ORIGINAL ARTICLE

UDC: 616.1-089:617-089.163
DOI: 10.2298/VSP1304396V

Effect of pretreatment with omega-3 polyunsaturated fatty acids (PUFAs) on hematological parameters and platelets aggregation in patients during elective coronary artery bypass grafting

Efekat omega-3 polinezasićenih masnih kiselina na hematološke parametre i agregaciju trombocita kod elektivne revaskularizacije srca

Milić Veljović*†, Ivana Mihajlović‡, Vesna Subota§, Mirjana Antunović†‖, Jasna Jevdjić¶, Ivo Udovičić*, Ana Popadić*, Tatjana Vulović¶

***Clinic of Anesthesiology and Intensive Care, §Institute for Medical Biochemistry, ‖Sector of Pharmacy, Military Medical Academy, Belgrade, Serbia; †Faculty of Medicine of the Military Medical Academy, University of Defence, Belgrade, Serbia; ‡Medicines and Medical Devices Agency of Serbia, Belgrade, Serbia; ¶Department of Anesthesiology, Clinical Center " Kragujevac", Kragujevac, Serbia**

Abstract

Bacground/Aim. Using omega-3 polyunsaturated fatty acids (PUFAs) in coronary artery bypass graft surgery (CABG) could provide protection against ischemic-reperfusion damage, prevention of postoperative arrhythmia and attenuation of inflammatory response. However, omega-3 PUFAs inhibit cyclooxygenase (and thus decrease the synthesis of thromboxane A2 from arachidonic acid in platelets), which leads to decreased platelet aggregation. In cardiac surgery it is necessary to achieve a balance between inhibition and full platelets function. It is as well as important to closely follow hematological parameters, impaired by CABG itself. Therefore, the aim of the study was to establish the effects of pretreatment with omega-PUFAs on hematological parameters and plateletes aggregation in patients with elective CABG. **Methods.** This prospective, randomized, placebo-controlled, single-center trial was performed on parallel groups. The patients (n = 40) undergoing elective CABG were randomized receiving preoperative intravenous omega-3 PUFAs (Omegaven® 10%) infusion (the PUFAs group) or the same volume of 0.9% saline solution infusion (the control group). Infusion was given a day before surgery and repeated four hours before starting extracorporeal circulation (CPB) *via* the peripheral vein at single doses of 100 mL (25 mL/h). Platelet function analysis was performed using multiple electrode aggregometry (MEA, multiplate-analyzer) before starting CPB and 2 h postoperatively for the patients of both groups. **Results.** There were no clinically relevant differences in baseline characteristics between the groups. Hematological parameters were not significantly different between the groups pre-, intra- and postoperatively. During the first 24 h after surgery, the loss of blood was similar in the PUFAs and the control group (680 ± 274 mL and 608 ± 210 mL, respectively; $p = 0.356$). Postoperatively, platelet aggregation was not significantly different between the PUFAs and the control group in adenosine diphosphate (ADP) test (39 ± 11 and 42 ± 15, respectively; $p = 0.701$), arachidonic acid (ASPI) test (64 ± 24 and 70 ± 27, respectively; $p = 0.525$) and trombin receptor-activating peptide (TRAP) test (68 ± 25 and 75 ± 26, respectively; $p = 0.396$), while their aggregation in collagen (COL) test was statistically significantly lower in the PUFAs related to the control group (32 ± 15 and 47 ± 20, respectively; $p = 0.009$). **Conclusion.** Acute pretreatment with omega-3 PUFAs insignificantly affected the activity of platelets and did not influence postoperative blood loss.

Key words:
fatty acids, omega-3; coronary artery bypass; platelet agregation; hematologic tests; hemorrhage

Apstrakt

Uvod/Cilj. Primenom omega-3 polinezasićenih masnih kiselina (PUFAs – *polyunsaturated fattly acids*) kod kardiohirurških operacija može se postići zaštita od ishemijsko-reperfuzionih oštećenja, prevencija postoperativnih aritmija i smanjenje inflamatornog odgovora. Međutim, omega-3 PUFAs inhibiraju ciklooksigenazu (ovo smanjuje sintezu tromboksana A2 iz arahidonske kiseline u trombocitima), što smanjuje agregaciju trombocita. Kod kardiohirurških operacija neophodno je postići ravnotežu između inhibicije i pune funkcije trombocita. Takođe, važno je pratiti hemato-

Correspondence to: Milić Veljović, Clinic of Anesthesiology and Intensive Care, Military Medical Academy, Crnotravska 17, 11 000, Belgrade, Serbia.

