Parenteralna antikoagulacijska terapija pri akutnom koronarnom sindromu

Parenteral anticoagulant therapy with acute coronary syndrome

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U akutnom koronarnom sindromu (ACS) jedan od najznačajnijih terapijskih postupaka uključuje primjenu parenteralne antikoagulacijske terapije. Patofiziološko obrazloženje značenja antikoagulacijske terapije leži u središnjoj ulozi procesa tromboze pri aterotrombotskoj bolesti koja se nalazi u osnovi akutne i kronične koronarne bolesti. U akutnoj rupturi aterosklerotskog plaka, koja je najčešće uzrok akutne koronarne bolesti, dolazi do adhezije trombocita na ogoljeli endotel te do agregacije trombocita na rupturirani aterosklerotski plak i stvaranje koaguluma — tromba. Prema tome i u liječenju ACS središnju ulogu pored primjene odgovarajuće antiagregacijske terapije ima odgovarajuća parenteralna trombolitička i antikoagulacijska terapija.

Za razliku od prije 20 godina, danas na raspolaganju imamo cijelu paletu snažnih parenteralnih trombolitika i antikoagulansa s dokazanom učinkovitosti. Iz skupine trombolitika to su streptokinaza, urokinaza, alteplaza i tenekteplaza, iz skupine heparina to su nefrakcionirani heparini (UFH) i niskomolekularni heparini (enoksaparin, nadroparin, dalteparin), iz skupine direktnih inhibitora trombina to su bivalirudin i hirudin, zatim ispitivani su i inhibitori sinteze vitamina K (varfarin), a kao najnoviji parenteralni antikoagulans pojavio se unazad nekoliko godina neizravni inhibitor faktora Xa — fondaparinuks.

Brojna istraživanja pokazala su različite razine korisnosti primjene navedenih lijekova u ACS, te su poslužila kao znanstvena osnova danas važećih smjernica za liječenje STEMI (nova inačica Smjernica Europskog kardiološkog društva upravo je objavljena!) i NSTEMI.

Prema Smjernicama Europskog kardiološkog društva (ESC) za liječenje NSTEMI iz 2007. god., uz primjenu antitrombocitne terapije kod svih bolesnika indicirana je i primjena antikoagulantne terapije. Postoje razlike u preporukama ovisno o planiranoj strategiji liječenja (kod ranog invazivnog ili konzervativnog liječenja preporučena primjena fondaparinuksa), primjena fondaparinuksa u navedenoj indikaciji savjetuje se s obzirom na to da se trenutno smatra najučinkovitijim i najsigurnijim parenteralnim antikoagulansom i to u dozi od 2,5 mg s.c. jednom dnevno. Prema Smjernicama Američkog kardiološkog društva za liječenje STEMI iz 2008. god., indicirana je upotreba UFH, niskomolekularnog heparina ili fondaparinuksa kroz 8 dana.

Ove spoznaje, koje su sada ugrađene u službene Smjernice ESC za NSTEMI i Smjernice Američkog kardiološkog društva za liječenje STEMI rezultat su velikih međunarodnih multicentričnih randomiziranih dvostruko sli-

In acute coronary syndrome (ACS) one of the most important therapeutic procedures includes the use of parenteral anticoagulant therapy. Pathophysiological explanation of the meaning of anticoagulant therapy lies in the central role of the thrombosis process with atherothrombotic disease within the acute and chronic coronary disease. Acute atherosclerotic plaque rupture which is the most frequent cause of acute coronary disease leads to thrombocyte adhesion on pitted endothelium and to aggregation of thrombocytes on ruptured atherosclerotic plaque and generation of coagulum — thrombus. Accordingly, even in the treatment of ACS, the central role apart from the use of suitable antiaggregation therapy there is a suitable parental thrombolytic and anticoagulant therapy.

Unlike the situation some 20 years ago, today we have a whole range of strong parenteral thrombolytics and anticoagulants available with proven efficiency. The group of thrombolytics includes streptokinase, urokinase, alteplase and tenecteplase, the group of heparins includes unfractionated heparins (UFH) and low-molecular-weight heparins (enoxaparin, nadroparin, dalteparin), the group of direct thrombin inhibitors includes bivalirudin and hirudin, then inhibitors of synthesizing the K vitamin (warfarin) have been researched, and the indirect factor Xa inhibitor - fondaparinux appeared as the most recent parenteral anticoagulant several years ago.

A number of researches have showed different levels of benefits from the use of the above drugs in ACS and have been used as a scientific basis for applicable guidelines today for the treatment of STEMI (a new version of the Guidelines of the European Cardiac Society has just been published!) and NSTEMI.

