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Original article

Effect of omega-3 on brain natriuretic peptide and echocardiographic findings in heart failure: Double-blind placebo-controlled randomized trial

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ABSTRACT

Background: Possible beneficial effects of dietary omega-3 supplementation on patients with congestive heart failure (CHF) were investigated.
Methods and results: 100 patients with CHF who had a tri-chamber pacemaker and automated defibrillator were initially recruited, and 70 agreed to participate.38 patients received 2 g/day of omega-3 and 32 received placebo capsules. BNP level, 6-min walk test and echocardiographic parameters were recorded at baseline and after 6 months of treatment.
BNP levels decreased significantly after 6 months in the omega-3 group, from 1766.2 ± 1978.1 pg/mL to 1159.4 ± 1430.9 pg/dL ($P < 0.005$). Tei index and late diastolic velocity index were significantly improved in treated group. Mortality and hospitalization rates did not differ.
Conclusion: The beneficial effects of omega-3 supplementation in patients with CHF were not as clear as hypothesized; however, omega-3 fatty acids can result in small changes in plasma BNP levels and modest improvements in echocardiographically assessed diastolic function (Clinical trial.gov registration: NCT01227837).

1. Introduction

Heart failure is considered a major problem in both developed and developing countries, as one of the leading causes of morbidity and burden of disease.[1,2] It is estimated that around 23 million people are affected worldwide, with a prevalence of approximately 2% in the adult population in developed countries.[3] The prevalence of heart failure increases with age, and is higher than 66 per 1000 among those aged 80–89 years.[4,5] The mainstays of treatment are symptomatic therapy and efforts to slow the progression of the disease, as there is no definite treatment.[6] Several therapeutic medications have been introduced with various degrees of efficacy; however, they are not all effective and each has specific side effects which sometimes worsen the patient's general condition.[6] Numerous efforts have been made to develop newer and safer medications to treat heart failure symptoms.

N-3 polyunsaturated fatty acids (PUFA), also known as omega-3 fatty acids, reduce the risk of cardiovascular events in patients with chronic heart conditions.[7] At doses of 3–4 g/day, they are now widely used as lipid-lowering agents that mainly reduce levels of triglycerides.[8] Recently there have been reports of the beneficial effects of PUFA in patients with congestive heart failure (CHF).[9–11] Omega-3 supplementation can decrease plasma levels of inflammatory markers that contribute to the exacerbation and progression of CHF, including N-terminal pro-brain natriuretic peptide (NT-proBNP).[12,13] Some authors have concluded that omega-3 supplementation can prevent the development and progression of CHF, and it was shown in this connection that omega-3 fatty acids decrease the rate of sudden cardiac death in patients with CHF.[14–16] Omega-3 fatty acids also decrease the incidence of atrial fibrillation in these patients.[16–18]

However, there is still controversy over the actual efficacy and safety of omega-3 supplements as an alternative therapeutic agent for CHF.[15] In this double-blind placebo-controlled randomized clinical trial we aimed to investigate the effect of omega-3 supplementation on plasma concentrations of BNP, a diagnostic marker of CHF and its severity, along with its possible beneficial effects on the 6-min walk test and echocardiographic indicators in patients with class II or III heart failure in Shiraz, Iran.

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2. Materials and methods

2.1. Participants and recruitment

This double-blind placebo-controlled randomized trial was conducted in Shiraz (southern Iran) during a 1-year period from April 2008 to April 2009. The criteria for eligibility for recruitment were class II or III CHF resulting from underlying ischemic heart disease, previous registration with or admission to hospitals affiliated with Shiraz University of Medical Sciences, recorded ejection fraction (EF) of less than 40% on echocardiography, use of cardiac resynchronization therapy (CRT) and an automatic implantable cardiac defibrillator (AICD) for at least 6 months prior to registration, and no previous omega-3 supplementation. Patients with symptomatic CHF and hospital admission in the preceding 3 months, and any rhythm other than normal sinus rhythm, were excluded. Normal functioning of CRT and AICD was confirmed in all patients prior to registration. All medications were synchronized and each patient received digoxin, an angiotensin-converting enzyme inhibitor, a diuretic, a beta-blocker and a nitro group agent as oral medications.

