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The Effects of Omega-3 on Liver Damage after Acute Myocardial Infarction: A Randomized Controlled Clinical Trial

Maryam Moghimian [1], Seyed-Hosein Abtahi-Eivary [2], Mahmood Reza Nematollahi [3], Abbas Ebadi [4], Ali Alami [5], Narjes Bahri [6,*]

[1] Department of Basic Sciences, School of Medicine, Gonabad University of Medical Sciences, Gonabad, IR Iran
[2] Department of Biochemistry and Nutrition, Faculty of Medicine, Gonabad University of Medical Sciences, Gonabad, IR Iran
[3] Department of Internal Medicine, Faculty of Medicine, Gonabad University of Medical Sciences, Gonabad, IR Iran
[4] Department of Medical Emergency, Bohlool Hospital, Gonabad University of Medical Sciences, Gonabad, IR Iran
[5] Department of Epidemiology and Biostatistics, School of Public Health, Gonabad University of Medical Sciences, Gonabad, IR Iran
[6] Department of Midwifery, Faculty of Medicine, Social Development and Health Promotion Center, Gonabad University of Medical Sciences, Gonabad, IR Iran

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ABSTRACT

Background: Abnormal liver function test results are often observed in patients with acute Myocardial Infarction (MI).

Objectives: This study aimed to evaluate the effects of omega-3 fatty acids on Alanine Aminotransferase (ALT) activity elevation after MI-induced liver injury.

Methods: In this randomized clinical trial, 75 patients with acute MI were randomly allocated to an intervention and a control group. The intervention group received 1 gram per day equal to three capsules of Pikasol (fish oil) for three months, while the control group received the routine treatment after MI. In all samples, plasma concentrations of ALT were assessed on the admission day and 2, 30, 60, and 90 days after the intervention. The data were analyzed using the SPSS 16 software, and $P < 0.05$ was set as the level of statistical significance.

Results: The results showed no significant differences between the two groups regarding age, sex, Body Mass Index (BMI), and systolic and diastolic blood pressure. The results also indicated no significant differences between the two groups concerning the serum level of ALT on the day of admission ($P = 0.68$), day 2 ($P = 0.79$), day 30 ($P = 0.86$), day 60 ($P = 0.09$), and day 90 ($P = 0.64$).

Conclusion: The study results suggested that the patients receiving omega-3 supplementation following MI had similar ALT levels to those who received no supplementations. However, further studies with larger sample sizes are needed to confirm the results.

1. Background

It is well known that liver function disturbances occur commonly in cardiac disease and patients with acute and chronic heart failure develop manifestations from the liver (1). In fact, abnormal liver function test results are often observed in patients with acute Myocardial Infarction (MI) (2).

The remote outcomes of Ischemia Reperfusion (IR) are most often seen in pulmonary, renal, hepatic, and cardiovascular systems, and can result in development of the systemic inflammatory response and various organ dysfunction syndromes, accounting for 30 - 40% of mortality in intensive care units (1, 3). One of the important remote organ injuries in myocardial IR may be liver injury, which is believed to be a consequence of free-radical generation in the liver (4). The incidence of liver injury is increasing worldwide. Viral infection, alcohol or drug toxicity, and many other factors including IR can cause damage to hepatocytes. Therefore, these factors may cause inflammatory and oxidant reactions in the liver (5). In this context, acute central necrosis of the liver was first described histologically in congestive heart failure by Kiernan in 1833 (6). Some studies have also shown that an abrupt increase in serum hepatic transaminase related to cardiogenic shock could reveal extensive hepatocellular

*Corresponding author: Narjes Bahri Department of Midwifery, Faculty of Medicine, Social Development and Health Promotion Center, Gonabad University of Medical Sciences, Gonabad, IR Iran.
Cellphone: +98- 9155000489,
Email: nargesbahri@yahoo.com.

necrosis (7). Clinicians are often encountered with elevated liver enzymes in patients with MI (8). The recognition and diagnosis of cardiac hepatopathy are important as liver damage can influence the prognosis and outcome of the cardiac disease. However, there is no specific therapy for ischemic hepatitis.