loške parametre koji su poremećeni samom hirurškom intervencijom. Cilj ove studije bio je da se utvrde efekte preoperativne infuzije omega-3 PUFAs na hematološke parametre i agregaciju trombocita kod bolesnika koji su podvrgnuti elektivnoj revaskularizaciji miokarda. **Metode.** Ova prospektivna, randomizovana, placebom kontrolisana studija vršena je na paralelnim grupama. Bolesnici (n = 40) planirani za elektivni hirurški zahvat revaskularizacije miokarda primali su infuziju omega-3 PUFAs (Omegaven® 10%) ili istu količinu 0,9% NaCl, po 100 mL (25 mL/h)/dan pre hirurške intervencije i četiri sata pre početka vantelesnog krvotoka. Analiza funkcije trombocita u obe grupe vršena je metodom *multiple electrode aggregometry* (MEA) pre početka vantelesnog krvotoka i dva sata nakon završetka intervencije. **Rezultati.** Nije bilo značajne razlike u vrednostima hematoloških parametara između grupa, pre-, intra- i postoperativno. Tokom 24 sata postoperativno, gubitak krvi bio je sličan u grupi koja je primala omega-3 PUFA i kontrolnoj grupi koja je primala placebo (680 ± 274 mL i 608 ± 210 mL, respektivno; p = 0,356). Postoperativo, nije postojala statistički značajna razlika u agregaciji trombocita između grupe koja je primala omega-3 PUFA i u kontrolnoj grupi koja je primala placebo u adenozin difosfat (ADP) testu (39 ± 11 i 42 ± 15, respektivno; p = 0,701), ASPI testu (64 ± 24 i 70 ± 27; respektivno; p = 0,525) i trombin receptor-aktivirajući peptid (TRAP) testu (68 ± 25 i 75 ± 26, respektivno; p = 0,396). Agregacija u kolagen (COL) testu bila je statistički značajno manja u grupi koja je primala omega-3 PUFA u odnosu na kontrolnu grupu (32 ± 14 i 47 ± 20, respektivno; p = 0,009). **Zaključak.** Preoperativna primena omega-3 PUFAs jednako utiče na agregaciju trombocita, kao i placebo u kontrolnoj grupi, osim kod COL testa čije su vrednosti statistički značajno niže u grupi tretiranoj omega-3 PUFAs u odnosu na kontrolnu grupu, ali to ne utiče na postoperativne gubitke krvi.

Ključne reči:
masne kiseline, omega-3; aortokoronarno premošćavanje; trombociti, agregacija; hematološki testovi; krvarenje.

Introduction

Bleeding is a common complication of cardiac surgery with cardiopulmonary bypass (CPB), which can require transfusion of blood products [1–3] and in 3% ± 6% of cases mediastinal re-exploration [4]. Among causes of excessive bleeding, platelet dysfunction is considered to be the most important in the early postoperative period. During coronary artery bypass graft (CABG) surgery there is the opposition between the benefit of platelet inhibition to reduce the risk of pre-operative infarction and postoperative occlusion of anastomosed coronary arteries, and the need to maintain full platelet function for optimal hemostasis in surgical incisions.

Previous studies have demonstrated beneficial effects of omega-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in platelet functions [5]. Whereas the predominant product of arachidonic acid (AA) in platelets, thromboxane A_2 (TXA_2) is a platelet agonist, the corresponding product of EPA, thromboxane A_3 (TXA_3), is virtually biologically inert. In contrast, both prostaglandin I_2 derived from AA, and prostaglandin I_3 derived from EPA, are potent vasodilators and platelet inhibitors [6]. Supplementation of omega-3 PUFAs resulted in a shift towards the production of more favorable eicosanoids that inhibit platelet aggregability [7].

Omega-3 PUFAs are commonly considered to have antithrombotic effects, based on increased bleeding times at very high doses (e.g. 15 g/day) [8]. Conversely, in human trials, omega-3 PUFA consumption has no consistent effects on platelet aggregation or coagulation factors [9, 10]. No excess clinical bleeding risk has been seen in randomized clinical trials of fish or fish oil consumption, including people undergoing surgery or percutaneous intervention and/or also taking aspirin or warfarin [8, 11].

We have recently shown that preoperative administration of omega-3 PUFAs has cardioprotective effect in patients with CPB manifested in increased oxygen extraction and lactate uptake with simultaneous decrease of serum troponin I and creatinin kinase myocardial band (MB) levels [12]. In the frame of the same study, we followed the effect of omega-3 PUFAs on their influence on postsurgical patients platelet aggregation. According to the previous findings of the other authors [11, 13] that omega-3 PUFAs do not affect bleeding in the same or similar categories of patients we assumed that they will not provoke bleeding surpassing the risk expected in the control group of patients.

The aim of the study was to establish the relationship between hematological parameters and the activity of plateletes in patients with elective CABG pretreated by 3-omega PUFAs.

Methods

This prospective, randomized, placebo-controlled study was performed on parallel groups. Study enrollment occurred between August 2010 and September 2011. The study protocol was approved by the Ethical Committee of Military Medical Academy, and all the patients gave written informed consent.

