Omega-3 Supplementation in the Prevention of Contrast Induced Nephropathy in Patients Undergoing Elective Percutaneous Coronary Intervention: A Randomized Placebo-Controlled Trial

Farzaneh Foroughinia, Mahtabalsadat Mirjalili, Ehsan Mirzaei, Alireza Oboodi

1Clinical Neurology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran.
2Clinical Pharmacy Department, Shiraz University of Medical Sciences, Shiraz, Iran.
3Student Research Committee, Shiraz University of Medical Sciences, Shiraz, Iran.

Abstract

Purpose: Contrast-induced nephropathy (CIN) is the third cause of hospital-acquired renal failure and is associated with significant morbidity and mortality. Several studies have revealed the protective role of omega-3 in prevention and treatment of some kidney injuries. This study was conducted to examine the effect of omega-3 supplementation on the markers of renal function and to evaluate its potential in the prevention of CIN in patients undergoing elective percutaneous coronary intervention (PCI).

Methods: In this double-blind, randomized clinical trial, 85 eligible patients scheduled for PCI was randomly divided into omega-3 (a single 3750 mg dose of omega-3 as well as routine intravenous hydration) or control (placebo plus routine intravenous hydration) groups. Serum creatinine (SCr) and cystatin C levels were measured at baseline and 24 hours after PCI.

Results: Our results indicated that post-PCI cystatin C levels were significantly decreased in the omega-3 group compared to the control group ($P < 0.001$). Although less upward manner was seen in the level of 24-hour creatinine in the omega-3 group, it did not reach the significance level ($P = 0.008$).

Conclusion: The positive effect of omega-3 on cystatin C levels showed that it may have a protective role in the prevention of CIN in post-PCI patients with normal kidney function. However, to better assess this effect, it is highly recommended to design future studies with higher doses and longer duration of therapy with omega-3 plus long-term follow up.

Introduction

Today, contrast agents have been increasingly administered for diagnostic and therapeutic purposes. However, they may result in clinical complications, such as contrast-induced nephropathy (CIN). CIN can lead to serious problems, including renal function impairment which may be followed by a longer hospital stay, an increased rate of morbidity and mortality, and a higher financial cost. It accounts for about 11% of all hospital-acquired renal insufficiencies. Around 1%-2% of the general population and up to 50% of high-risk subgroups will experience this problem following coronary angiography (CA) or percutaneous coronary intervention (PCI). The renal insufficiency caused by receiving contrast agents during PCI may increase the risk of subsequent cardiac events and mortality in a dose-dependent manner during and after PCI even in patients with normal renal function. Nowadays, besides to serum creatinine (SCr), a new marker of renal function named cystatin C is used to assess renal status after PCI. It is a more sensitive and superior marker than SCr in the detection of acute kidney injury in the early stages of renal dysfunction.

Although CIN can occur in any patient with exposure to contrast agents, some patients are more prone to encounter with this problem, such as patients with diabetes, hypertension, chronic heart failure, renal insufficiency, volume depletion, hemodynamic instability, older age, and those receiving hyperosmolar and higher doses of contrast media.

Although different researches have been done on the prevention of CIN, no proven strategies exist till now. The official guideline published by the American College of Radiology suggests administration of prophylactic intravenous hydration in high-risk patients for CIN at least 6 hours before and after exposure to contrast media.