The 100 patients initially considered eligible were contacted and invited to participate in the study. The study protocol was described to them, and they were informed that their anonymity would be protected and they had the right to withdraw from the study at any time during the trial. Of the 100 patients we approached, 70 agreed to participate. After contacting patients to register for the trial, the protocol and possible side effects were described in detail and written informed consent was obtained from each participant.

Physicians who were unaware of the protocol interviewed each patient with a standardized questionnaire to record personal and demographic data along with information about medications and other risk factors of CHF. A simple randomization technique was used to allocate patients to one of the two treatment protocols in the study. A nurse who was unaware of the patients' medication and condition randomized participants and delivered medications (placebo or omega-3) to patients. Medications were given to patients in the same unlabeled package, and were relabeled only after the study was completed. In group A, 38 patients received omega-3 supplements, and in group B (control), 32 patients received a placebo supplement. Participants in both groups were matched for age and sex and were unaware of which treatment arm they were assigned to. Fig. 1 shows the recruitment and allocation process.

2.2. Protocol definition and implementation

Group A received omega-3 supplementation in the form of capsules at a does of 2 g/day (two capsules per day each containing 1000 mg omega-3 fatty acid) for 6 months. Group B received placebo capsules that contained distilled water with color of omega-3 capsules, twice per day.

The patients' other medications were continued during the trial. All patients were followed monthly at the Faghihi Hospital echocardiography center by the same physician, who was unaware of their treatment allocation. In monthly meetings with the study nurse, who was unaware of the treatment allocation, each patient was given a month's supply of the medication and any questions they had were answered.

At baseline and before treatment began, 4 mL of blood was drawn from each individual to measure baseline plasma concentration of BNP. Patients were then asked to perform a 6-min walk test and a cardiologist performed conventional and tissue-specific echocardiographic studies (ACUSON S 2000™ Cardiovascular, Siemens, Erlangen, Germany). All data were recorded in each patient's spreadsheet. After 6 months echocardiography, BNP determination and the 6-min walk test were repeated in all participants, and outcome analysis was performed as per the protocol or according to intention to treat.

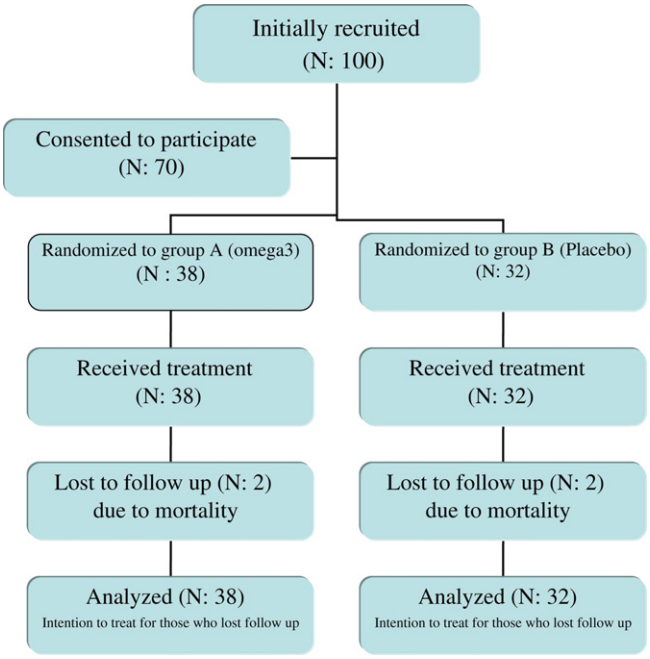

Fig. 1. Patient allocation and study design.