Forty patients scheduled to undergo their first on-pump CABG surgery were included in the study. For recruitment, patients needed to be older than 18 years of age, in normal sinus rhythm, and in stable hemodynamic conditions before surgery. Patients were excluded in cases of emergency CABG, redo CABG, combined CABG and any other cardiac procedure, Q-wave myocardial infarction in the last six weeks, unstable angina, or poor left ventricular function, those with abnormal coagulation tests, including a history of coagulopathy and preoperative treatment with other anticoagulants. All the participants denied the intake of any antiagregation medication during the previous five days. All the patients were treated by the same surgical and anesthesiologist team.

Eligible patients were assigned to one of the two study arms according to a computer-generated randomization list: the control (placebo) group (usual care), and the usual care plus PUFAs group.

The PUFAs infusion consisted of 100 mL of a lipid emulsion with a high content of omega-3 PUFAs (Omegaven® 10%, Fresenius Kabi, Bad Homburg, Germany). The same batch of Omegaven® was used throughout the study, and 100 mL of the lipid emulsion contained 1.25–2.82 g of EPA and 1.44–3.09 of DHA. Infusion was given a day before surgery and repeated 4 h before starting CPB *via* the peripheral vein at single doses of 100 mL (25 mL/h). The patients in the control group received an equal volume of 0.9% saline.

Preoperative sedation with 5 mg of intramuscular midazolam was administered to patients on call to the operating room. All the patients received prophylactic preoperative antibiotics (cefazolin 2 g preincision, and 2 g post-CPB; or if allergic to penicillin, vancomycin 1 g preincision and 500 mg post-CPB). The same anesthesiologist administered standardized total intravenous anesthesia using sufentanil, midazolam, propofol and pancuronium.

Immediately before CPB, 300 IU/kg heparin was administered intravenously, followed by additional doses as necessary to maintain an activating clotting time exceeding 500 sec. Protamine was administered as 1 mg /100 IU of the heparin dose after complete separation from CPB.

All the patients had CABG with the use of CPB, which was conducted with a roller pump and a membrane oxygenator primed with a solution. During CPB, pump flow was set at 2.4 times the body surface area, and mean arterial pressure maintained between 50 mmHg and 60 mmHg. The temperature was allowed to drift with active rewarming at the end of CPB. Myocardial protection was afforded with cold potassium cardioplegia. A single-clamp technique was used, and cardioplegia was given in an anterograde fashion. In all the patients, the left internal mammary artery harvested and anastomosed to the left anterior descending artery. The rest of the grafts were constructed using the great saphenous vein.

After a total release of the aortic cross-clamp, epicardial atrial or ventricular pacing wires were placed. Aortic and venous cannulas were removed after an appropriate test dose of protamine, and the surgery proceeded with closure of the pericardium and sternum.

After the surgery, the patients were followed up in the Intensive Care Unit (ICU) and were weaned off mechanical ventilation when they fulfilled the following criteria: hemodynamic stability, peripheral temperature of more than 36 °C, cooperatively, and no major bleeding.

Blood for hemoglobin (Hb) concentration, hematocrit (Hct), platelet count and coagulation profile determination including international normalised ratio (INR) and activated partial thromboplastin time (aPTT), was taken from a radial arterial catheter before start CPB and 2 h after arrival in the ICU for all the patients in the two groups. Transfusion of blood products and management of postoperative bleeding intra- and postoperatively were determined by following institutional algorithm. Platelet function analysis was performed using the multiple electrode aggregometry (multiplate-analyzer) before started CPB and 2 h after arrival in the ICU for all the patients of both groups. The method has been described in detail elsewhere [14]. Platelet aggregation was initiated using arachidonic acid (ASPI test), adenosine diphosphate (ADP test), thrombin receptor–activating peptide (TRAP test) and collagen (COL test) using commercially available test reagents. Increased impedance caused by attachment of platelets to the test cell electrodes was continuously measured over 6 min. Platelet aggregation was quantified as the area under the aggregation curve [AUC(U)]. Reference ranges for healthy subjects obtained from the manufacturer were 79–141 U for the ASPI test, 41–99 U for the ADP test, 92–151 U for the TRAP test, and 61–108 U for COL test.

The results were presented as mean values with standard deviation. The significance of differences betwen the study groups was analyzed using the *t*-test. Due to great variability of some data, the Wilcoxon matched pairs test and the Mann-Whitney *U*-test were also used. Comparison between more than two groups was done by using the Kruskal-Wallis test.

A *p*-value less than 0.05 was taken to be significant. The obtained data were processed through the Stat for Windows, R.4.5. Software package.

