Stručni rad

Klopidogrel — terapija koja se temelji na kliničkim dokazima

Professional article

Clopidogrel — a therapy based on well-established clinical evidence

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SAŽETAK: *Akutni koronarni sindrom predstavlja problem sustava zdravstvene skrbi budući da je svake godine uzrok velikog broja hospitalizacija. U nedavno objavljenoj studiji uspoređena je učinkovitost i sigurnost originalnog s Krkinim klopidogrelom. Uključeno je ukupno 160 bolesnika s nestabilnom anginom i akutnim infarktom miokarda bez elevacije ST segmenta. Bolesnici su liječeni s nefrakcioniranim heparinom te su slučajno podijeljeni u dvije skupine. Bolesnici u prvoj skupini su, uz acetilsalicilnu kiselinu, dobivali originalni klopidogrel, dok su oni u drugoj skupini dobivali Krkin klopidogrel. Analizirana je učestalost ozbiljnih koronarnih događaja i sigurnost tijekom razdoblja praćenja od 150 dana. Rezultati su potvrdili jednaku terapijsku ekvivalentnost obzirom da nisu utvrđene statistički značajne razlike u terapijskoj učinkovitosti i sigurnosti između originalnog i Krkinog klopidogrela.*

KLJUČNE RIJEČI: *akutni koronarni sindrom, acetilsalicilna kiselina, klopidogrel.*

UDK *615.014.2=163.42=111*

ABSTRACT: *Acute coronary syndrome is a problem of the healthcare system as it causes a large number of hospitalizations every year. In the recent study efficacy and safety of the originator's clopidogrel and Krka's clopidogrel was compared. The total of 160 patients with unstable angina and non-ST-segment elevation myocardial infarction were included. All patients were treated with unfractionated heparin and were randomly assigned to two treatment groups. The patients of the first group received, in addition to acetylsalicylic acid, the originator's clopidogrel, whereas the patients of the second group received Krka's clopidogrel. The frequency of serious coronary events and safety during 150 days of the observation were analyzed. The results confirmed therapeutic equivalence as they showed no statistically significant differences in the therapeutic efficacy and safety between originator's and Krka's of clopidogrel.*

KEYWORDS: *acute coronary syndrome, acetylsalicylic acid, clopidogrel.*

CITATION: *Kardio list. 2010;5(5-6):81-83.*

Akutni koronarni sindrom (ACS) predstavlja značajan problem za sustav zdravstvene skrbi obzirom da svake godine uzrokuje veliki broj hospitalizacija[1]. Prema podacima iz ACS registra, broj bolesnika s akutnim infarktom miokarda bez elevacije ST-segmenta (NSTEMI) se zadnjih godina povećao u usporedbi s brojem bolesnika s infarktom miokarda s elevacijom ST-segmenta (STEMI)[2,3].

Kombinacija antiagregacione i antitrombocitne terapije predstavlja osnovno liječenje za bolesnike s NSTEMI i preventivnu terapiju komplikacija kod pacijenata s koronarnom bolesti srca (CHD). U skladu s najnovijim preporukama[4,5], preporuča se da svi bolesnici s ACS započnu uzimati klopidogrel u udarnoj dozi od 300 mg, a zatim u dozi održavanja od 75 mg/dnevno. Liječenje klopidogrelom bi trebalo trajati 12 mjeseci.

Učinkovitost i sigurnost Krkinog klopidogrela je već ranije dokazano u studijama sigurnosti i učinkovitosti nakon odobrenja, kao i vlastitim kliničkim studijama[6-9].

Cilj nedavne randomizirane, otvorene, usporedne, prospektivne studije je bio istražiti učinke antitrombocitne terapije na kliničke ishode kod bolesnika s NSTEMI. U 160 bolesnika s nestabilnom anginom i NSTEMI uspoređena je učinkovitost i sigurnost originalnog i Krkinog klopidogrela (Zyllt©).