The study protocol was reviewed and approved by the Shiraz University of Medical Sciences Ethics Committee. The protocol design and reporting complied with the Consolidated Standards of Reporting Trials (CONSORT) statement.[19]

2.3. Outcome measures

Three different outcomes were measured to compare the efficacy of omega-3 fatty acid administration in patients with CHF. Brain natriuretic peptide, a hormonal peptide that increases significantly in CHF due to increased filling pressure of the atria, was assessed as an indicator of CHF severity and a prognostic factor. Plasma BNP concentration was measured at baseline and after 6 months of treatment with a chemiluminescent enzyme immunoassay, for which 4 mL of blood was drawn from an antecubital vein in each patient, transferred to tubes with no anticoagulant, centrifuged at 2000 rpm and frozen at −20 °C. Elecsys proBNP sandwich immunoassay kits (Roche Diagnostics, Mannheim, Germany) were used to measure NT-ProBNP concentration in each blood sample, and the results were reported in μg/mL.

Two-dimensional and conventional tissue-specific echocardiography was performed by the same cardiologist throughout the study, who was unaware of which group the participants had been assigned to. Echocardiographic studies were done at baseline and after 6 months to record wall motion, filling pressure and EF to evaluate the possible beneficial effects of omega-3 supplements.

2.4. 6-min walk test

Patients were asked to perform the 6-min walk test on a flat surface at baseline and after 6 months. Walking distance was measured in meters and distances were recorded in each participant's spreadsheet.

2.5. Statistical analysis

All data are reported as the mean ± standard deviation. Baseline and 6-month echocardiographic findings, the results of the 6-min walk test and plasma BNP concentrations were compared within each treatment group and between groups A and B with the Kolmogorov–Smirnov one-sample test. All statistical analyses were done with SPSSv. 11.5 software. *P* values less than 0.05 were considered statistically significant.

3. Results

During the course of the trial 3 patients in group A and 1 patient in group B withdrew from the study. Another 3 patients (1 in group B and 2 in group A) died during the trial. These patients were included in the intention to treat analysis. Table 1 summarizes the demographic characteristics, baseline BNP concentrations and echocardiographic features in participants in both groups at the start of the study.

The average distance walked at baseline was 281.7 ± 108.4 m in group A and 264.2 ± 117.5 m in group B ($P = 0.83$). However, after 6 months no significant increase was seen in patients who received omega-3 supplements compared to the placebo group (319 ± 103.8 vs. 274.1 ± 127.9, $P = 0.06$) (Table 2 and Table 3).

After 6 months, a significant decrease in plasma BNP concentration was observed in patients who received omega-3 compared to baseline (1766.2 ± 1978.1 pg/mL vs. 1159.4 ± 1430.9 pg/mL, $P < 0.005$). In the placebo group the decline from baseline levels was not statistically significant after 6 months (Table 2).

The Tei index decreased significantly more after 6 months in group A than in group B. The late diastolic velocity (Am) index improved significantly more in the omega-3 group than in the placebo group. Almost all echocardiographic indices improved significantly after 6 months in participants who received omega-3. However, the changes compared to the placebo group were statistically significant only for Tei index and Am index. Table 3 summarizes the mean changes in echocardiographic parameters in both groups after 6 months.

No significant differences between groups were found for the incidence of myocardial infarction or hospitalization due to worsening CHF. Mortality rate did not differ significantly between groups during the 6-month study period. In group A, 2 patients (4.2%) died after a major cardiovascular event (including myocardial infarction), and in group B, 1 patient died (3.6%, $P = 0.73$).

4. Discussion

Earlier research found that omega-3 supplementation has beneficial effects on mortality and hospital admissions in patients with CHF.[11,20,21] This fatty acid is associated with a reduced response of myocytes to noradrenaline, which plays an important role in worsening CHF as a neurohormonal response.[16] The effect of omega-3 was attributed to its ability to lower intracellular calcium and inhibit myocyte activity. Several trials have demonstrated the antiarrhythmic properties of omega-3 PUFA in patients with a history of myocardial infarction.[21,22] Other research has reported the antiarrhythmic potential of omega-3 acid ethyl esters, which can prevent recurrent atrial fibrillation in patients with no structural heart disease.[7,18] Fiaccavento et al noted that omega-3 PUFA prolonged survival and inhibited myocardial pathologies in hamsters with cardiomyopathy.[10]

To our knowledge no studies have been done to evaluate the effect of omega-3 supplementation on echocardiographic parameters in CHF patients. We investigated the effect of 2 g/day of omega-3 on echocardiographic parameters in patients with class II or III heart failure due to ischemic causes. We saw a significant improvement in most echocardiographic parameters after 6 months; however, these changes were not significant compared to

Table 1
Demographic features of patients in both groups.