Results

The results of the study are presented in Tables 1 to 3 dealing with baseline and operative characteristics of the patients (Table 1), the effect of CPB procedure on hematologi-

Table 1

Baseline and operative characteristics of the patients in the control and PUFAs group

Parameter	Control group	PUFAs group	*p*
Age (years)	62.4 ± 7	65.3 ± 8	0.56
Gender (m/f)	18/2	17/3	0.36
Weight (kg)	89.8 ± 6	92.1 ± 5	0.48
Height (cm)	176.4 ± 4	178.5 ± 3	0.06
LVEF (%)	54 ± 6	53 ± 9	0.1
CPB (min)	101.4 ± 21	95.5 ± 17	0.29
Aortic cross-clamp time (min)	42.5 ± 9	38.9 ± 8	0.66
CABG (number)	2.9 ± 0.8	2.8 ± 0.7	0.65
Total heparin dose (units × 1,000)	27.7 ± 1.5	27.6 ± 2.2	0.86
Total protamin dose (mg)	279 ± 13	282 ± 19	0.638

Data presented as mean value ± standard deviation. PUFA – polyunsaturated fatty acids; LVEF – left ventricular ejection fraction; CPB – cardiopulmonary bypass; CABG – coronary artery bypass grafting.

cal parameters (Table 2), the effect of CPB procedure on the activity of platelets in the control and the PUFAs group of patients (Table 3), and peri- and postoprative complications.

and postoperative requirements for allogenic RBCs, FFP and platelet units were similar in both groups of patients, with no statistically significant difference.

Table 2

Hematological data in the patients subjected to CPB

Parameter	Control group	PUFAs group	*p*
Prior to operation			
hemoglobin (g/L)	134 ± 4.2	134 ± 3.2	0.535
hematocrit (%)	38 ± 2.7	37 ± 2.4	0.628
platelets (x10^9/L)	255 ± 42	259 ± 57	0.823
INR	1.06 ± 0.03	1.08 ± 0.03	0.139
aPTT (sec)	38.8 ± 3.9	39.6 ± 3.3	0.493
On arrival to ICU			
hemoglobin (g/L)	111 ± 8.3	109 ± 8.5	0.542
hematocrit (%)	29 ± 6.9	29.4 ± 2.3	0.832
platelets (× 10^9/L)	132 ± 34	129 ± 43	0.796
INR	1.17 ± 0.07	1.18 ± 0.14	0.703
aPTT (sec)	44.2 ± 4.5	45.8 ± 5.9	0.345
Transfusion requrements			
Intraoperative			
allogenic RBCs (units)	1.3 ± 0.7	1.4 ± 0.8	0.738
FFP (units)	0.5 ± 0.8	0.4 ± 0.8	0.946
platelets (units)	0	0	
Postoperative (0–24 h)			
allogenic RBC (units)	1.9 ± 0.7	1.9 ± 0.8	0.946
FFP (units)	1.7 ± 1	1.9 ± 0.9	0.529
platelets (units)	1.2 ± 1.3	1.35 ± 1.35	0.738
Postoperative blood loss 0–24 h (mL)	608 ± 210	680 ± 274	0.356

Data presented as mean value ± standard deviation. CPB – cardiopulmonary bypass; PUFA - polyunsaturated fatty acids; INR-international normalization ratio; aPTT – activated partial thromboplasin time; ICU – intensive care unit; RBC – red blood cells; FFP – fresh frozen plasma.

Table 3

The influence of polyunsaturated fatty acids (PUFAs) on the platelet aggregation in multiple electrode aggregometry

Parameter	Area under curve (U), $\bar{x}$ ± SD		*p*
	control group	PUFAs group	
ADP test (41–99 U)*			
preoperative	61.4 ± 20	57.8 ± 20	0.587
postoperative	42.3 ± 15	39.4 ± 11	0.701
ASPI test (79–141 U)*			
preoperative	92.6 ± 23	90.2 ± 20	0.719
postoperative	70.1 ± 27	64.9 ± 24	0.525
TRAP test (92–151 U)*			
preoperative	96.8 ± 23	95.4 ± 23	0.845
postoperative	75.1 ± 26	68.1 ± 25	0.396
COL test (61–108)*			
preoperative	68.2 ± 17	64.4 ± 16	0.465
postoperative	47.7 ± 20	32.3 ± 15	0.009

Data presented as mean value ± standard deviation. ADP – adenosine diphosphate; ASPI – arachidonic acid-induced platelet aggregation; TRAP – thrombin receptor activating peptide; COL – collagen; *reference ranges for healthy subjects.

Table 1 shows that the baseline and operative characteristics of the patients included in the study did not differ between the control and the PUFAs group in any of the observed parameters. This equally relates intraoperative CPB (101.4 min *vs* 95.5 min; $p = 0.29$), aortic cross-clamp time (42.5 min *vs* 38.9 min; $p = 0.66$), CABG number (2.9 min *vs* 2.8; $p = 0.65$) and total heparin use (27.7 min *vs* 27.6 units × 1,000; $p = 0.86$), and postoperative interventions: total protamine dose (279 mg *vs* 282 mg; $p = 0.63$).

