International Journal of Cardiology 176 (2014) 577–582

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Early eicosapentaenoic acid treatment after percutaneous coronary intervention reduces acute inflammatory responses and ventricular arrhythmias in patients with acute myocardial infarction: A randomized, controlled study

Masayuki Doi [a,*], Kazumasa Nosaka [a], Toru Miyoshi [b], Mutsumi Iwamoto [a], Masahito Kajiya [a], Keisuke Okawa [a], Rie Nakayama [a], Wataru Takagi [a], Ko Takeda [a], Satoshi Hirohata [c], Hiroshi Ito [b]

[a] Department of Cardiology, Kagawa Prefectural Central Hospital, 1-2-1 Asahi-machi, Takamatsu, Kagawa 760-8557, Japan
[b] Department of Cardiovascular Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Okayama 700-8558, Japan
[c] International Center, 2-1-1 Tsushimanaka, Okayama 700-8530, Japan

ARTICLE INFO

Article history:
Received 21 April 2014
Received in revised form 7 August 2014
Accepted 9 August 2014
Available online 19 August 2014

Keywords:
Eicosapentaenoic acid
Acute myocardial infarction
Complication
Arrhythmia

ABSTRACT

Objective: We examined whether early loading of eicosapentaenoic acid (EPA) reduces clinical adverse events by 1 month, accompanied by a decrease in C-reactive protein (CRP) values in patients with acute myocardial infarction (MI).
Background: Acute MI triggers an inflammatory reaction, which plays an important role in myocardial injury. EPA could attenuate the inflammatory response.
Methods: This prospective, open-label, blinded endpoint, randomized trial consisted of 115 patients with acute MI. They were randomly assigned to the EPA group (57 patients) and the control group (58 patients). After percutaneous coronary intervention (PCI), 1800 mg/day of EPA was initiated within 24 h. The primary endpoint was composite events, including cardiac death, stroke, re-infarction, ventricular arrhythmias, and paroxysmal atrial fibrillation within 1 month.
Results: Administration of EPA significantly reduced the primary endpoint within 1 month (10.5 vs 29.3%, $p = 0.01$), especially the incidence of ventricular arrhythmias (7.0 vs 20.6%, $p = 0.03$). Peak CRP values after PCI in the EPA group were significantly lower than those in the control group (median [interquartile range], 8.2 [5.6–10.2] mg/dl vs 9.7 [7.6–13.9] mg/dl, $p < 0.01$). Logistic regression analysis showed that EPA use was an independent factor related to ventricular arrhythmia until 1 month, with an odds ratio of 0.29 (95% confidence interval, 0.09 to 0.96, $p = 0.04$).
Conclusions: Early EPA treatment after PCI in the acute stage of MI reduces the incidence of ventricular arrhythmias, and lowers CRP values.

1. Introduction

Acute myocardial infarction (MI) triggers an inflammatory reaction, which plays an important role in myocardial injury [1]. Inflammatory markers, such as C-reactive protein (CRP), reflect the extent of myocardial necrosis and correlate with cardiac outcomes following acute MI [2–7]. However, an effective intervention which reduces inflammatory response after acute MI remains unknown.

n−3 polyunsaturated fatty acid (PUFA), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), can attenuate inflammatory response by modulating several pathways. Thromboxanes and leukotrienes derived from n−3 PUFAs are usually much less potent local mediators than the corresponding n−6 PUFA derivatives in orthodox pathways [8,9]. EPA and DHA also have local anti-inflammatory effects that might be difficult to detect with circulating biomarkers. EPA and DHA are precursors to resolvins, protectins, and other inflammation-resolving mediators that have potent anti-inflammatory properties and enhance the resolution of inflammation [10–13]. Several studies have shown that n−3 PUFAs have anti-arrhythmic effects in patients with healed MI [14,15]. However, whether this anti-arrhythmic effect

Abbreviations: AA, arachidonic acid; CK, creatine kinase; CRP, C-reactive protein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MI, myocardial infarction; PCI, percutaneous coronary intervention; PUFA, polyunsaturated fatty acid.