Demographic features	Treatment group	Placebo group	*P* value*
Age (years)	56	58	0.4
Male gender (%)	58	61	0.34
Smoking (%)	34	28	0.2
Diabetes (%)	39	32	0.38
Hypercholesterolemia (%)	24	30	0.8
High blood pressure (%)	23	34	0.5

*Indicate the level of significance of *P*.

Table 2
Plasma BNP level, 6-min walk test results and echocardiographic parameters at baseline and after 6 months in the two groups.

Variables	Group	Baseline	After 6 months	*P* value*
Plasma BNP (pg/mL)	Omega-3	1766.23 ± 1978	1159.4 ± 1430.9	0.0005
	Placebo	1802 ± 1670	2121.5 ± 2703.9	0.32
6-min walk test (m)	Omega-3	284.2 ± 111.57	319.27 ± 103.8	0.0005
	Placebo	262 ± 121.74	274.15 ± 127.9	0.49
End systolic diameter (mm)	Omega-3	50.56 ± 12.37	53.35 ± 10.81	0.01
	Placebo	50.42 ± 13.69	53.76 ± 12.41	0.02
End diastolic diameter (mm)	Omega-3	61.83 ± 9.61	64.32 ± 11.65	0.03
	Placebo	61.15.11.42	64.15 ± 12.23	0.04
Ejection fraction (%)	Omega-3	30.59 ± 9.23	31.75 ± 9.40	0.13
	Placebo	31.69 ± 9.12	34.26 ± 9.09	0.01
Left ventricular mass (gr)	Omega-3	284.51 ± 106.41	242.91 ± 89.58	0.004
	Placebo	269.3 ± 87.33	256.3 ± 95.18	0.42
End systolic volume (cc)	Omega-3	101.51 ± 38.21	99.29 ± 42.23	0.37
	Placebo	101.11 ± 52.88	111.19 ± 71.3	0.22
EM index (cm/s)	Omega-3	14.91 ± 6.33	13.43 ± 4.2	0.06
	Placebo	15.61 ± 10.47	11.88 ± 4.87	0.08
AM index (cm/s)	Omega-3	11.41 ± 4.22	10.25 ± 4.36	0.025
	Placebo	12.06 ± 6.05	11.22 ± 4.37	0.52
SM (cm/s)	Omega-3	12.02 ± 3.96	9.4 ± 3.57	0.000
	Placebo	11.13 ± 4.01	9.33 ± 4.08	0.08
Tei index	Omega-3	0.9 ± 0.35	0.8 ± 0.25	0.04
	Placebo	0.8 ± 0.31	0.9 ± 0.36	0.31

*$P < 0.05$ is considered statistically significant. BNP: brain natriuretic peptide; Em: early diastolic velocity; Am: late diastolic velocity; Sm: systolic velocity.

Table 3
Mean changes in plasma BNP levels, 6-min walk test results and echocardiography parameters after 6 months in the omega-3 and placebo groups.