Table 2 shows that hematological data regarding preoperative and on the arrival to ICU, as well as intraoperative

Regarding transfusion requirements and postoperative blood loss, there were no statsitically significant differences between the control and the PUFAs group in allogenic red blood cells (RBCs) (1.9 *vs* 1.9; $p = 0.94$), fresh frozen plasma (FFP) (1.9 *vs* 1.7; $p = 0.52$) and platelete (1.2 *vs* 1.35; $p = 0.73$) units, as well as in postoperative blood loss (608 ± 210 mL *vs* 680 ± 274 mL, $p = 0.356$).

Table 3 shows that the level of platelet aggregation reached the reference values in both groups of patients and in all four performed tests, indicating thus their normal values. In all instances, the observed values were above, but closer

to the lower levels of aggregators reference potencies given in the brackets.

The second part of the results concerns the intergroup differences in the platelet aggregation pre-, and postoperatively. In that respect, almost all the tests showed equal activity of plateletes before the surgical intervention in the PUFAs group in relation to the control group of patients. Postoperatively, platelet aggregation was not significantly different between the PUFAs and the control group in the ADP test (39 ± 11 *vs* 42 ± 15; $p = 0.701$), ASPI test (64 ± 24 *vs* 70 ± 27; $p = 0.525$) and TRAP test (68 ± 25 *vs* 75 ± 26; $p = 0.396$), while their aggregation in COL test was statistically significantly lower in the PUFAs related to the control group (32 ± 15 *vs* 47 ± 20; $p = 0.009$).

Postoperative complications were similar in both groups of patients. In the control group, one patient died of cardiac failure on the second postoperative day, two patients had perioperative infarction, three patients needed inotropic support. In the PUFAs group, one patient underwent reexploration for bleeding, one had a respiratory failure and two patients needed inotropic support. Due to the low number of the observed complications, no statistical comparison was performed.

Discussion

We studied the relatoinship between omega-3 PUFAs, which may influence the activity of platelets, and the hematological parameters liable to imapirment in patients with CPB, and found that in spite of the marked decrease in the postoperative activity of platelets, more pronounced in the PUFAs group of patients in relation to placebo in the COL test, they did not affect any of the observed intra- and postoperative hematological parameters (blood loss, RBC, FFP and platelet requirements).

Due to the separate study types, discussion is given in two parts: the effect of CPB on hematological parameters, and the influence of omega-3 PUFAs in CPB procedure on the activity of platelets.

The effect of CPB on hematological parameters

Statistically significant differences were postoperatively found in both groups of the studied patients in some hematological parameters, like Hb and Htc levels and platelet counts, but not in the others as INR and aPTT. This is very important, since bleeding after cardiac surgery may ensue either from surgical (anastomoses, sternum, cannulation sites) or nonsurgical sites. If bleeding becomes excessive or causes hemodynamic disorders, reexploraton of mediastinal wound is necessary. In our study, one patient in the PUFAs group underwent reexploration for bleeding. Studies from the other authors have shown that reexploration can be associated with multiple negative outcomes such as renal failure, sepsis, atrial fibrilation, prolonged mechanical ventilation and hospital stay and, most notably, increased mortality and costs [1–4].

There have also been studies in which patients with coronary bypass grafting [15–17], endarterectomy [18, 19], and femoral artery catheterization [20–22] were given omega-3 PUFAs. In these studies, identically with our results, the risk of clinically significant bleeding was virtually nonexistant. However, in this respect, one has to keep in mind the review of Bays [23] in which he concluded that although there is little evidence for increased risk of clinically significant bleeding with omega-3 PUFAs supplementation, clinicians should be aware of this as a theoretical possibility.

The influence of omega-3 PUFAs in CPB procedure on the activity of platelets

The results of our study show that preoperative activity of platelets in both groups of patients were in the range of reference values for all of the four used tests. Conversely, after the surgical intervention, their activity was statistically significantly reduced, with easily noticable lower values in PUFAs group in relation to placebo, particularly in COL test.

This finding is very relevant, because platelets play an important role in maintaining normal hemostatic function. Their disfunction is a major cause of excessive bleeding in the early postoperative period after CPB procedures [24, 25], not found in our patients. Transient impairment of platelet function is mediated by platelet activation during passage through the synthetic, nonendothelial surface of the extracorporeal circuit, used also in our patients with twofold decrease in their count, and involves the secondary release and partial depletion of α-granules. Platelet dysfunction may also be related to other factors [24]. Hypothermia related CPB influences platelet function and coagulation [26], the effect which can persist into the ICU [27], and be more pronounced as the time on CPB increases [28, 29].

Multiple electrode platelet aggregometry (MEA) used in our study, allows the assessment of platelet function without centrifugation steps [30], and has proven sensitive for platelet inhibition induced by aspirin and clopidogrel, as well as for the effects of CPB and of hypothermia on platelet aggregation [31–34]. The test has also been found to be able to detect impaired hemostasis after CPB surgery [35–37] and to identify patients before and after cardiac surgery with enhanced risk of bleeding and of blood transfusion [38, 39].