Bolesnici su u obje skupine liječeni s nefrakcioniranim heparinom (UHF) u obliku intravenozne infuzije te su nasumično podijeljeni u dvije skupine: bolesnici u prvoj skupini su, uz acetilsalicilnu kiselinu, dobivali originalni klopidogrel, dok su bolesnici u drugoj skupini dobivali Krkin klopidogrel. Oba klopidogrela su bolesnicima davana u udarnoj dozi od 300 mg te kasnijim dozama održavanja od 75 mg/dan[6].

Analizirana je učestalost ozbiljnih koronarnih događaja — smrt, povratne angine pektoris, STEMI, perkutane koronarne intervencije ili CABG (primarni ishod) na 8., 15., 30. i 150. dan praćenja. Nakon 150 dana studije nije bilo značajnih razlika u mortalitetu, učestalosti STEMI, povratne angine pektoris i intervencijama revaskularizacije (**Slika 1**)[6].

Također nije bilo razlika tijekom praćenja (na 8., 15., 30. dan). Tijekom 150 dana su u prvoj skupini zabilježena dva smrtna slučaja (2%), a u drugoj skupini nisu zabilježeni smrtni slučajevi, a statistički značajne razlike u mortalitetu nije registrirana. Treba napomenuti da je ponovni in-

Acute coronary syndrome (ACS) is a significant problem of the healthcare system as it causes a large number of hospitalizations every year[1]. According to the data from the ACS registry, the number of patients with non-ST-segment elevation myocardial infarction (NSTEMI) has increased in recent years in comparison to the number of patients with ST-segment elevation myocardial infarction with (STEMI)[2,3].

The combination of antiplatelet agents and antithrombotic therapy represents base treatment for patients with NSTEMI and coronary heart diseases (CHD) complications prophylaxis. In accordance with the latest recommendations[4,5] all the patients with ACS are recommended immediate intake of clopidogrel in a loading dose of 300 mg with a subsequent long-term intake of 75 mg/day. The treatment with clopidogrel should last for 12 months.

The efficacy and safety of Krka's clopidogrel was proven previously in post-authorisation safety and efficacy studies and own clinical studies[6-9].

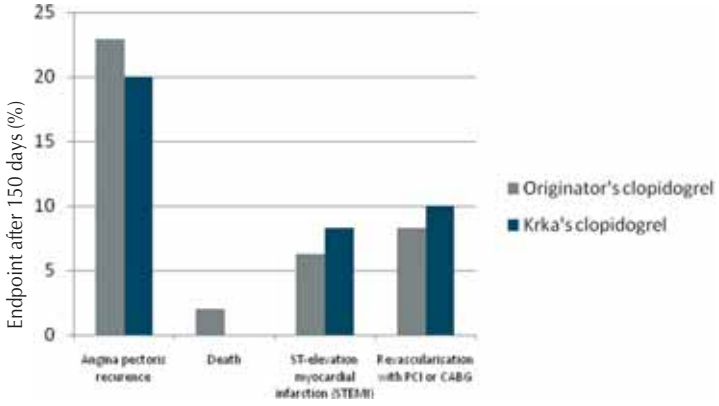
The aim of the recent randomized, open, comparative, prospective study was to investigate the effects of antiplatelet therapy on the clinical course in patients with NSTEMI. The comparative efficacy and safety of the originator's and Krka's clopidogrel (Zyllt©) were studied in 160 patients with unstable angina and NSTEMI.

The patients in both groups were treated with unfractionated heparin (UFH) as intravenous infusion and were randomly assigned to two treatment groups: the patients of the first group received, in addition to acetylsalicylic acid, the originator's clopidogrel, whereas the patients of the second group received Krka's clopidogrel. Both clopidogrels were given to the patients in a loading dose of 300 mg with subsequent long-term intake of 75 mg/day[6].

Frequency of serious coronary events — death, recurrent angina pectoris, STEMI, percutaneous coronary intervention or CABG (primary end point) on 8th, 15th, 30th and 150th day of the monitoring were analyzed. After 150 days of the study there were no statistically significant differences in mortality, frequency of STEMI, recurrent angina pectoris and revascularization interventions (**Figure 1**)[6].