Variables	Treatment group (%)	Placebo group (%)	*P* value*
Plasma BNP levels pg/mL (% decline from baseline)	606.8 ± 1325.6 pg/mL (1.1% ± 100%)	1100.6 ± 4899 pg/mL (−0.3% ± 56%)	0.47
6-min walk test (% change from baseline in m)	35 ± 61.2 (18% ± 29%)	12.1 ± 90.2 (5% ± 35%)	0.06
Aortic orifice (mm)	29 ± 4.5	30 ± 4	0.07
Left atrial size (mm)	42 ± 7	40 ± 6	0.17
PAT (msec)	118 ± 30	126 ± 3	0.14
End systolic diameter (mm)	−8 ± 17	−9 ± 15	0.41
End diastolic diameter (mm)	−4 ± 13	−5 ± 13	0.36
Ejection fraction (%)	7 ± 26	10 ± 24	0.28
Left ventricular mass (cc)	10 ± 30	2 ± 25	0.14
End systolic volume (cc)	−1 ± 40	−13 ± 45	0.15
EM index (cm/s)	−0.1 ± 35	−9 ± 39	0.16
AM index (cm/s)	−7 ± 30	19 ± 91	0.04
SM index (cm/s)	−16 ± 39	−6 ± 43	0.18
Tei index	4 ± 33	−23 ± 57	0.011

*$P < 0.05$ is considered statistically significant. PAT: pulmonary acceleration; Em: early diastolic velocity; Am: late diastolic velocity; Sm: systolic velocity.

those in patient who received the placebo. Although the improvements in the omega-3 supplementation group were small, the beneficial effects cannot be overlooked, and included improvements in the Tei and late diastolic velocity indices as markers of diastolic left ventricular function. Omega-3 PUFA had no significant impact on the 6-min walk results or plasma BNP levels compared to the placebo, although some beneficial effects were observed in both groups. The lack of a statistically significant improvement in patients with class II and III heart failure in this study may be a result of the small number of patients enrolled, and as found in earlier studies, the degree of improvement with any therapy for patients with class II and II heart failure is not large. For example, improvements in survival with angiotensin-converting enzyme inhibitors in patients with heart failure were seen in only 16% of the patients treated in all classes of heart failure not in refractory heart failure patients like ours.[23]

Plasma BNP concentration is an indicator of the severity of heart failure, and increases exponentially as cardiac condition worsens.[24–28] Zhao et al studied 76 patients with CHF and reported that omega-3 supplements significantly reduced inflammatory markers and NT-ProBNP. They concluded that omega-3 supplementation may reduce mortality in patients with heart failure.[12] We used the same dose of omega-3 as Zhao and colleagues (2 g/day). They reported a mean decrease in plasma NT-ProBNP levels of 138 ± 82 pg/mL after 3 months, compared to a decrease of 606 ± 1325.6 pg/mL in our patients after 6 months. Unlike us, Zhao and colleagues found a significant decrease in BNP levels in their treatment group compared to their placebo group. However, like us, they found no significant improvement in EF after treatment with the PUFA (2% increase in EF, $P > 0.05$).

Omega-3 supplementation did not change the echocardiographic parameters, and did not result in any improvement in systolic function markers. However, it significantly improved the Tei index, a sensitive marker of diastolic function. In the late stages of CHF any minor change in echocardiographic indexes may significantly affect the course of the disease, although changes in echocardiographic parameters are small and do not predict the survival benefit with any therapies. Additional long-term studies in larger series of patients are thus needed to determine the significance of these changes in response to omega-3 PUFA supplementation.

Our findings showed some advantages of dietary omega-3 supplementation in patients with class II and III heart failure who did not respond to routine medical therapy, and who had a biventricular pacemaker for mechanical support. In particular, omega-3 fatty acid improved echocardiographic parameters and lowered plasma BNP concentrations in the short term. Although the effects were small, these potential benefits in patients with severe heart failure merit further attention considering that omega-3 supplementation is safe and has few side effects.[18]

5. Limitations

The small sample size could have affected the results, especially with regard to BNP plasma levels. Therefore a larger sample size could help measure the beneficial effects of omega-3 fatty acids on plasma BNP levels more accurately. This trial showed an overall beneficial effect of omega-3 supplementation in patients with CHF, especially in echocardiographic parameters. However, larger multicenter clinical trials should be conducted with longer follow-up periods to more accurately determine the benefits of omega-3 supplementation with regard to BNP levels, and to characterize its influence on long-term morbidity and mortality in patients with CHF.

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Disclosures

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Conflicts of Interest

All authors have none to declare.

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