The mechanism of favorable antithrombotic effects of omega-3 PUFAs found in our study are complex. It has been shown that alteration of fatty acid composition by omega-3 PUFAs incorporation into platelet membranes can alter not only membrane permeability, but also modulate function and activity of membrane receptors and transporters [40, 41]. The COL test reagent, being the most sensitive in our study, contains collagen, which activates the platelets by the collagen receptor. Following its binding to the receptors, AA is released, which is the substrate of platelet enzyme cyclooxygenase (COX). COX transforms AA into TXA_2, a potent platelet activator. With a blockade of COX, the formation of TXA_2 is inhibited and therefore inhibited platelet activation is usually detected, as happened to be in our patients.

In most studies either no effect on platelet aggregation was found with omega-3 fatty acids or no difference in effect was seen between the treatments and the control. Kwon et al. [42] noted that with 2 mg of collagen, a significant decrease in

platelet aggregation was found at three weeks on canola oil diet, which reverted to baseline by eight weeks. Freese et al. [43] reported that the decrease in collagen-induced aggregation in the fish oil supplement arm did not return to baseline during a 12 week follow-up period.

Overall, although there is heterogeneity among the studies, there is a trend toward a net reduction of coronary artery restenosis with fish oil supplementation, estimated by the meta-analysis to lower such a risk for 14% [21, 44]. The optimal degree of platelet inhibition is unclear and must be confirmed in trials evaluating cardiovascular outcomes and sould be balanced with the excessive risk of bleeding [45]. In any case, the results of our study show that the postoperative inhibition of platelet aggregation by PUFAs, particularly pronounced in the COL test, did not affect the intra- and postoperative hematological parameters, with the risk of bleeding, as the most dangerous, being equal to the placebo group. This finding undoubtedly speaks in favour of omega-3 PUFAs use as cardioprotectors in patients with open heart surgery, found in our recent study [12].

Conclusion

The results of our study show that acute omega-3 PUFAs pretreatment of patients subjected to CBP grafting did not affect INR, aPTT and bleeding volume, while the postoperative platelet count dropped twofold, equally in the PUFAs and placebo treated groups. The activity of platelets was statistically significantly lower after surgical intervention in both groups of patients, particularly markedly pronounced in the COL test in the PUFAs group, but with no negative effect on bleeding.

Acknowledgments

We would like to present our appreciation and thanks to Prof. Bogdan Bošković who provided research support and was an active participant in the preparation of this manuscript.

Declaration of Conflicting Interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