* Corresponding author. Tel.: +81 87 811 3333; fax: +81 87 802 1188.
E-mail addresses: mdoimd@gmail.com (M. Doi), kn_orch@yahoo.co.jp (K. Nosaka), miyoshit@cc.okayama-u.ac.jp (T. Miyoshi), mutsum0808@yahoo.co.jp (M. Iwamoto), kajiyanneko@yahoo.co.jp (M. Kajiya), drop-in-bigriver@hotmail.co.jp (K. Okawa), rie59828@yahoo.co.jp (R. Nakayama), t_wataru1206@yahoo.co.jp (W. Takagi), kou@chp-kagawa.jp (K. Takeda), hirohas@cc.okayama-u.ac.jp (S. Hirohata), itomd@md.okayama-u.ac.jp (H. Ito).

http://dx.doi.org/10.1016/j.ijcard.2014.08.055
0167-5273/

of n − 3 PUFAs can be observed and is clinically meaningful in patients with acute MI are unknown.

Therefore, we studied the effect of early EPA use within 24 h after percutaneous coronary intervention (PCI) in the acute stage of acute MI on CRP levels after reperfusion. We also examined clinical outcomes, including arrhythmic events within 1 month in patients with acute MI.

2. Methods

2.1. Study population and study protocol

This study was a prospective, single-center, randomized, open-labeled trial. The study protocol was approved by the ethics committee of Kagawa Prefectural Central Hospital, and written informed consent was obtained from all of the patients. Between November 2010 and December 2012, 155 consecutive acute MI patients treated with PCI within 24 h of symptom onset were eligible for the study (Fig. 1). MI was diagnosed according to the Joint ESC/ACCF/AHA/WHF Task Force for the Redefinition of Myocardial Infarction [16]. Exclusion criteria were cardiogenic shock, severe renal insufficiency requiring dialysis or continuous hemofiltration, cardiopulmonary arrest, emergent coronary artery bypass, and failure of PCI. Before PCI, all of the patients received 200 mg aspirin and 300 mg clopidogrel. PCI was performed with conventional techniques by the femoral or radial approach. Intravenous heparin (10,000 IU) was administered after arterial access was obtained, to achieve an activated clotting time over 200 s. Intravenous heparin was continued for 48 h after angioplasty. Postprocedural antithrombotic therapy consisted of 100 mg aspirin daily and 75 mg clopidogrel daily. No patients received glycoprotein inhibitors during the present study period.

Fig. 2 shows the study protocol. Eligible participants were assigned to either administration of 1800 mg/day of EPA or without EPA by a research technician, according to a computer-generated, randomization plan, which included stratification by age and sex. Patients in both groups received 2 mg/day of pitavastatin concomitantly. EPA treatment was started within 24 h after PCI. Any anti-arrhythmic drug, except for a β blocker, was not allowed to be administered for prophylactic purposes.

2.2. Clinical endpoints

The primary endpoint was composite clinical outcomes, including cardiac death, stroke, re-infarction, ventricular arrhythmias, and paroxysmal atrial fibrillation. Secondary endpoints were the peak CRP value after PCI, MI size estimated by peak creatine kinase (CK), and left ventricular ejection fraction at 2 weeks after onset of acute MI.

2.3. Data collection

Blood sampling was performed on admission and at days 2, 3, 4, 5, 7, and 14 after PCI, and CRP, CK and CK-MB levels were measured at the central laboratory of Kagawa Prefectural Central Hospital. Concentrations of EPA, DHA and AA on admission were measured at SRL Company, Tokyo, Japan. Standard echocardiography was performed at 2 weeks after acute MI. Data regarding primary and secondary outcomes were carefully collected from clinical charts and the diagnosis was confirmed by an investigator who was blinded to treatment allocation. Ambulatory electrocardiography monitoring was mandatory from the day of the infarction to day 5. Ambulatory electrocardiography monitoring was then allowed to be continued according to the physician's decision. Electrocardiography was also recorded according to symptoms, such as palpitation, tachycardia, and hypotension. Arrhythmia before EPA use was not included as a primary outcome. Ventricular arrhythmia was defined as ventricular tachycardia (a minimum of three consecutive beats of ventricular origin at a rate of >200 beats per minute, or a minimum of five consecutive beats of ventricular origin at a rate of >120 beats per minute) and ventricular fibrillation observed at any time during hospitalization. The occurrence of paroxysmal atrial fibrillation was also recorded. We measured the corrected QT interval (QTc, milliseconds) through day 2 to day 4 of acute MI, and determined maximal QTc for further analysis. Data obtained from the initiation of EPA to day 30 were used for analysis.

