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Klopidogrel kod pacijenata nakon ugradnje aortokoronarne premosnice: početni rezultati studije ZEUS

Clopidogrel in patients after coronary artery bypass graft surgery: preliminary results of ZEUS study

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SAŽETAK: *U ovoj novoj kliničkoj studiji provedenoj na pacijentima s aterosklerozom koronarnih arterija nakon ugradnje aortokoronarne premosnice (CABG), upotreba klopidogrela (Zyllt®, Krka) je u usporedbi s upotrebom acetilsalicilne kiseline (ASA) rezultirala povoljnijom kliničkom prognozom. Kod svih pacijenata liječenih klopidogrelom, ADP-ovisna agregacija trombocita je značajno smanjena te nije laboratorijski zapažena otpornost. Nisu zabilježeni slučajevi nestabilne angine, akutnog infarkta miokarda ili smrti te nije bilo ni većih ni manjih krvarenja ili alergijskih reakcija na klopidogrel. Slabija antitrombocitna aktivnost ASA, prisutnost otpornosti na ASA kod nekih pacijenata i njezina povezanost s nepovoljnim koronarnim epizodama potiče korištenje potentnijih antitrombocitnih lijekova, kao što je klopidogrel, kao i njegovu kombinaciju s ASA, poglavito u visokorizičnih pacijenata.*

KLJUČNE RIJEČI: *koronarna bolest srca, aortokoronarna premosnica, klopidogrel, acetilsalicilna kiselina, antitrombocitna otpornost*

ABSTRACT: *In this recent clinical study conducted in coronary artery atherosclerosis patients after coronary artery bypass graft (CABG) surgery, the use of clopidogrel (Zyllt®, Krka) resulted in a more favourable clinical cardiovascular prognosis compared with the use of acetylsalicylic acid (ASA). In all patients treated with clopidogrel, ADP-dependent platelet aggregation was significantly decreased and no laboratory resistance was observed. No cases of unstable angina, acute myocardial infarction, or death were registered and there were no major or minor hemorrhages or allergic reactions to clopidogrel. The weaker antiplatelet activity of ASA, the presence of ASA resistance in some patients and its association with unfavourable coronary events increasingly stimulate the use of more potent antiplatelet agents, such as clopidogrel, as well as its combination with ASA, especially in high-risk patients.*

KEYWORDS: *coronary heart disease, coronary artery bypass graft surgery, clopidogrel, acetylsalicylic acid, antiplatelet resistance*

Antitrombocitni lijekovi predstavljaju ključnu skupinu lijekova koje se preporučaju za profilaksu vaskularnih epizoda kod pacijenata s koronarnom patologijom aterosklerotskog podrijekla, uključujući i pacijente nakon kardiokirurške revaskularizacije. Pacijentima s koronarnom bolesti srca (KBS) se nakon kirurškog zahvata ugrađivanja aortokoronarne premosnice (CABG) često daje acetilsalicilna kiselina (ASK)[1]. Davanje doze ASK od 75-650 mg/dnevno unutar 48 sati nakon CABG, smanjuje rizik infarkta miokarda (IM) za 48% i rizik moždanog udara za

Antiplatelets are the key group of medicines recommended for the prophylaxis of vascular events in patients with coronary pathology of atherosclerotic origin, including post-coronary revascularization patients. After coronary artery bypass graft (CABG) surgery, patients with coronary heart disease (CHD) are often given acetylsalicylic acid (ASA)[1]. The administration of ASA in a dose of 75-650 mg/day within 48 hours after CABG reduced the risk of myocardial infarction (MI) by 48%, and the risk of stroke by 50%; however, its administration later than 48

50%. Primjena ASK nakon 48 sati od početka intervencije je povezana s nesignifikantnim snižavanjem stope postoperativne smrtnosti[2]. Posljednjih godina je bilo sve više i više izvještaja o otpornosti pacijenata na aspirin. Vode se rasprave o optimalnim metodama dijagnoze rezistencije na ASK, te o mogućim mehanizmima njezinog razvoja. Sukladno s podacima iz literature, rezistencija na ASK je primijećena u 5-45% slučajeva[3-6]. U studijama agregacije trombocita, u kojima je korištena svjetlosna agregometrija (arahidonska kiselina je korištena kao agonist), otpornost na ASK je bila 6% [(interval pouzdanosti (CI) 95%: 0-1)]. U studijama u kojima su korišteni bedside uređaji za analizu trombocita, prosječna učestalost otpornosti na ASK je bila znatno viša, 26% (95% CI: 21-31)[7]. Pacijenti s laboratorijskom otpornosti na ASK spadaju u rizičnu skupinu za nastanak koronarnih epizoda; ovo se naročito odnosi na pacijente nakon revaskularizacije. Kao rezultat, studije učinkovitosti i sigurnosti tienopiridina kod pacijenata nakon CABG kirurškog zahvata postaju sve važnije.