Other pharmacologic precautions include minimization of the dose of contrast media and the use of iso-osmolar or low-osmolar contrast media. Furthermore, several
It is reported that omega-3 have
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or a 10% or higher increase in cystatin
In a study, it was
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by the
Shiraz University of Medical Sciences (SUMS) between
laboratory of two tertiary care heart center affiliated to
clinical trial was performed in the cardiac catheterization
A double-center, prospective, randomized double-blind
Materials and Methods
The mechanism of CIN is not fully understood. The
suggestive mechanisms are direct toxicity of contrast
media on the renal tubular epithelium, as well as inducing
oxidative stress, inflammatory responses, ischemic injury,
and renal tubular obstruction.
Clinical studies have shown that omega-3
polyunsaturated fatty acids (PUFAs) can play an effective
role in the reduction of inflammatory conditions in
kidney diseases. It is reported that omega-3 have
potential therapeutic effects for patients with renal disease
and can improve kidney function. In a study, it was
shown that omega-3 supplementation in diabetic patients
with hypertriglyceridemia can decrease albuminuria and
maintain renal function in a dose dependent manner.
Although several studies reported the beneficial effects
of omega-3 PUFAs in different kidney diseases, no
randomized clinical trial have assessed its potential role in
the prevention of CIN in setting of coronary stenting,
based on available databases. Therefore, we conducted this
study to evaluate the efficacy of omega-3 supplementation
in the prevention of CIN in patients undergoing elective
PCI.

Materials and Methods
A double-center, prospective, randomized double-blind
clinical trial was performed in the cardiac catheterization
laboratory of two tertiary care heart center affiliated to
 Shiraz University of Medical Sciences (SUMS) between
May 2015 and June 2016. The trial was registered by the
Iranian Registry of Clinical Trials ( identifier: IRCT2016041920441N4; https://www.irct.ir/). All
participants signed an informed consent before being
enrolled in the study.

Study population
Candidate patients for elective PCI with ages between 18
to 80 years old and an estimated glomerular filtration rate (eGFR) above 60 mL/min/1.73 m² were eligible to be
enrolled in this study. Patients were excluded if they had
one of these excluding factors, including positive history
of omega-3 supplementation on a regular basis in the last
two years prior to admission; history of emergency
coronary angioplasty; history of acute renal failure or
end-stage renal failure requiring dialysis; history of heart
bypass surgery in the last 3 months; history of allergy to
aspirin, clopidogrel, and omega-3; report of unsuccessful
PCI; positive signs of active bleeding; history of GI
bleeding or peptic ulcer in the last one month; and history
of NAC or vitamin C usage during last month.

Study endpoints
The primary endpoint was the differences in post-PCI
Scr and cystatin C between the study groups. Differences
in pre/post-PCI creatinine and cystatin C among each
group and the development of CIN were recorded as
secondary endpoints. CIN was defined as a rise in the
Scr concentration ≥0.5 mg/dL or 25% above baseline
within 48-72-hour or a 10% or higher increase in cystatin
C concentration within 24-h after exposure to contrast
agent.14

**Statistical analysis**

All data analysis was performed using the statistical package for social sciences version 21 (SPSS Inc, Chicago, USA). The Kolmogorov–Smirnov test was used to evaluate whether the variables were normally distributed which proved that the data distribution was non-normal. Categorical variables were presented as absolute and relative (percentage) frequencies. Continuous variables were expressed as mean ± standard deviation (SD). The independent samples t test was used to compare baseline and demographic parameters between study and control groups. The repeated measure ANOVA test was applied to compare the changes in the investigated markers from baseline to 24-hour follow-up between two groups. P values < 0.05 were considered significant.

**Results and Discussion**

The CONSORT flow diagram of the clinical trial is shown in Figure 1. During the study period, a total number of 85 patients were recruited in the study, 43 and 42 cases in the omega-3 and control groups, respectively.

Demographic, clinical, and biochemical variables are reported in Table 1. The patients had the mean age of 56.7±7.28 and 61.3±5.74 and gender distribution of 30 (71.4%) and 31 (72.1%) male in the control and omega-3 groups, respectively. There were no significant differences amongst groups except in age, history of hypertension, and beta-blocker consumption. No significant differences were observed between both groups in terms of the type and the volume of contrast agent (P = 0.847).

