Utjecaj kontinuiranog prilagođavanja doze klopido- grela prema rezultatima agregometrijskih mjerenja na kliničke ishode u akutnom koronarnom sindromu

Effect of continuous platelet function testing based clopidogrel dose adjustment on clinical outcomes in acute coronary syndrome

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KLJUČNE RIJEČI: reaktivnost trombocita, akutni koronarni sindrom, klopido-
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KEYWORDS: platelet reactivity, acute coronary syndrome, clopidogrel, individualized therapy, clinical outcome.

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UVOD: Povišena reaktivnost trombocita (RT) uz klopido-
grele je prethodnik lošijeg ishoda u akutnom koronarnom
sindromu (AKS) i nakon perkutane koronarne intervencije
(PCI). Za sada nije poznato može li se smanjiti utjecaj povi-
šene RT na kliničke ishode. U ovoj studiji se željelo ispitati
može li se kod bolesnika s ACS-om liječenih s PCI ponav-
ljanim prilagođavanjem doze klopido-
grele kroz 12 mjeseci
prema vrijednostima RT nad-
vladati povišena RT i tako po-
boljšati ishodi.

PACIJENTI I METODE: Učinjen je probir nad 461 konse-
kutivnim bolesnikom s AKS-om. Isključni kriterij je imalo
120 bolesnika (kontinuirana primjena inhibitora glikoprote-
inskih IIb/IIIa receptora, trombociti $<150 \times 10^9/L$, kreatinin
 $>200 \mu\text{mol/L}$, hematokrit $<30\%$, kronična primjena antiko-
agulantnih lijekova i dob >80 godina). Ostalim bolesnicima
($n=341$) mjerena je RT 12-24 sata nakon PCI. Bolesnici s
povišenom RT uz klopido-
grele ($n=87$; 25,5%) randomizirani
su u skupinu liječenu standardnim dozama klopido-
grele (kontrolna skupina) ($n=44$) i ispitivanu skupinu ($n=43$). Krv
za mjerenje RT-a je vađena 1., 2., 3., 7., 30. dan te 2., 3., 6., 9.
i 12. mjesec nakon PCI. Za mjerenje RT korišten je Multi-
plate® uređaj. Doza klopido-
grele prilagođavana je prilikom
svakog mjerenja RT, a bolesnici su dobili do tri doze zasi-
ćenja od 600 mg te 75 mg-300 mg klopido-
grele kao dozu održavanja da bi se postigla i održavala optimalna vrijed-
nost RT (19-46U).

REZULTATI: Pojavnost ishemijskih događaja (hospitali-
zacija zbog ishemijskih događaja, revaskularizacija cilj-
ne lezije, nefat-
alni infarkt miokarda, tromboza u stentu, cerebrovasku-
larni infarkt, kardiovaskularna smrt) bila je značajno veća u
kontrolnoj skupini bolesnika u odnosu na ispitivanu skupi-
nu (16,7 bolesnika; $p=0,034$). Nije bilo razlike u krvarenjima
(2,3 bolesnika; $p=1,000$).

ZAKLJUČAK: Rezultati ukazuju da je povišena RT uz klo-
pidogrel podesiv čimbenik rizika i da bi individualizirana
antitrombocitna terapija prilagođavana prema vrijednosti-
ma RT mogla donijeti kliničku korist kod ovih bolesnika.

INTRODUCTION: High on-treatment platelet reactivity
(HTPR) on clopidogrel is a predictor of recurrent isch-
emic events in acute coronary syndrome (ACS) patients
treated with percutaneous coronary intervention (PCI).
Whether it is a modifiable risk factor remains unclear.
The aim of this study was to evaluate the effect of serial
clopidogrel dose adjustment based on platelet function
testing (PFT) to overcome HTPR phenotype and improve
clinical outcomes of patients with HTPR after successful
PCI in ACS.

PATIENTS AND METHODS: We screened 461 con-
secutive ACS patients. Exclusion criteria was present in
120 patients (continuous postinterventional glycoprotein
(GP) IIb/IIIa receptor inhibitor perfusion, thrombocyto-
penia ($<150 \times 10^9/L$), creatinine $>200 \mu\text{mol/L}$, anemia (Hc
 $<30\%$), chronic anticoagulation therapy and advanced
age (>80 years)). Patients without exclusion criteria
($n=341$) underwent PFT 12-24 hours following PCI. Pa-
tients with determined HTPR on clopidogrel ($n=87$; 25,5%)
were included in the study and randomized to standard
dose clopidogrel (control) group ($n=44$) and interven-
tional group ($n=43$). PFT using Multiplate® function analyzer
was performed on day 1, 2, 3, 7, 30 and at month 2, 3, 6, 9
and 12 after initial PCI. Clopidogrel dose was adjusted at
each PFT in the interventional group with patients tak-
ing up to three 600 mg loading doses and a range of 75-
300 mg clopidogrel maintenance dose to achieve optimal
platelet reactivity (19-46U).

RESULTS: Composite of ischemic events (hospitaliza-
tion due to ischemia, target vessel revascularization,
non-fatal myocardial infarction, in-stent thrombosis,
stroke, cardiovascular death) was significantly higher
in control group (16 vs 7 patients; $p = 0.034$). There was
no difference in total bleeding outcomes (2 vs 3 patients;
 $p=1.000$).

CONCLUSION: HTPR on clopidogrel might be a modi-
fiable risk factor for ischemic events. Personalized an-
tiplatelet therapy based on PFT might bring clinical ben-
efit in ACS patients treated with PCI.

LITERATURE

- Price MJ, Endemann S, Gollapudi RR, et al. Prognostic significance of post-clopidogrel platelet reactivity assessed by a point-of-care assay on thrombotic events after drug-eluting stent implantation. *Eur Heart J*. 2008;29(8):992-1000.
- Bonello L, Tantry US, Marcucci R, et al; Working Group on High On-Treatment Platelet Reactivity. Consensus and future directions on the definition of high on-treatment platelet reactivity to adenosine diphosphate. *J Am Coll Cardiol*. 2010;56(12):919-33.

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