S petogodišnjom prisutnošću na međunarodnom tržištu, s više od 70.000 do sada uspješno liječenih pacijenata, te uz učinkovitost i sigurnost dokazanu u studijama sigurnosti nakon autorizacije i studijama učinkovitosti, kao i vlastitim studijama, Krkin klopidogrel (Zyllt®) omogućava terapiju temeljenu na kliničkim dokazima[8,9]. Među njegovim najnovijim provedenim kliničkim studijama je bila studija ZEUS (Зилт у пациентов с атеросклерозом)[9].

Cilj ove otvorene, randomizirane, komparativne studije je bio istražiti učinak na trombocite i koagulacijsku hemostazu, uspoređujući Krkin klopidogrel s ASK, procijeniti učestalost laboratorijske rezistencije na te lijekove, te istražiti tromjesečnu prognozu kod pacijenata nakon CABG. Ukupno 94 pacijenta s KBS, muškarca u dobi od 45 do 72 godine s početno povišenom ADP-induciranom agregacijom trombocita (PAADP 5mM) i adrenalinom-induciranom agregacijom trombocita (PAadr 10 mcg/ml) je randomizirano u dvije skupine koje su liječene klopidogrelom (75 mg/dnevno; n = 44) ili ASK (75-100 mg/dnevno; n = 50). Kod svih pacijenata trombociti i koagulacijska hemostaza izmjereni su prije CABG, 12-14 dana i tri mjeseca nakon CABG. Pacijenti koji, prema agregatometrijskim nalazima, unutar dva tjedna terapije s jednim od lijekova (ASK ili klopidogrel), nisu reagirali na terapiju su klasificirani u skupinu pacijenata otpornih na antitrombocitne lijekove. Tijekom tromjesečnog razdoblja praćenja, također je procijenjena učestalost sljedećih koronarnih epizoda: nastup angine pektoris, IM ili koronarne smrti. Također su praćeni događaji vezani za terapiju, kao što s manja ili veća krvarenja i alergijske reakcije[9].

Studijom se pokazalo da su prije CABG ("wash-out" period) bile prisutne promjene trombocita i koagulacijske hemostaze. Manifestirale su se kao umjerena endotelioza i aktivacija intravaskularne koagulacije. Kod mnogih pacijenata je zapažen visoki PAADP i PAAdr. Ove promjene hemostaze mogu ukazivati na ozbiljni trombogeni rizik, naročito u postoperativnom razdoblju. Tijekom liječenja klopidogrelom i ASK-om je opažena pozitivna dinamika trombocita i koagulacijske hemostaze: razina fibrinogena je bila znatno niža u skupini koja je uzimala klopidogrel od skupine koja je uzimala ASK; 12-14 dana i 3 mjeseca nakon CABG PAADP je bio znatno smanjen kod 100% pacijenata na klopidogrelu; nije zabilježena laboratorijska otpornost. Kod pacijenata koji su primali ASK, PAADP je

hours from the beginning of the intervention was associated with a non-significant reduction in postoperative mortality[2]. In recent years, there have been more and more reports about patients, resistance to ASA. Discussions are held about optimal methods for the diagnosis of ASA resistance, and about possible mechanisms of its development. According to the literature data, resistance to ASA is observed in 5-45% of the cases[3-6]. In the studies of platelet aggregation, which used light aggregometry (the arachidonic acid was used as the agonist), resistance to ASA was 6% [(95% confidence interval (CI): 0-1)]. In the studies using point-of-care platelet function-analyzing devices, the average frequency of resistance to ASA was significantly higher, 26% (95% CI: 21-31)[7]. Patients with laboratory resistance to ASA belong to the risk group for developing coronary events; this applies particularly to post-revascularisation patients. As a result, studies of the efficacy and safety of thienopyridines in patients after CABG surgery are becoming more and more relevant.

Having been present on the international market for 5 years, with 70,000 patients successfully treated so far and with the efficacy and safety proven in post-authorisation safety and efficacy studies and own clinical studies, Krka's clopidogrel (Zyllt®) provides a therapy based on well-established clinical evidence[8,9]. Among the latest clinical studies conducted with it is the ZEUS study (Зилт у пациентов с атеросклерозом)[9].

The aim of this open, randomised, comparative study was to investigate the effect of Krka's clopidogrel in comparison with ASA on vascular-platelet and coagulation hemostasis, and to assess the frequency of laboratory resistance to these agents and a 3-month prognosis in patients after CABG surgery. In total, 94 CHD patients, 45-72-year-old men with initially elevated ADP-induced platelet aggregation (PAADP 5mM) and adrenaline-induced platelet aggreagation (PAadr 10 mcg/ml), were randomised into two treatment groups to receive either clopidogrel (75 mg/day; n = 44) or ASA (75-100 mg/day; n = 50). In all patients, parameters of vascular-platelet and coagulation hemostasis were measured before CABG, 12-14 days and 3 months after CABG surgery. The patients not responding, according to aggregatometry findings, to 2-week therapy with one of the medicines (ASA or clopidogrel), were classified to the group of patients resistant to antiplatelets. During the three-month follow-up period, the frequency of the following coronary events was also evaluated: onset of angina pectoris, MI or coronary death. Therapy-related events, such as minor and major hemorrhages, and allergic reactions were also monitored[9].