Strategies to minimize the generation of reactive oxygen species after ischemic liver injury included vitamin C and vitamin E therapy, glutathione, and allopurinol (9). Nevertheless, no data have supported the routine clinical use of these treatments. In this regard, it has become evident in both epidemiological studies and clinical trials that marine n-3 Polyunsaturated Fatty Acids (PUFAs) may protect against ischemic heart disease (10). Dietary n-3 PUFAs might reduce fatal MI, malignant ventricular arrhythmias, and sudden cardiac death, as reported in animals (11). In rat models of liver IR, the severity of liver injury could be blunted by diets that included juniper berry oil and fish oil compared to those including linoleic acid (12). Additionally, clinical trials in post-infarction patients confirmed decreased mortality with a daily intake of fish or fish oil without causing changes in blood pressure, blood lipids, or new cardiac emergencies (13). It has also been indicated that using dietary supplements, such as omega-3 fatty acids, might help alleviate liver injury in Non-Alcoholic Fatty Liver Disease (NAFLD) (14).

Although there has been considerable research on the effects of PUFAs in vitro and in animal models, clinical research has been relatively limited. Much less is known about the effect of PUFAs in patients with MI. Moreover, no data have been reported on improvement of hepatic dysfunction in these patients.

2. Objectives

In view of the beneficial effects that PUFAs appear to exert against ischemic heart disease, the present study aims to investigate the effect of supplementation with omega-3 fatty acids on liver injury induced by MI.

3. Patients and Methods

3.1. Trial Design

The study design was a single-blind randomized controlled trial including two parallel arms in a 1:1 ratio. The protocol of this study was approved by the Research Council of Gonabad University of Medical Sciences under registration code 92/78923. This study was also registered in Iranian Registry of Clinical Trials (IRCT, registration code: IRCT2013060213550N1). The clinical trial was reported based on the CONSORT statement 2010 checklist (15).

3.2. Participants and Setting

This study was conducted on patients with acute MI according to World Health Organization's (WHO) criteria (typical clinical symptoms, electrocardiographic changes, and enzyme changes) in coronary care unit of 22 Bahman hospital in Gonabad. The inclusion criteria of the study were having no history of liver disease and other potential causes of acute and chronic liver injury, such as viral hepatitis, metastatic liver disease, cardiogenic shock, and heart failure, and having no history of stroke within the last six months. The exclusion criteria were having a previously known history of hepatic dysfunction and acute hepatobiliary diseases, having a recent history of operation of hepatobiliary diseases, having a past history of benign or malignant chronic liver diseases, having a history of traumatic liver during this disease course, and other factors leading to liver dysfunction (drug abuse, drinking, poison, and hepatotoxic medications).

3.3. Sample Size and Randomization

According to previous studies, the prevalence of liver damage was 0.35. The researchers expected that omega-3 consumption would reduce the hepatic damage to 10%. Therefore, considering the significance level of 95% and test power of 80% and using the following formula, a 84-subject sample size was determined for the study (42 subjects in each group).

$$n = \left[2\left(Z_{1-\alpha/2} + Z_{1-\beta}\right)^2 * \bar{P}(1-\bar{P})\right]/(P1-P2) = 42$$

[Z 1-α/2= 1.96, Z 1-β = 0.84, P1= 0.35, P2= 0.10].

The study subjects were selected by census. In this way, all patients who visited the hospital during the study and had the inclusion criteria were entered into the study. The subjects were then randomly assigned to intervention and control groups via permuted block randomization. Afterwards, the patients who had the exclusion criteria were excluded from the study. The sampling process continued to reach the required sample size (Figure 1).

3.4. Intervention and Outcomes

The intervention group received omega-3 (fish oil containing eicosapentaenoic acid (180 mg) and docosahexaenoic acid (120 mg); 1 gram per day equal to one capsule of Pikasol) for three months, while the control group received the routine treatment for MI. Blood test was performed to assess the serum level of Alanine Aminotransferase (ALT) as the outcome measure. The tests were performed on admission and days 1, 2, 30, 60, and 90. ALT activities were also measured by conventional methods using an Olympus AU-2700 analyzer (Olympus Co., Tokyo, Japan).