There were also no differences during the follow up (on 8th, 15th, 30th day). There were two death cases in the first group during the 150 days (2%), and no death cases in the second group, so there was no statistically significant difference in mortality. It should be noted that the develop-

Figure 1. *Frequency of unfavourable events in treatment groups after 150 days of study.*



PCI - percutaneous coronary intervention, CABG - coronary artery bypass graft

Table 1. *Frequency of unfavourable events in treatment groups during 150 days of study.*

	8th day		15th day		30th day		150th day	
	I* n=100	II** n=60	I* n=100	II** n=60	I* n=100	II** n=60	I* n=96	II** n=60
Combination of outcomes, n (%)	16 (16)	9 (15)	25 (25)	12 (20)	30 (30)	15 (25)	38 (39.9)	23 (38.3)
Death, n (%)	0	0	0	0	0	0	2 (2)	0
Myocardial infarction, n (%)	4 (4)	3 (5)	4 (4)	3 (5)	4 (4)	3 (5)	6 (6.25)	5 (8.3)
Recurrent angina, n (%)	10 (10)	3 (5)	17 (17)	6 (10)	20 (20)	9 (15)	22 (22.9)	12 (20)
Revascularization, n (%)	2 (2)	3 (5)	4 (4)	3 (5)	6 (6)	3 (5)	8 (8.3)	6 (10)

*originator's clopidogrel, **Krka's clopidogrel

farkt miokarda bio uzrok oba smrtna slučaja. Učestalost kombiniranog evaluacijskog kriterija tijekom 150 dana je bila 39,9% u prvoj skupini, što se nije značajno statistički razlikovalo od učestalosti u drugoj skupini, koja je iznosila 38,3% (**Tablica 1**). Rezultati dokazuju terapijsku ekvivalentnost Krkinog i originalnog klopidogrela.

Sigurnost liječenja je predstavljala sekundarni evaluacijski kriterij. Glavni znaci ovog kriterija su bili krvarenja te trombocitopenija (trombociti <100x10^9/l). U razdoblju od 150 dana u studiji nisu zabilježena nikakva krvarenja ili trombocitopenija. Niti jedan bolesnik nije prekinuo liječenje zbog nuspojava. Četiri bolesnika su se povukla iz studije zbog različitih uzroka[6].

Rezultati studije su značajni. Nisu ustanovljene statistički značajne razlike u terapijskoj učinkovitosti (utjecaj na ishode) i sigurnosti između originalnog i Krkinog klopidogrela. Rezultati studije se podudaraju s rezultatima meta-analiza studija učinkovitosti i sigurnosti originalnog klopidogrela i njegovih generičkih oblika[10]. Visoka učinkovitost i sigurnost klopidogrela bi bez sumnje mogla omogućiti izvrsno pridržavanje terapijskih uputa kod pacijenata koji su preboljeli ACS i bili podvrgnuti postupku revaskularizacije.

ment of recurrent MI was the reason for all death cases. The frequency of the combined evaluation criteria during the 150 days was 39.9% in the first group, which did not statistically significantly differ from the frequency of the combined criterion in the second group, which was 38.3% (**Table 1**). The results proved the therapeutic equivalence of Krka's and orginator's clopidogrel.

Treatment safety represented a secondary evaluation criterion. The main signs of this criterion were strong and weak bleeding, and thrombocytopenia (platelets <100x 10^9/l). In the period of 150 days there were no bleedings and thrombocytopenias observed in the study. No patients discontinuated the treatment due to adverse reactions. There were 4 patients withdrawn from the study because of various causes[6].

The recent study yielded important results. No statistically significant differences in the therapeutic efficacy (impact on firm endpoints) and safety between the originator's and Krka's clopidogrel were found. The results of the recent study conform to the results of the meta-analysis of studies on efficacy and safety of the originator's clopidogrel and its generic form[10]. The high efficiency and safety of of clopidogrel could undoubtedly provide an excellent adherence to the treatment in patients who suffered ACS and underwent revascularization procedure.

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