The study demonstrated that before CABG surgery (wash-out period) changes in vascular-platelet and coagulation hemostasis were present. They were manifested as a moderate endotheliosis and activation of intravascular coagulation. In many patients, high PAADP and PAAdr were observed. These hemostasis changes can indicate a serious thrombogenic risk, especially in the postoperative period. During clopidogrel and during ASA treatment, positive dynamics of vascular-platelet and coagulation hemostasis were observed: the fibrinogen level was significantly lower in the clopidogrel group than in the ASA group; 12-14 days and 3 months after CABG surgery, PAADP was significantly reduced in 100% of the patients receiving clopidogrel; no laboratory resistance was observed. In patients recei-

12-14 dana i 3 mjeseca nakon CABG operacije bio povišen u 24% (n = 12) slučajeva (pacijenti otporni na ASK), a u 76% (n = 38) slučajeva je bio smanjen tri puta (pacijenti osjetljivi na ASK)[9].

Potrebno je spomenuti odsutnost koronarnih epizoda (nestabilna angina pektoris, akutni IM) i smrtnih ishoda tijekom razdoblja praćenja u skupini koja je primala klopidogrel. U ASK skupini je jedan pacijent imao akutni IM u drugom mjesecu praćenja, koji je nastupio zbog okluzije arterio-venoznog spoja potvrđene angiografijom premosnice. Kod tog pacijenta je laboratorijska otpornost na ASK ustanovljena tijekom tromjesečnog razdoblja praćenja. Nisu opažena krvarenja ili alergijske reakcije na klopidogrel u dozama od 75 mg/dnevno ili na ASK u dozama od 75-100 mg/dnevno[9].

Slabija antitrombocitna aktivnost ASK, prisutnost otpornosti na ASK kod nekih pacijenata i povezanost ASK s nepovoljnim koronarnim epizodama potiču nas na primjenu potentnijih antitrombocitnih lijekova, kao što je klopidogrel, kao i njegovu kombinaciju s ASK, poglavito kod kod visokorizičnih pacijenata. Pacijenti s KBS-om, koji se često kompliciraju kroničnim zatajivanjem srca, mogu se sigurno svrstati u visokorizičnu skupinu zbog učestalosti koronarnih epizoda i potrebe za pažnjom tijekom antitrombocitne terapije. Rizik se često proširuje u slučaju otpornosti na ASK[9].

Krkin klopidogrel je u ovoj prospektivnoj studiji tromjesečnog praćenja pacijenata s KBS-om nakon CABG, donio vrlo ohrabrujuće rezultate, uz odsutnost laboratorijske rezistencije na lijek te odsutnost koronarnih epizoda[9]. Bit će potrebne daljnje kliničke studije kako bi se nastavilo istraživanje kardiovaskularnih epizoda tijekom dugotrajnog davanja klopidogrela pacijentima nakon CABG.

ving ASA, PAADP was elevated in 24% (n = 12) of the cases 12-14 days and 3 months after CABG surgery (ASA-resistant patients), and in 76% (n = 38) it was reduced by three times (ASA-sensitive patients)[9].

The absence of coronary events (unstable angina pectoris, acute MI) and fatal outcomes has to be mentioned in the clopidogrel group during the follow-up period. In the ASA group, one patient had an acute MI in the second month of the follow-up, caused by an occlusion of the arterio-venous shunt confirmed by bypass angiography. In this patient, laboratory resistance to ASA was found during 3 months of the follow-up. Neither minor nor major hemorrhages or allergic reactions to clopidogrel in the dose of 75 mg/day or ASA in the dose of 75-100 mg/day were observed[9].

The weaker antiplatelet activity of ASA, the presence of ASA resistance in some patients and its association with coronary events increasingly stimulate the use of more potent antiplatelet agents, such as clopidogrel, as well as the combination of clopidogrel with ASA, in particular in high-risk patients. Patients with CHD, often complicated with chronic heart failure, can certainly be included into the high-risk group based on coronary events and the need for special attention during the antiplatelet therapy. This risk is frequently augmented in the presence of ASA resistance[9].

Krka's clopidogrel led to very encouraging results, with absence of laboratory resistance to the medicine and of coronary events, in this prospective 3-month follow-up of patients with CHD after CABG surgery[9]. Further clinical studies will be necessary to continue the research of cardiovascular events during long-term administration of clopidogrel in patients after CABG surgery.

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