3.5. Statistical Analysis

The data were expressed as number and percentages for qualitative variables and as mean ± SD or median with interquartile range (if the data were not normally distributed) for quantitative ones. Normal distribution of the data was tested using Kolmogorov-Smirnov test. Since several variables were not normally distributed, non-parametric statistical tests were applied. Repeated measures ANOVA was also used to analyze the data. All analyses were performed using the SPSS 20.0 (SPSS Inc. Chicago, IL) and R 3.3.0 software. Significance level was set at $P < 0.05$.

3.6. Ethical Considerations

The trial protocol was approved by the regional Ethics Committee (code: 92/78923). Written informed consents for participation in the study were obtained from all participants. Besides, the data were gathered and analyzed anonymously.

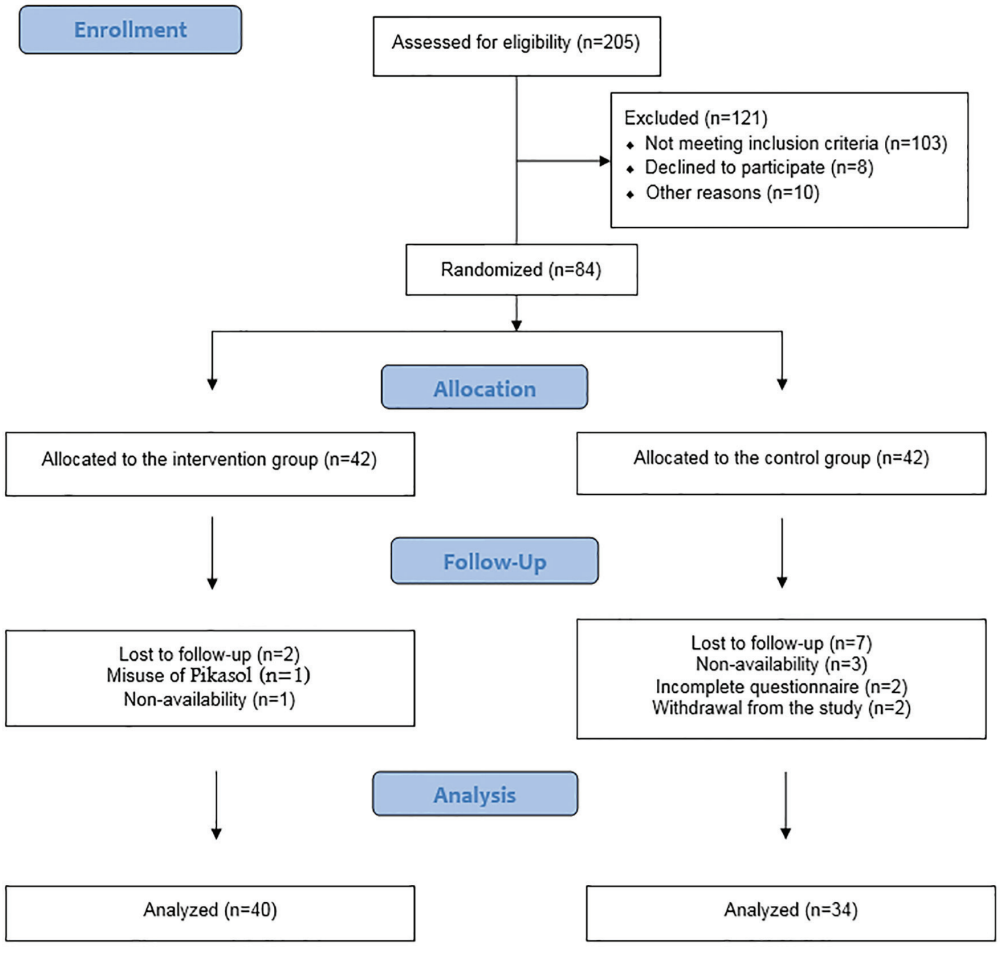

Figure 1. CONSORT Flowchart of the Study

4. Results

Out of the 84 participants, nine left the study. Finally, 40 participants from the intervention group and 35 ones from the control group completed the study. Some of the baseline characteristics of the two groups have been presented in Table 1. The results showed no significant differences between the two groups with respect to age, sex, BMI, and systolic and diastolic blood pressure ($P > 0.05$).

Serum ALT levels were measured on day of admission, day 2, day 30, day 60, and day 90 after MI. The results of student's t-test showed no significant differences between the two groups in terms of serum ALT levels on day of admission ($P = 0.68$), day 2 ($P = 0.79$), day 30 ($P = 0.86$), day 60 ($P = 0.09$), and day 90 ($P = 0.64$) (Table 2).