REFERENCES

1. *Karkouti K, Wijeysundera DN, Yau TM, Beattie WS, Abdelnaem E, McCluskey SA, et al.* The independent association of massive blood loss with mortality in cardiac surgery. Transfusion 2004; 44: 1453–62.
2. *Eikelboom JW, Mehta SR, Anand SS, Xie C, Fox KA, Yusuf S.* Adverse impact of bleeding on prognosis in patients with acute coronary syndromes. Circulation 2006; 114(8): 774−82.
3. *Christensen MC, Krapf S, Kempel A, von Heymann C.* Costs of excessive postoperative hemorrhage in cardiac surgery. J Thorac Cardiovasc Surg 2009; 138(3): 687−93.
4. *Moulton MJ, Creswell LL, Mackey ME, Cox JL, Rosenbloom M.* Reexploration for bleeding is a risk factor for adverse outcomes after cardiac operations. J Thorac Cardiovasc Surg 1996; 111(5): 1037–46.
5. *Park Y, Harris W.* EPA, but not DHA, decreases mean platelet volume in normal subjects. Lipids 2002; 37(10): 941–6.
6. *Hendra T, Betteridge DJ.* Platelet function, platelet prostanoids and vascular prostacyclin in diabetes mellitus. Prostaglandins Leukot Essent Fatty Acids 1989; 35(3): 197−212.
7. *Raheja BS.* Role of nutrition in the pathogenesis of NIDDM. J Assoc Physicians India 1993; (Suppl 1): 18−24.
8. *Mozaffarian D, Marchioli R, Gardner T, Ferazzeti P, O'Gara P, Latini R*, et al. The ω-3 fatty acids for prevention of postoperative atrial fibrillation (OPERA) trial-rationale and design. Am Heart J 2011; 162(3): 56–63.e3.
9. *Wang C, Chung M, Lichtenstein A, Balk E, Kupelnick B, DeVine D,* et al. Effects of omega-3 fatty acids on cardiovascular disease. Evid Rep Technol Assess (Summ) 2004; (94): 1– 8.
10. *Balk E, Chung M, Lichtenstein A, Chew P, Jupelnick B, Lawrence A,* et al. Effects of omega-3 fatty acids on cardiovascular risk factors and intermediate markers of cardiovascular disease. Evid Rep Technol Assess (Summ) 2004; (93): 1–6.
11. *Reis GJ, Boucher TM, Sipperly ME, Silverman DI, McCabe CH, Baim DS*, et al. Randomised trial of fish oil for prevention of restenosis after coronary angioplasty. Lancet 1989; 2(8656):177–81.
12. *Veljovic M, Popadic A, Vukic Z, Ilic R, Trifunovi Z, Mandaric V,* et al. Myocardial protection during elective coronary artery bypasses grafting by pretreatment of omega-3 polyunsaturated fatty acids. Vojnosanit Pregl 2013; (In Press).
13. *Mozaffarian D, Wu JH.* Omega-3 fatty ccids and cardiovascular disease; Effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol, 2011; 58(20): 2047–67.
14. *Toth O, Calatzis A, Penz S, Losonczy H, Siess W.* Multiple electrode aggregometry: a new device to measure platelet aggregation in whole blood. Thromb Haemost 2006; 96(6): 781–8.
15. *Eritsland J, Arnesen H, Gronseth K, Fjeld NB, Abdelnoor M.* Effect of dietary supplementation with n-3 fatty acids on coronary artery bypass graft patency. Am J Cardiol 1996; 77(1): 31–6.
16. *DeCaterina R, Giannessi D, Mazzone A, Bernini W, Lazzerini G, Maffei S*, et al. Vascular prostacyclin is increased in patients ingesting omega-3 polyunsaturated fatty acids before coronary artery bypass graft surgery. Circulation 1990; 82(2): 428–38.
17. *Mariscalco G, Braga SS, Banach M, Borsani P, Bruno VD, Napoleone M, et al.* Preoperative n-3 polyunsatured fatty accids are associated with a decrease in the incidence of early atrial fibrillation following cardiac surgery. Angiology 2010; 61(7): 643−50.
18. *Thies F, Garry JM, Yaqoob P, Rerkasem K, Williams J, Shearman CP*, et al. Association of n-3 polyunsaturated fatty acids with stability of atherosclerotic plaques: a randomized controlled trial. Lancet 2003; 361(9356): 477– 85.
19. *Rapp JH, Connor WE, Lin DS, Porter JM.* Dietary eicosapentaenoic acid and docosahexaenoic acid from fish oil: their incorporation into advanced human atherosclerotic plaques. Arterioscler Thromb 1991; 11(4): 903–11.
20. *Johansen O, Brekke M, Seljeflot I, Abdelnoor M, Arnesen H.* N-3 fatty acids do not prevent restenosis after coronary angioplasty: results from the CART study. Coronary Angioplasty Restenosis Trial. J Am Coll Cardiol 1999; 33(6): 1619 –26.
21. *Maresta A, Balduccelli M, Varani E, Marzilli M, Galli C, Heiman F*, et al. Prevention of postcoronary angioplasty restenosis by omega-3 fatty acids: main results of the Esapent for Prevention of Restenosis ITalian Study (ESPRIT). Am Heart J 2002; 143(6): E5.
22. *Gajos G, Rostoff P, Undas A, Piwowarska W.* Effects of polyunsaturated omega-3 fatty acids on responsiveness to dual antiplatelet therapy in patients undergoing percutaneous coronary intervention: the OMEGA-PCI (OMEGA-3 fatty acids after pci to modify responsiveness to dual antiplatelet therapy) study. J Am Coll Cardiol 2010; 55(16): 1671–8.