According to the Guidelines of the European Society of Cardiology (ESC), for the treatment of NSTEMI from 2007, the use of anticoagulant therapy has been indicated along with the use of the antithrombotic therapy with all the patients. There are differences in recommendations subject to planned treatment strategy (with early invasive or conservative treatment, the use of fondaparinux has been recommended), the use of fondaparinux in the stated indication is advised since it is currently considered to be the most efficient and safest parenteral anticoagulant in dose of 2.5 mg s.c. once a day. According to the American STEMI Guidelines for the treatment of from the year 2008, the use of UFH, low-molecular-weight heparin or fondaparinux throughout the period of 8 days has been indicated.

This information that has been included in the official ESC Guidelines for NSTEMI and the American STEMI Guidelines is the result of large international multi-centric ran-

jepih studija OASIS (*Organization to Assess Strategies in Ischemic Syndromes*) 5 i OASIS 6.

U studiji OASIS 5 ispitivala se primjena fondaparinuksa u usporedbi s enoksaparinom kod bolesnika sa nestabilnom anginom pektoris (UA) i NSTEMI. U studiji OASIS 6 ispitivala primjena fondaparinuksa kod bolesnika sa STEMI unutar 12h od početka simptoma, a koji su bili stratificirani u grupe s i bez indikacije za antikoagulantno liječenje, te su ovisno o grupi u kojoj su bili primali fondaparinuks ili UFH (s indikacijom za antikoagulantno liječenje), odnosno fondaparinuks ili placebo (bez indikacije za antikoagulantno liječenje).

Rezultati studije OASIS 5 pokazali su da je fondaparinuks učinkovit kao enoksaparin u smanjenju učestalosti složenih ciljeva: smrtnosti, reinfarciranja i refraktorne ishemije 9. dana liječenja; da značajno smanjuje rizik smrtnosti (za 17%) u usporedbi s enoksaparinom, od 30. do 180. dana; te da značajno smanjuje (za 48%) učestalost velikih krvarenja za razliku od enoksaparina. Fondaparinuks je indiciran svim bolesnicima s UA/NSTEMI u kojih urgentna PCI nije indicirana. ESC preporučuje fondaparinuks za UA/NSTEMI bolesnike; ali za vrijeme PCI treba dodati UFH!

Rezultati studije OASIS 6 pokazali su da fondaparinuks značajno smanjuje smrtnost ili pojavu reinfarkta kod bolesnika sa STEMI, no bez povećavanja učestalosti krvarenja u odnosu na UFH i placebo; korist liječenja fondaparinuksom postaje vidljiva već 9. dana i prisutna je do 6. mjeseca; korist je vidljiva kod bolesnika kod kojih se ne primjenjuje reperfuzijska terapija i kod onih koji su primili trombolitičku terapiju, uz manju učestalost ozbiljnog krvarenja; sveukupno je smanjena stopa smrtnosti u grupi koje je primala fondaparinuks. Jedino u slučaju primarne PCI nije bilo dodatne koristi od primjene fondaparinuksa.

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domized double blind studies OASIS (*Organization to Assess Strategies in Ischemic Syndromes*) 5 and OASIS 6.

The use of fondaparinux in comparison with enoxaparin with patients with unstable angina pectoris (UA) and NSTEMI has been researched in the study OASIS 5. The use of fondaparinux has been researched in the study OASIS 6 with patients with STEMI within 12 hours from the onset of symptoms that were stratified into groups with or without indications for anticoagulant treatment and depending on the group in which they received fondaparinux or UFH (with indication for coagulant treatment) or fondaparinux or placebo (without indications for anticoagulant treatment).

The results of the OASIS 5 study have showed that fondaparinux is as efficient as enoxaparin in reducing the frequency of complex endpoints: mortality, reinfarction and refractory ischemia on the 9th day of treatment; that it greatly reduces the mortality risk (by 17%) in comparison with enoxaparin, from 30-180 day; and it greatly reduces (by 48%) the frequency of major bleeding unlike the enoxaparin. Fondaparinux is indicated with all patients with UA/NSTEMI in which urgent PCI has not been indicated. ESC recommends fondaparinux for UA/NSTEMI patients; but during the time of PCI, UFH is to be added!

The findings of OASIS 6 have showed that fondaparinux greatly reduces mortality or reinfarction occurrence with patients with STEMI, but without rise in frequency of bleeding in comparison with UFH and placebo; the benefit of treatment with fondaparinux will become obvious on the 9th day and is present till the 6th month; the benefit is obvious with patients with whom reperfusion therapy is not applied and with those who have received thrombolytic therapy with reduced frequency of serious bleeding; the mortality rate has been, generally, reduced in the group receiving fondaparinux. Only in the case of primary PCI there has no been additional benefit from the use of fondaparinux.