The results of repeated measures ANOVA showed that the within group effect was not significant based on Greenhouse-Geisser method ($P = 0.07$). Accordingly, no significant differences were observed in the two groups regarding ALT levels during the study ($P = 0.49$) (Table 2).

The results indicated that ALT plasma activity increased in about 40.7% of the patients ($n = 16$) in the omega-3 group and 28% of those ($n = 10$) in the control group on day 2. This was significant compared to normal ranges although there was no significant difference between the two groups. The less frequent elevation of ALT observed in this study included delayed peak between days 1 and 3 and more prolonged return to the baseline.

5. Discussion

The present randomized clinical trial aimed to investigate the occurrence of elevated ALT levels in patients with acute MI. The results revealed that omega-3 therapy did not have any significant effects on the primary outcome. The less frequent elevation of ALT observed in this study included delayed peak between days 1 and 3 and more prolonged return to the baseline, suggesting a possible hepatic release of ALT rather than a primary cardiac source.

Patients with higher liver enzyme elevations were likely to have an anterior MI location. Indeed, the higher ALT values in the study groups could be related to MI as it has become evident that some types of liver injury secondary to acute MI could be responsible for this phenomenon (16). However, the quantitative analysis showed that the release of ALT in most of these patients conformed to the myocardial release pattern. Previous studies on acute MI patient populations have also shown similar patterns of ALT release (17). These data were also supported by other reports, which showed that ALT was elevated in 48.2% of patients and elevations greater than 10-times the Upper Limit of Normal (ULN) occurred in 58 patients with MI (3.3%) (8). In the same vein, the prevalence of hypoxic liver injury was considerably high (22%) in Moon's cohort study (18). Conversely, extra release of hepatic ALT in acute MI was not observed by Glesen (19). In uncomplicated infarctions also, plasma activities of ALT did not exceed the ULN. ALT release can be explained by

Table 1. Baseline Sociodemographic Characteristics of the Two Groups

Variables		Control group, (n = 40)	Omega-3 group (n=35)	P-value
Age (Mean ± SD)		61.77 ± 12.85	61.94 ± 11.50	0.95 [a]
Sex, n (%)	Male	25 (69.4%)	23 (59.0%)	0.34 [b]
	Female	11 (30.6%)	16 (41.0%)	
Body mass index (Mean ± SD)		26.88 ± 4.42	25.39 ± 3.56	0.11 [a]
Systolic blood pressure (Mean ± SD)		14.10 ± 2.67	13.85 ± 1.79	0.63 [a]
Diastolic blood pressure (Mean ± SD)		87.63 ± 1.74	8.74 ± 1.34	0.96 [a]

[a] Independent samples t-test was used, [b] Chi-square test was used.
P < 0.05 indicates statistical significance

Table 2. Comparison of Serum ALT Levels in the Two Groups during the Study

ALT Groups	Admission (Mean ± SD)	Day 2 (Mean ± SD)	Day 30 (Mean ± SD)	Day 60 (Mean ± SD)	Day 90 (Mean ± SD)
Omega-3 group	35.90 ± 23.01	40.20 ± 20.77	36.83 ± 37.63	31.16 ± 8.35	31.56 ± 11.82
Control group	36.38 ± 21.62	34.07 ± 12.44	33.61 ± 19.29	33.07 ± 14.89	31.46 ± 16.11
P-value [a]	0.68	0.79	0.86	0.09	0.64
P-value [*]	within group = 0.07		between group = 0.49		

[a] t-test was used, P < 0.05 indicates statistical significance.
[*] Repeated measures ANOVA was used, P < 0.05 indicates statistical significance

myocardial damage up to approximately 48 h after acute MI. Further release of ALT in the absence of creatinine kinase release after 48 h is highly specific to liver damage and is not related to infarct size (20). Besides, liver cells necrosis as a result of heart failure is well known (21, 22). This would presumably be due to hepatic congestion or relative hypotension associated with larger MIs.

ALT is primarily concentrated in hepatocytes and renal tubular epithelium, but some activity is present in skeletal and cardiac muscles (23). It has been proposed that mild increases in liver enzyme levels indicate systemic inflammation that emanates from hepatic inflammation (24).

