by an automatic analyzer (TajhizatSanjesh Company, Iran) using reagents from Man Company (Cat. no. 101020). To determine serum cystatin C concentration, sandwich enzyme-linked immunosorbent assay was used (Human cystatin C quantikine ELISA kit, DSCTC0, R and D systems, USA). Laboratory tests were done by the same laboratory and the same technique and all staffs were blinded to the study protocol.

The secondary endpoint was CIN development. In this study, CIN definition based on serum creatinine was applied (a rise in the serum creatinine concentration ≥0.5 mg/dL or 25% above baseline assessed 24 h after exposure to the contrast agent).

Ethical issues

The research followed the tenets of the Declaration of Helsinki. All patients signed a written informed consent form to participate in the study. This project was also approved by the Ethics committee of Shiraz University of Medical Sciences (registrationcode# IR.SUMS.REC.1394.207). This study was extracted from pharm D, Thesis of Elnaz Rohani

Rad. All participants signed an informed consent before being enrolled in the study.

Statistical analysis

All data analysis was performed using the statistical package for social sciences version 21 (SPSS Inc, Chicago, USA). Variables were tested for normality using the Kolmogorov-Smirnov statistic. Our data were normal, therefore; independent *t*-test was applied to evaluate differences for continuous variables between groups and paried *t*-test was performed to compare continuous variables before and after the intervention in each group. Pearson's Chi-square was used to measure the differences in proportions when required assumptions were met; otherwise, the Fisher's exact test was used. Categorical variables were described with absolute and relative (percentage) frequencies. Continuous variables were expressed as mean ± standard deviation (SD). A *P* value of less than 0.05 was considered to be statistically significant.

Results

The CONSORT flow diagram of the clinical trial is showed in Figure 1. At the end of the study, 37 and 43 patients were recruited to the omega-3 and control group, respectively. Demographic characteristics of the patients are presented in Table 1. No statistically significant differences were observed between basic clinical characteristics, medical, and medication history of the two groups. All patients received non-ionic contrast agents with no significant differences in contrast volume between the study groups.

Although elevation of 24-h cystatin C was seen in both arms; that was not significantly different between the groups ($P = 0.124$). Comparing the differences between baseline and 24-h cystatin C among study groups, no significant difference was observed ($P = 0.339$). The serum concentrations of creatinine and cystatin C before and after PCI are summarized in Table 2.

Results of paired *t*-test showed no significant differences between pre-post intervention serum creatinine in both omega-3 ($P = 0.921$) and control ($P = 0.241$) groups. On the other hand, there were significant differences between pre-postintervention levels of cystatin C in omega-3 ($P = 0.000$) and control ($P = 0.000$) groups.

The incidence of CIN was evaluated according to the elevation of serum creatinine. CIN occurred in 4 (9.3%) patients in the control group and 6 (16.2%) patients in the omega-3 treated ones. However, this difference was not statistically significant ($P = 0.50$). Six men and four women were reported to experience CIN. There were no significant differences between the patients with or without CIN according to the age, weight, eGFR, medication history, and type and volume of contrast agents.

Discussion

This randomized pilot trial was conducted to assess the impact of omega-3 supplementationon 24-h serum