The change in SCr and cystatin C level at baseline and 24 h after PCI for each study group is presented in Table 2. Average concentrations of SCr and cystatin C levels were significantly increased in both groups after PCI (P <0.001) and this increase was more remarkable in the control group (Figures 2 and 3). However, on comparison between omega-3 and control groups, changes in SCr was not found to be statistically significant (P=0.08). On the other hand, analysis of the data revealed that there was a significant difference between both groups in the changes of concentration of cystatin C level after PCI (P<0.001). Therefore, treatment with omega-3 was more effective on the level of cystatin C than SCr.

Evaluation of patients' cystatin C markers did not show any CIN occurrences in the two groups. On the other hand, evaluation of creatinine showed one case of CIN occurrence in the omega-3 group (1.1%). Data analysis via the chi-square test revealed that no significant difference

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**Figure 1.** CONSORT trial flow diagram.

Legend: Randomized, double-blind, parallel-design, two-armed study (registered trial IRCT2016041920441N4). The 86 eligible subjects were randomly assigned to receive either omega-3 supplement plus routine hydration therapy (n = 44) or placebo plus routine hydration therapy (n = 44). The measurements and analysis were performed at 24 hours with 85 participants (n = 43 omega-3 group and n = 42 control group) while 3 subjects withdrew.
was observed between the two groups with regards to the occurrence of CIN ($P = 0.506$). Meanwhile, no significant difference was observed between the mean of age, weight and GFR between this patient and the rest of patients who were not afflicted by CIN.

According to the available literatures, this trial is the first randomized study evaluating the potential role of omega-3 supplement, as an antioxidant, in the prevention of CIN in patients treated with PCI.

CIN is an important medical issue, since it may lead to medical problems, such as acute renal failure, prolonged hospital stays, consequent complications, increased mortality rate, as well as higher medical cost. It has reported that even small increases in SCr and cystatin C levels caused by intravascular radiocontrast administration after CA are associated with adverse outcomes.\textsuperscript{21,22}

Up to now, numerous agents have been studied for the prevention of CIN. Despite strong logic behind the implementation of these substances, most of them were not that efficient. Hopefully, reported clinical trials provided relatively acceptable results in the use of antioxidants, such as N-acetylcysteine and ascorbic acid, as well as intravenous fluids including sodium bicarbonate in this setting.\textsuperscript{10-14}

Several studies have shown that supplementation with EPA and DHA, essential fatty acids of omega-3, can attenuate inflammatory diseases, including myocardial infarction.\textsuperscript{23-28} There are evidences that omega-3 fatty acids are capable of being used as adjunctive therapies in specific kidney diseases, such as Immunoglobulin A (IgA) nephropathy, chronic renal diseases, dialysis and renal cancers.\textsuperscript{29} Possible mechanisms suggested for the positive effects of omega-3 in the prevention of chronic kidney diseases are increasing the amount of eicosanoids and the endothelium derived relaxing factor in the blood, as well as decreasing the amount of inflammatory cytokines, such as IL-6, IL-1ra, TNF-alpha, sIL-6r and TGF-beta, blood pressure, serum triglycerides, and platelet aggregation.\textsuperscript{30-34} As a result, in this study, omega-3 was selected as the

### Table 1. Demographic data of the study and control groups

| Parameters                        | Omega-3 group (n = 43) | Control group (n = 42) | $P$ value |
|-----------------------------------|------------------------|------------------------|-----------|
| Sex: Male, No. (%)                | 31 (72.1)              | 30 (71.4)              | 0.946     |
| Age, year, mean ± SD              | 61.3 ± 5.74            | 56.7 ± 7.28            | 0.001     |
| Weight, kg, mean ± SD             | 76.74 ± 12.93          | 78.66 ± 8.15           | 0.312     |
| Diabetes mellitus, No. (%)        | 11 (25.6)              | 17 (40.5)              | 0.144     |
| Smoker, No. (%)                   | 7 (16.3)               | 8 (19)                 | 0.738     |
| Dyslipidemia, No. (%)             | 6 (14)                 | 6 (14.3)               | 0.965     |
| Hypertension, No. (%)             | 29 (67.4)              | 19 (45.2)              | 0.039     |
| GFR                               | 86.89 ± 10.02          | 94.71 ± 17.87          | 0.090     |