It was demonstrated that cytokines synthesis by the ischemic myocardium could directly be responsible for post-MI apoptosis in the limbic system, but other signal transduction mechanisms could be involved, as well (25). IR injury is a common and inevitable problem after revascularization therapy. The mediators from the ischemic tissue affect other organ systems. The remote effects of IR are most often seen in the pulmonary, renal, hepatic, and cardiovascular systems, and can result in an increase in the systemic inflammatory response and many organ dysfunction syndromes (3). The liver possesses a high capacity of protection and regeneration in response to mechanical and chemical injuries. Liver cells are capable of rapid proliferation during liver regeneration (26-28). Determination of cardiac hepatopathy is essential since it can affect the prediction and outcome of the heart disease (7). Strategies to minimize liver injury have included vitamin C and vitamin E therapy, glutathione, and allopurinol. However, no studies have supported the routine clinical use of these treatments.

In the present study, details about liver function in patients with MI and ALT elevations were not collected. This could have helped determine if cardiac tissue, hepatic tissue, or both were the source of ALT elevations.

Marine n-3 PUFAs may protect against ischemic heart disease (29). A previous study indicated that fish oil decreased hepatic reperfusion damage in low flow, reflow perfusion a rat model (30). In mechanistic studies, omega-3 fatty acids appeared to inhibit the fast, voltage-dependent sodium currents and the L-type calcium currents in excitable cardiac tissues (31). Moreover, essential fatty acids constitute an important component of all cell membranes and influence membrane fluidity and the behavior of membrane-bound enzymes and receptors (32). Prostaglandin E1 (PGE1) also presented protection after reperfusion via a variety of mechanisms, including development of liver perfusion (33). PGE1 protected cultured human liver sinusoidal endothelial cells from apoptosis through inhibiting the release of inducible nitric oxide synthase and matrix metalloproteinase (34).

Recently, it was reported that acute post-ischemia treatment with PUFAs remarkably exacerbated cerebral IR injury partly through augmented oxidative burden (35). It is notable that there are many intra-individual variabilities in liver tests, which may decrease the sensitivity to detect significant changes in this parameter with interventions. It should also be noted that all the current study patients presented with MI and only moderately elevated liver function test values at baseline.

The effects of omega-3 Long Chain-Poly Unsaturated Fatty Acid (LC-PUFA) supplementation in the present study confirmed the results of the previous investigations. However, a controversy was raised from the study performed by Lo et al. (36), which stated that dietary supplementation with fish oil did not decrease hepatic damage in rats after warm IR. A systematic review and meta-analysis was also carried out on nine studies (five randomized controlled trials) involving a total of 355 individuals to investigate omega-3 LC-PUFA supplementation in adults with NAFLD. LC-PUFA was given in doses from 0.25 to 13.7 g/day and the duration of therapy ranged from 8 weeks to 12 months. The results indicated that omega-3 fatty acids significantly decreased AST but not ALT levels (37). On the other hand, a recent systematic review of available randomized controlled trials, which included sub-analysis of the efficacy of n-3 PUFA supplementation in reducing ALT levels failed to

provide a definitive conclusion regarding its efficacy in reducing liver fat in humans (38).

There are several limitations to this study, the most notable of which being the lack of a placebo-treated group. In addition, the duration of the intervention and dose of omega-3 PUFA might alter the effects of supplementation. Yet, the duration of the treatment was similar to that in other trials using supplements, such as omega-3 PUFAs, to provide reliable therapeutic results.

Overall, the present study results suggested that patients receiving omega-3 supplementation following MI had similar ALT levels to those receiving no supplementations. However, these results are needed to be confirmed in future studies containing larger sample sizes.

5.1. Conclusion

This study suggested that patients receiving omega-3 supplementation following MI had similar ALT levels to those receiving no supplementations. However, further studies with larger sample sizes are required to be conducted on the issue.

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Authors' Contribution

Study design and concept: M M, N B, H A, M N, A A, and A E; Data acquisition: M M and M N; Analysis and interpretation: N B, M M, and A A; Drafting of the manuscript: N B and M M

All authors have read the draft of the manuscript and have confirmed its final version.

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The authors have no financial interests related to the material in the manuscript.

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