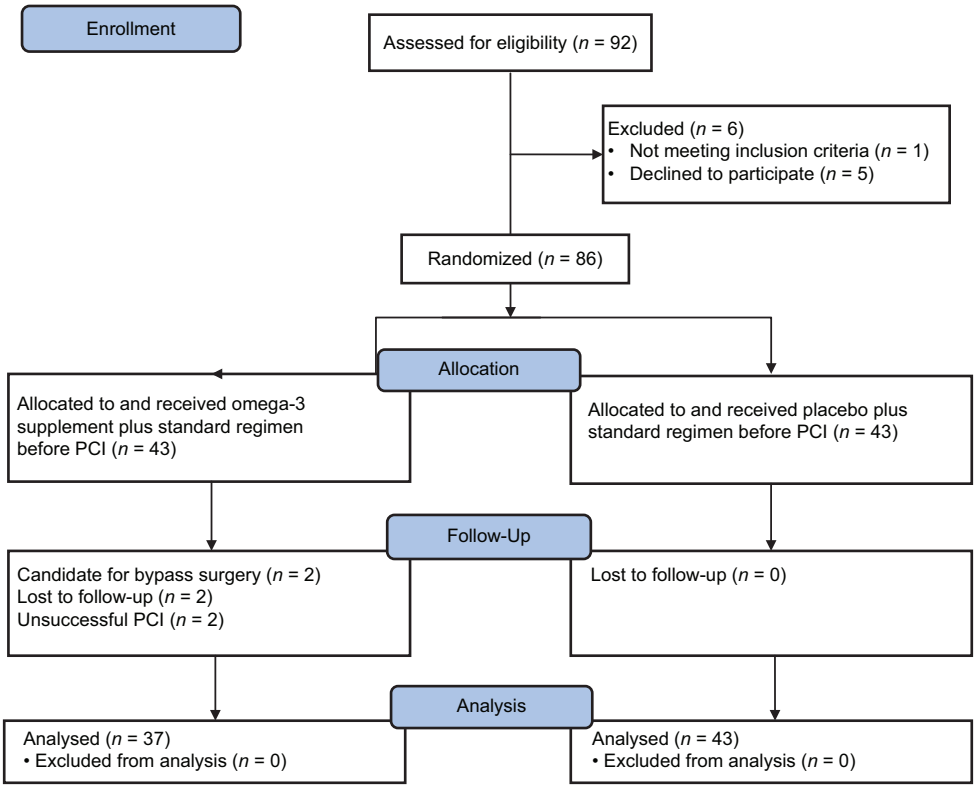

Figure 1: Flow diagram of the trial

Table 1: Demographic data and clinical features in the two groups

Parameters	Omega-3 Group (*n*=37)	Control Group (*n*=43)	*P*
Sex, Male, *n* (%)	24 (64.9%)	24 (55.8%)	0.41[a]
Age, year, mean±SD	66.72±9.75	65.39±9.38	0.65[b]
Diabetes Mellitus, *n* (%)	12 (32.4%)	16 (37.2%)	0.66[a]
Smoker, *n* (%)	13 (35.1%)	15 (34.9%)	0.98[a]
Hyperlipidemia, *n* (%)	24 (64.9%)	25 (58.1%)	0.54[a]
Hypertension, *n* (%)	29 (78.4%)	34 (79.1%)	0.94[a]
History of Myocardial Infarction, *n* (%)	4 (10.8%)	4 (9.3%)	0.82[a]
History of Coronary Intervention, *n* (%)	7 (18.9%)	13 (30.2%)	0.24[a]
Statin, *n* (%)	33 (89.2%)	37 (86%)	0.74[a]
Beta Blockers, *n* (%)	27 (73%)	33 (76.7%)	0.79[a]
Calcium Channel Blockers, *n* (%)	11 (29.7%)	15 (39.4%)	0.64[a]
ACEI and/or ARBs, *n* (%)	18 (48.6%)	24 (55.8%)	0.65[a]
Aspirin, *n* (%)	33 (89.2%)	41 (95.3%)	0.40[a]
Baseline glomerular filtration rate, ml/min/1.73 m^2, mean±SD	49.99±9.16	52.90±10.16	0.11[b]
Volume of contrast media, mL, mean±SD	116.22±37.37	120.93±41.16	0.59[b]

[a]Based on Pearson's Chi-square test; [b]Based on Mann Whitney U test

Table 2: Serum creatinine and cystatin C levels at baseline and 24 h after the procedure in the two groups

Marker	Time of Sampling	Omega-3 Group (*n*=37)	Control Group (*n*=43)	*P*[a]
Creatinine (mg/dl)	Baseline, mean±SD	1.26±0.45	1.08±0.36	0.058
	After procedure, mean±SD	1.27±0.48	1.16±0.33	0.211
	P[b]	0.921	0.241	
Cystatin C (mg/l)	Baseline, mean±SD	1.09±0.54	0.83±0.32	0.012
	After procedure, mean±SD	3.23±1.65	2.68±1.51	0.124
	P[b]	0.000	0.000	
	Baseline-after procedure difference, mean±SD	2.14±1.37	1.84±1.37	0.339

[a]Based on independent *t*-test, [b]Based on paired *t*-test

creatinine and cystatin C as well as CIN occurrence in CKD patients undergoing PCI. Since CKD is one of the major risk factors for CIN,[2,3] in this study, we focused in this category. Based on the available literature, no previous trial was found to investigate the efficacy of the omega-3 supplement on serum biomarkers of kidney function in CKD patients doing coronary stenting.

The main findings of present study were as follows: (1) less increasing trend in the level of post-PCI creatinine was seen in the omega-3 group compared to the control group; however, this difference could not reach the significance level; (2) less increasing tendency in the level of post-PCI cystatin C was detected in the control group that was not significant between the two groups.