23. *Bays HE*. Safety considerations with omega-3 fatty acid therapy. Am J Cardiol 2007; 99(6A): 35C–43C.
24. *Murüthi EW, Belcher PR, Rao JN, Chaudhry MA, Nicol D, Wheatley DJ*. The effects of heparin and extracorporeal circulation on platelet counts and platelet microaggregation during cardiopulmonary bypass. J Thorac Cardiovasc Surg 2000; 120(3): 538−43.
25. *Makar M, Taylor J, Zhao M, Farrohi A, Trimming M, D'Attellis N*. Perioperative coagulopathy, bleeding, and hemostasis during cardiac surgery. A comprehensive review. ICU Director 2010; 1(1): 17−27.
26. *Dacey LJ, Munoz JJ, Baribeau YR, Johnson ER, Lahey SJ, Leavitt BJ*, et al. Reexploration for hemorrhage following coronary artery bypass grafting: Incidence and risk factors. Northern New England Cardiovascular Disease Study Group. Arch Surg 1998; 133(4): 442−7.
27. *Frumento RJ, O'Malley CM, Bennett-Guerrero E*. Stroke after cardiac surgery: A retrospective analysis of the effect of aprotinin dosing regimens. Ann Thorac Surg 2003; 75(2): 479−83; discussion 483−84.
28. *Basran S, Frumento RJ, Cohen A, Lee S, Du Y, Nishanian E,* et al. The association between duration of storage of transfused red blood cells and morbidity and mortality after reoperative cardiac surgery. Anesth Analg 2006; 103(1): 15−20.
29. *Spiess BD, Royston D, Levy JH, Fitch J, Dietrich W, Body S,* et al. Platelet transfusions during coronary artery bypass graft surgery are associated with serious adverse outcomes. Transfusion 2004; 44(8):1143−8.
30. *Seyfert UT, Haubelt H, Vogt A, Hellstern P*. Variables influencing Multiplate(TM) whole blood impedance platelet aggregometry and turbidimetric platelet aggregation in healthy individuals. Platelets 2007; 18(3): 199–206.
31. *Rahe-Meyer N, Winterhalter M, Boden A, Froemke C, Pipenbrock S, Calatzis A,* et al. Platelet concentrates transfusion in cardiac surgery and platelet function assessment by multiple electrode aggregometry. Acta Anaesthesiol Scand 2009; 53(2): 168–75.
32. *von Pape KW, Dzijan-Horn M, Bohner J, Spannagl M, Weisser H, Calatzis A*. Control of aspirin effect in chronic cardiovascular patients using two whole blood platelet function assays. PFA-100 and Multiplate. Hamostaseologie 2007; 27(30): 155–60, quiz 161−2. (German)
33. *Sibbing D, von Beckerath O, Schomig A, Kastrati A, von Beckerath N*. Platelet function in clopidogrel-treated patients with acute coronary syndrome. Blood Coagul Fibrinolysis 2007; 18(4): 335–9.
34. *Paniccia R, Antonucci E, Maggini N, Romano E, Gori AG, Marcucci R,* et al. Assessment of Platelet Function on Whole Blood by Multiple Electrode Aggregometry in High-Risk Patients With Coronary Artery Disease Receiving Antiplatelet Therapy. Am J Clin Pathol 2009; 131(6): 834−42.
35. *Mengistu AM, Wolf MW, Boldt J, Rohm KD, Lang J, Piper SN*. Evaluation of a new platelet function analyzer in cardiac surgery: a comparison of modified thromboelastography and whole-blood aggregometry. J Cardiothorac Vasc Anesth 2008; 22(1): 40−6.
36. *Görlinger K, Jambor C, Hanke AA, Dirkmann D, Adamzik M, Hartmann M,* et al. Perioperative coagulation management and control of platelet transfusion by point-of-care platelet function analysis. Transfus Med Hemother 2007; 34(6): 396−411.
37. *Steinlechner B, Dworschak M, Birkenberg B, Duris M, Zeidler P, Fischer H,* et al. Platelet dysfunction in outpatients with left ventricular assist devices. Ann Thorac Surg 2009; 87(1): 131−7.
38. *Rahe-Meyer N, Winterhalter M, Hartmann J, PattisonA, Hecker H, Calatzis A,* et al. An evaluation of cyclooxygenase-1 inhibition before coronary artery surgery: aggregometry versus patient self-reporting. Anesth Analg 2008; 107(6): 1791−7.
39. *Rahe-Meyer N, Winterhalter M, Boden A, Froemke C, Pipenbrock S, Calatzis A,* et al. Platelet concentrates transfusion in cardiac surgery and platelet function assessment by multiple electrode aggregometry. Acta Anaesthesiol Scand 2009; 53(2): 168−75.
40. *von Schacky C, Weber PC*. Metabolism and effects on platelet function of the purified eicosapentaenoic and docosahexaenoic acids in humans. J Clin Invest 1985; 76(6): 2446−50.
41. *Thorngren M, Gustafson A*. Effects of 11-week increases in dietary eicosapentaenoic acid on bleeding time, lipids, and platelet aggregation. Lancet 1981; 2(8257): 1190–3.
42. *Kwon JS, Snook JT, Wardlaw GM, Wardlaw GM, Hwang DH*. Effects of diets high in saturated fatty acids, canola oil, or safflower oil on platelet function, thromboxane B2 formation, and fatty acid composition of platelet phospholipids. Am J Clin Nutr 1991; 54(2): 351−8.
43. *Freese R, Mutanen M, Valsta LM, Salminen I*. Comparison of the effects of two diets rich in monounsaturated fatty acids differing in their linoleic/alpha-linolenic acid ratio on platelet aggregation. Thromb Haemost 1994; 71(1): 73−7.
44. *Cairns JA, Gill J, Morton B, Roberts R, Gent M, Hirsh J, et al.* Fish oils and lowmolecular-weight heparin for the reduction of restenosis after percutaneous transluminal coronary angibplasty. The EMPAR Study. Circulation 1996; 94(7): 1553−60.
45. *Serebruany VL*. Aggressive antiplatelet strategies: time to reconsider? Eur Heart J 2007; 28(18): 2183– 4.

Received on December 5, 2011.
Revised on January 9, 2012.
Accepted on January, 12, 2012.