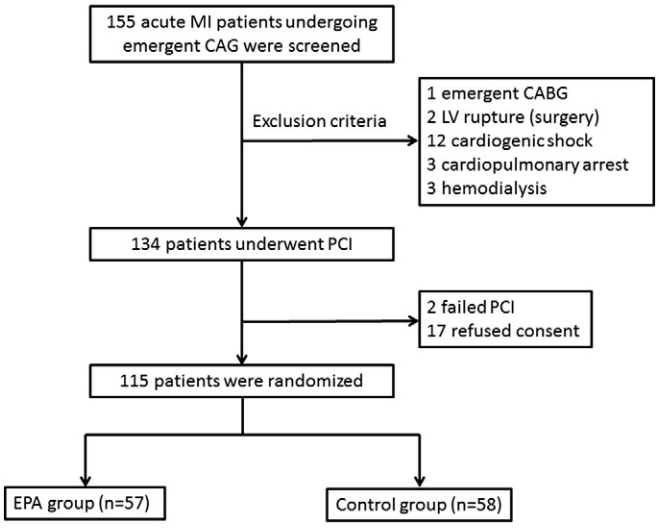

Fig. 1. Selection of patients and assignment to the EPA and the control groups. MI; myocardial infarction; CAG; coronary angiography; PCI, percutaneous coronary intervention; EPA, eicosapentaenoic acid.

2.4. Statistical analysis

At the time of the study design, limited clinical data were available for sample size estimation. We assumed that EPA would reduce the prevalence of the primary outcomes from 30 to 10%. Therefore, 98 patients were recruited in the study to enable such a reduction to be detected (power, 80%; $\alpha = 0.05$). All variables were tested for normal distribution with the Kolmogorov–Smirnov test. Variables that were confirmed as having a normal distribution were summarized as mean ± standard deviation. The median and the first and third quartiles were used for data that were not normally distributed. Continuous variables were compared using the paired or unpaired Student's *t* test or the Mann–Whitney U test, as appropriate. Multivariate logistic regression analysis was performed to determine independent factors related to composite clinical outcomes and to the peak CRP value using significant factors in univariate analysis. A p value of <0.05 was considered statistically significant. Statistical analysis was performed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL).

3. Results

3.1. Study population

Fig. 1 shows the trial profile. From the initial 155 patients with acute MI, three patients were excluded because they did not undergo PCI (n = 1, emergency coronary artery bypass surgery; and n = 2, left ventricular rupture that needed surgery). Additionally, 18 patients were excluded (n = 12, cardiogenic shock; n = 3, cardiopulmonary arrest; and n = 3, on hemodialysis). For the remaining 134 patients undergoing emergent PCI, 17 refused consent and two had failed PCI. Finally, 115 patients were enrolled and were randomly assigned to the EPA group (57 patients) and the control group (58 patients).

Table 1 shows baseline patients' characteristics, coronary anatomy, and angiographic results of the two groups. Baseline characteristics, severity of heart failure on admission, and the site of MI were comparable between the two groups. Approximately two thirds of the patients had total occlusion before PCI in both groups, and thrombolysis in myocardial infarction-3 flow was achieved in 86 and 88% of patients in the control and EPA groups, respectively. There were no significant differences in baseline plasma concentrations of EPA and arachidonic acid, the ratio of EPA to arachidonic acid, hemoglobin and serum creatinine concentrations, and the lipid profile before PCI.

3.2. Primary outcome

Table 2 compares the clinical outcomes of the two groups. The incidence of composite endpoints was significantly lower in the EPA group than in the control group (10.5 vs 29.3%, p = 0.01). The reduction in primary outcome was mainly due to a decrease in ventricular arrhythmias. The incidence of ventricular arrhythmias, including ventricular fibrillation and ventricular tachycardia, was significantly lower in the EPA group than in the control group (7.0 vs 20.6%, p = 0.03). Post-hoc analysis showed that early ventricular arrhythmia within 48 h of randomization occurred in 3.5% of patients in the EPA group and in 10.3% in the control group (p = 0.15). Late ventricular arrhythmia after 48 h of randomization occurred in a lower proportion of patients in the EPA group than in the control group (3.5 vs 15.5%, p = 0.03). In the control group, five patients (8.6%) had paroxysmal atrial fibrillation, but only one patient had paroxysmal atrial fibrillation in the EPA group. To determine independent factors related to composite clinical outcomes and ventricular arrhythmic events, we performed logistic regression analyses. Univariate analysis showed that EPA use was significantly associated with composite clinical outcomes and the presence of ventricular