The pathogenesis of CIN is only partially understood. CIN results from the action of several mechanisms such as vasoconstrictive forces leading to medullary ischemia,[12] direct toxic effects on renal tubular cells,[12] and damage resulted from oxygen radicals.[13] Sex, age, smoking, diabetes mellitus, dyslipidemia, hypertension, history of myocardial infarction, and previous PCI has been identified as risk factors affecting the incidence of CIN.[4] Analysis of the results of this study indicated no significant differences between the two groups with respect to these risk factors.

To date, numbers of investigations have evaluated different preventive strategies, but most of them have little efficiency.[14] Despite a strong rationale for the use of vasodilators, the results of such drugs have been disappointing. On the other hand, reported clinical trials showed the relatively acceptable effect of antioxidants such as N-acetyl cysteine and ascorbic acid in the prevention of CIN.[8,9]

Due to the accepted antioxidant effect of omega-3, we assumed that omega-3 may have potential for the prevention of CIN. Previous studies have demonstrated the dramatic and undeniable effects of omega-3 for improving heart function and treatment of cardiovascular diseases.[15,16] Moreover; beneficial effects of omega-3 on various renal diseases such as diabetic nephropathy, cyclosporine nephrotoxicity, and IgA nephropathy have been previously reported.[17] Despite some reports that confirmed the beneficial effects of omega-3 in the treatment of kidney diseases,[18] some others did not find any association between omega-3 and treatment of kidney diseases or reduction of its complications.[19] The reason for this inconsistency might be related to different study protocol done in various trials (difference in doses of omega-3, concentrations of EPA and DHA, duration of treatment, the sample size, and the population type of patients).[17]

Although the exact mechanism of omega-3 in improving renal function is still unclear, several mechanisms have been postulated including anti-inflammatory effect, reduction in the production of pro-inflammatory leukotrienes, preventing the infiltration of neutrophils into kidney tissue in the inflammatory process, preventing the release of arachidonic acid from kidney cells, increasing in the renal vasodilatory capacity, antioxidant properties, and reducing the risk for the development of end stage renal disease.[11,20,21]

In our previous study, we evaluated the effect of omega-3 on the levels of creatinine and cystatin C in post-PCI patients with normal kidney function. According to the results, omega-3 significantly decreased cystatin C increment in all patients ($P < 0.001$) after elective PCI while it was remarkably effective on creatinine level only in normotensive cases ($P = 0.029$).[22] In contrast, results of this study did not show any positive effect of omega-3 neither on post-PCI creatinine nor cystatin C in patients with CKD undergoing elective PCI. One of the reasons for this lack of effect for omega-3 could be the significant higher baseline cystatin C in patients treated with omega-3. Therefore, in order to decrease the confounding effect of this marker, differences between 24-h and baseline cystatin C were compared among the two groups. However, no statistically significant difference was detected between the study groups ($P = 0.339$). In addition, dynamic changes of serum creatinine within 48-72 hours after administration of contrast agent is the most common marker used for the diagnosis of CIN.[1] However, we just had 24-h serum sample because of several factors such as discharge of patients after 24 hours and unavailability of patients after that. If we have access to 48-h and 72-h creatinine levels, the differences between the two groups may be more pronounced.

Our results represented the total occurrence of CIN in 10% of the studied patients. Although the incidence of CIN in our study was similar to other studies in Iran,[23,24] it was more encountered in the omega-3 group ($P = 0.50$) which was against the result of the study done by Pezeshgi *et al*. These investigators showed the significant lower incidence of CIN in patients received N-acetylcysteine before and after coronary angiograpgy than those treated with saline.[24] One of the reasons for the lack of positive effect of omega-3 in the prevention of CIN could be the issue that in most studies, patients with kidney diseases were treated with higher doses of omega-3 for longer periods of time,[17] while our patients just received a single dose of omega-3 within 12 h before PCI. Another reason might be more severe renal and cardiovascular disease in the omega-3 group compared to the control group. Severe renal disease was supported by the higher baseline level of cystatin C in the omega-3 group while the significant left anterior descending (LAD) involvement in the omega-3 group represents severe cardiovascular disease in this group. These factors might have had a negative influence in the efficacy of omega-3 in decreasing the incidence of CIN in the studied patients. In addition, the standard therapy may have led to an insignificant effect of omega-3; however; it is not ethical to deprive patients of standard pre-PCI treatment.

Conclusions

In conclusion, a single dose of omega-3 before PCI is not effective in reducing the incidence of CIN in patients with CKD. To better evaluate the effect of omega-3 in the prevention of CIN in patients with CKD undergoing PCI, further studies with higher and/or multiple doses of omega-3 with longer duration of follow-up are required.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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