**Used Medications**

| Statin, No. (%)                   | 32 (74.4)              | 25 (59.5)              | 0.144     |
| Beta Blockers, No. (%)            | 32 (74.4)              | 18 (42.9)              | 0.003     |
| CCB, No (%)                       | 11 (25.6)              | 12 (28.6)              | 0.756     |
| ACEI and/or ARBs, No. (%)         | 28 (65.1)              | 25 (59.5)              | 0.595     |
| Aspirin, No. (%)                  | 24 (55.8)              | 31 (73.8)              | 0.083     |

SD, standard deviation; GFR, glomerular filtration rate; CCB, calcium channel blockers; ACEI, angiotensin converting enzyme inhibitors; ARBs, angiotensin receptor blockers.

### Table 2. Mean baseline and follow up values for Serum Creatinine and Serum Cystatin C levels of test and control groups and results of Repeated measure ANOVA

| Variable           | Group          | Baseline Mean ± SD | Follow up Mean ± SD | Change | $P$ value |
|--------------------|----------------|-------------------|---------------------|--------|-----------|
| Serum creatinine   | Omega-3 group  | 0.944 ± 0.085     | 0.998 ± 0.128       | 0.054  | 0.08      |
|                    | Control        | 0.936 ± 0.132     | 1.043 ± 0.159       | 0.107  |           |
|                    | Total          | 0.940 ± 0.1104    | 1.020 ± 0.145       | 0.080  |           |
| Serum cystatin C   | Omega-3 group  | 0.588 ± 0.353     | 0.824 ± 0.593       | 0.136  | <0.001    |
|                    | Control        | 0.781 ± 0.388     | 1.535 ± 0.612       | 0.754  |           |
|                    | Total          | 0.683 ± 0.381     | 1.175 ± 0.697       | 0.492  |           |
Omega-3 supplementation in the prevention of contrast induced nephropathy

In an animal study, it was concluded that preventive administration of omega-3 in renal reperfusion injuries in rats could lead to a decrease in renal dysfunction, oxidative stress and histological damages. These positive outcomes may be resulted from the effects of omega-3 in augmenting the level of anti-inflammatory markers and protective factors in the kidney, reducing pre-inflammatory factors, and limiting the access to arachidonic acid; therefore, preventing the consequential inflammatory process. Previous studies have stated that long-term use of unsaturated omega-3 fatty acids could improve renal function and reduce the risk of developing advanced stages of kidney disease. For instance, EPA is capable of producing positive effects in patients with lupus nephritis by reducing the oxidative stress. One study mentioned that daily consumption of 1.86 g EPA and 1.5 g DHA for one year could suppress progression of albuminuria in subjects with type 2 diabetes mellitus and coronary artery disease. Another study revealed that using omega-3 in patients with diabetes and hypertriglyceridemia could prevent the progression of diabetic nephropathy and preserved GFR in a dose dependent manner. Omega-3 can be effective in renal diseases, even in low doses; as it was shown in a clinical trial in which administration of 0.85 g EPA and 0.57 g DHA slowed progression of kidney dysfunction in high-risk patients with IgA nephropathy and particularly those with advanced renal disease.

In our study, less upward manner in the levels of both SCr and cystatin C were seen in the omega-3-treated patients, therefore; the addition of omega-3 to routine hydration therapy may be effective in the prevention of CIN in patients undergoing PCI. In contrast to creatinine, statistically significant difference was noted between the omega-3 and control groups in the terms of serum cystatin C. Although the benefit of treatment with omega-3 in reducing cystatin C did not translate to clinical outcome including significant decrease in CIN occurrence, still it may be of value in the prevention of renal dysfunction in the late phase after PCI similar to the effect of drugs, such as angiotensin-converting enzyme inhibitors.

