

Clinical Research

Omega-3 Polyunsaturated Fatty Acids in Treatment of Patients with Coronary Heart Disease and Type 2 Diabetes Mellitus

Gulnara M. Imantaeva, MD, PhD*, Aisulu T. Mussagalieva, MD, PhD

Scientific Research Institute of Cardiology and Internal Diseases, Almaty, Kazakhstan

Abstract

Increased platelet aggregation is one of the major risk factors for cardiovascular events. However, recent studies have demonstrated the inhibition of platelet aggregation by omega-3 PUFAs. The aim of this work was to study the effect of the addition of omega-3 PUFAs to the combination of aspirin and clopidogrel on the platelet aggregation in patients with coronary heart disease. In all, 40 patients with coronary heart disease and diabetes mellitus type 2 undergoing PCI with stent implantation were included in the study. Clopidogrel in a 300 mg loading dose was given after drawing blood for baseline measurement of ADP-induced platelet aggregation. Patients were randomized into two groups. The first group included 20 patients who received 75 mg clopidogrel once daily, 100 mg aspirin once daily and 1000 mg omega-3 PUFAs daily. The second group included 20 patients who received 75 mg clopidogrel once daily and 100 mg aspirin daily. The ADP-induced platelet aggregation was performed twice, once before clopidogrel administration and once after one month. All the patients were genotyped for CYP2C19 polymorphism. No significant differences were noted among the genotype and allele frequencies of the cytochrome CYP2C19 gene between the two groups. The addition of omega-3 PUFAs to the standard dual antiplatelet therapy of aspirin and clopidogrel significantly decreased the ADP-induced platelet aggregation.

Key words: coronary heart disease, type 2 diabetes mellitus, platelet aggregation, treatment.

Introduction

The standard treatment for patients with acute coronary syndrome involves a combination of dual-antiplatelet therapy, aspirin and thienopyridine, which has been proven efficacious in reducing the rate of recurrent cardiac events, including stent thrombosis [1,2]. However, there is a significant inter-individual variability in response to these two drugs. The results

from several studies have shown that the CYP2C19 gene polymorphism (CYP2C19*2) was associated with a higher platelet reactivity in patients on clopidogrel, which in turn has been linked to a worsened clinical outcome post coronary stenting [3].

Over the last few years, interest in the role of omega-3 polyunsaturated fatty acids (PUFAs) in the prevention and management of cardiovascular disease has increased. In the GISSI-Prevenzione trial, supplementation with the intake of one fish oil capsule daily was shown to reduce the risk of sudden death in patients with recent myocardial infarction [4]. The mechanisms of the beneficial effect of omega-3 PUFAs on cardiovascular disease are multifactorial.

Increased platelet aggregation is one of the major risk

*Corresponding author: Gulnara M. Imantaeva, MD, PhD, Associate Professor, Scientific and Research Institute of Cardiology and Internal Diseases, 120, Aiteke Bi str., 050001, Almaty, Kazakhstan
Tel: 7-727-2676843. E-Mail: imantaeva@mail.ru

factors for cardiovascular events. However, recent studies have demonstrated the inhibition of platelet aggregation by omega-3 PUFAs [5].

The aim of our investigation was to study the effect of the addition of omega-3 PUFAs to the combination of aspirin and clopidogrel on platelet aggregation in patients with coronary heart disease.

Materials and methods

Totally, 40 patients with coronary heart disease and diabetes type 2 undergoing PCI with stent implantation were included in the study. Clopidogrel, in a 300 mg loading dose, was given after blood collection for baseline measurement of ADP-induced platelet aggregation. All the patients received beta-blockers, nitrates, ACE-inhibitors and statins. Patients were randomized into two groups.

The first group included 20 patients who received clopidogrel 75 mg once daily, aspirin 100 mg once daily and omega-3 PUFAs (Atheroblok, "Actavis") 1000 mg daily.

The second group included 20 patients who received clopidogrel 75 mg once daily and aspirin 100 mg daily.

Then, ADP-induced platelet aggregation was performed twice, once before clopidogrel administration and once after one month.

All the patients were genotyped for CYP2C19 polymorphism. The polymerase chain reaction was performed using the oligonucleotide primers to determine A681G polymorphism of the CYP2C19 gene [6]:

5'-CAGAGCTTGGCATATTGTATC-3'

5'-GTAAACACACAAAAGTAGTCAATG-3'

Results:

Table 1
The genotypes and alleles frequencies of CYP2C19 gene

Genotypes	Group 1 (n=20)	Group 2 (n=20)
CYP2C19*1*1	14 (69%)	15 (75%)
CYP2C19*1*2	6 (31%)	4 (20%)
CYP2C19*2*2	0	1 (5%)
Alleles		
CYP2C19*1	34 (85%)	34 (85%)
CYP2C19*2	6 (15%)	6 (15%)

The frequencies of the genotypes and alleles of the CYP2C19 gene are shown in Table 1.

No significant differences were noted among the genotype and allele frequencies of the cytochrome CYP2C19 gene between the two groups.

The baseline ADP-induced platelet aggregation in the first group was $77.76 \pm 2.7\%$, while in the second group it was

$79.5 \pm 1.7\%$ ($p > 0.05$). After one month of therapy, the level of ADP-induced platelet aggregation decreased significantly in both groups to $60.5 \pm 2.9\%$ in the first group and $69.3 \pm 2.8\%$ in the second group; however, in the first group, which had been receiving omega-3 PUFAs (Atheroblok), the ADP-induced platelet aggregation was lower by 8.8% compared with the second group.

No association between CYP2C19 gene genotypes and the levels of ADP-induced platelet aggregation was observed in these patients.

Discussion

Our study indicates that the triple therapy with aspirin, clopidogrel, and omega-3 PUFAs decreased the platelet ADP-induced aggregation more effectively than the standard dual antiplatelet therapy.

Recently, Grzegorz Gajos et al., demonstrated that the addition of omega-3 PUFAs to the combination of aspirin and clopidogrel significantly potentiated platelet response to clopidogrel post percutaneous coronary intervention [5].

The mechanisms of the favorable antithrombotic effects of omega-3 PUFAs are complex. Not only do they have a membrane stabilizing effect, there is also a competition of omega-3 PUFAs for cyclooxygenase activity with arachidonic acid, which lowers the production of the platelet-activating eicosanoids (e.g. thromboxane A₂), which in turn play an important role [7]. In a study in diabetic patients, Woodman et al. demonstrated the administration of omega-3 PUFAs was associated with a 30% decrease in platelet aggregability [8].

Conclusion

The addition of omega-3 PUFAs to the standard dual antiplatelet therapy with aspirin and clopidogrel significantly decreased the ADP-induced platelet aggregation.

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