Despite randomization, factors such as age and history of hypertension were statistically different between two groups; means patients in the omega-3 arm were older and had more history of hypertension than control group. Thus, to remove the cofounding effect of these variables, the repeated measure ANOVA test was used. Our analysis reported that the difference in age between study groups did not have any significant effect on kidney markers studied in this trial (P = 0.222 for creatinine, and P = 0.133 for cystatin C). On the other hand, our results showed that in normotensive and hypertensive patients, the rise of cystatin C level after PCI was significantly less in omega-3 group in comparison to control group (P < 0.001 in both hypertensive and normotensive patients) (Table 3). In other words, treatment with omega-3 was significantly effective on cystatin C levels regardless of hypertension. But considering SCr level, it was observed that our intervention was significantly more effective in patients without hypertension (P=0.029), in compare to patients with the history of hypertension (P=0.356) (Table 3). This result was not out of expectation since hypertension is one of the underlying risk factors affecting renal function following cardiac procedures and some studies showed that prior history of hypertension could be a good predictor of CIN.

This study had several limitations. The major limitation was that relatively few patients were evaluated. Second, patients were treated with a single dose of omega-3, while treating for longer period of time may reveal the positive effect of omega-3 much better. Third, the patient follow-up period was just 24 hours after PCI, while 72-hour SCr is more accurate than 24-h sample in the assessment of

### Table 3. Comparison of Mean baseline and follow up values for Serum Creatinine and Serum Cystatin C levels of test and control groups and results of Repeated measure ANOVA in patients with and without HTN

| Variable       | Group                | Baseline Mean ± SD | Follow up Mean ± SD | Change   | P value |
|----------------|----------------------|--------------------|---------------------|----------|---------|
| Serum creatinine| Omega-3 group       | 0.959 ± 0.650      | 0.956 ± 0.085       | -0.003   | 0.029   |
|                | Control              | 0.926 ± 0.138      | 1.026 ± 0.165       | 0.1      |         |
|                | Total                | 0.935 ± 0.115      | 1.003 ± 0.142       | 0.068    |         |
| Serum cystatin C| Omega-3 group       | 0.634 ± 0.397      | 0.761 ± 0.655       | 0.127    | <0.001  |
|                | Control              | 0.794 ± 0.304      | 1.569 ± 0.562       | 0.775    |         |
|                | Total                | 0.733 ± 0.346      | 1.264 ± 0.711       | 0.531    |         |
| Serum creatinine| Omega-3 group       | 0.941 ± 0.945      | 0.998 ± 0.128       | 0.057    | 0.356   |
|                | Control              | 0.947 ± 0.126      | 1.013 ± 0.143       | 0.066    |         |
|                | Total                | 0.943 ± 0.107      | 1.033 ± 0.147       | 0.09     |         |
| Serum cystatin C| Omega-3 group       | 0.565 ± 0.335      | 0.854 ± 0.571       | 0.289    | 0.004   |
|                | Control              | 0.765 ± 0.479      | 1.493 ± 0.670       | 0.728    |         |
|                | Total                | 0.644 ± 0.405      | 1.107 ± 0.686       | 0.463    |         |

HTN, Hypertension; SD, Standard deviation.

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CIN. Since patients were discharged 24 hours after PCI according to institutional program and most of them were from other cities, it was not possible to have their 72-hour blood sample for measuring the investigated markers.

Conclusion
The positive effect of omega-3 on cystatin C levels showed that it may have a protective role in the prevention of CIN in post-PCI patients with normal kidney function. However, to better assess this effect, it is highly recommended to design future studies with higher doses and longer duration of therapy with omega-3 plus long-term follow up.

Ethical Issues
Ethical approval was obtained from the ethics committee of the Shiraz University of Medical Sciences (ethics code: IR.SUMS.REC.1394.208).

Conflict of Interest
The Authors declare that there is no conflict of interest.

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