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Platelet Inhibition by Abciximab Bolus-Only Administration and Oral ADP Receptor Antagonist Loading in Acute Coronary Syndrome Patients: The Blocking and Bridging Strategy ☆

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ABSTRACT

Introduction: Current guidelines still recommend the bolus and infusion administration of glycoprotein IIbIIIa inhibitors in patients with high-risk acute coronary syndrome undergoing percutaneous coronary intervention. We sought to evaluate the extent of platelet inhibition by a blocking and bridging strategy with intracoronary abciximab bolus-only administration and oral loading of adenosine diphosphate receptor antagonists.
Patients and methods: Fifty-six consecutive high-risk acute coronary syndrome patients with bolus-only abciximab administration (0.25 mg/kg i.c.) and loading with 600 mg clopidogrel (55%) or 60 mg prasugrel (45%) were included in this study. Platelet aggregation induced by thrombin receptor-activating peptide and adenosine diphosphate was measured by multiple electrode aggregometry up to 7 days.
Results: Thrombin receptor-activating peptide induced platelet aggregation was significantly suppressed for a minimum of 48 h (45 ± 17 U) and returned to a normal range (>84 U) after 6 days (90 ± 26 U; $p < 0.001$). Co-medication with prasugrel significantly reduced adenosine diphosphate-induced ($p = 0.002$) and thrombin receptor-activating peptide-induced ($p = 0.02$) platelet aggregation compared with clopidogrel throughout the observation period. No stent thrombosis or repeat myocardial infarction occurred at 30-day follow-up.
Conclusions: Immediate *blocking* of platelet aggregation in high-risk acute coronary syndrome patients by intracoronary abciximab bolus-only administration and *bridging* to prolonged inhibition via oral blockade of ADP receptors effectively inhibited overall platelet reactivity for at least 48 h, questioning the value of continuous abciximab infusion. Co-medication with prasugrel vs. clopidogrel synergistically augmented platelet inhibition.

Introduction

Current acute coronary syndrome (ACS) guidelines recommend the bolus plus infusion administration of the glycoprotein IIb/IIIa receptor inhibitor (GPI) abciximab (Reopro®) on top of dual antiplatelet therapy for ST-elevation myocardial infarction (STEMI) and non-ST-elevation myocardial infarction (NSTEMI) patients with visible thrombus burden undergoing primary percutaneous coronary intervention (PCI) [1,2]. However, the underlying evidence for such use of abciximab dates back to the pre-stent era, without concomitant use of sufficient loading doses of adenosine diphosphate (ADP) receptor antagonists [3]. Notably, the abciximab bolus-only arm of the EPIC (Evaluation of 7E3 for the Prevention of Ischemic Complications) trial provided evidence in 2006 for sufficient clinical benefit during the first 24 h of treatment [4]. Nonetheless, this approach might only now seem appropriate, as systematic stent implantation and high oral loading doses of platelet ADP receptor antagonists (especially of newer generations like prasugrel [5]) reflect contemporary practice in ACS patients with STEMI.

The underlying rationale for the immediate *blocking* of platelet aggregation by bolus-only administration of abciximab and *bridging* to prolonged inhibition via administration of an oral ADP receptor antagonist is based on the hypothesis, that effective blockade of ADP (P2Y12) receptors following GPI administration synergistically augments overall platelet inhibition by preventing reactivation of platelet GPIIb/IIIa receptors as the effect of the initial GPI bolus subsides. This concept has been successfully demonstrated in NSTEMI patients with an

Abbreviations: ACS, acute coronary syndrome; ADP, adenosine diphosphate; GPI, glycoprotein IIb/IIIa receptor inhibitor; MEA, multiple electrode aggregometry; NSTEMI, Non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction; TRAP, Thrombin receptor-activating peptide.

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adequate clopidogrel response in a randomised comparison of intravenous abciximab vs. bolus plus infusion administration [6]. The FABOLUS SYNCHRO trial demonstrated that equivalent levels of platelet inhibition were achieved with both regimens of abciximab administration within the first 24 h of drug therapy.

In addition, sole oral loading even with newer generations of ADP receptor antagonists in STEMI patients results in suboptimal levels of platelet inhibition for at least 2 hours [7,8], leaving a non-therapeutic window of high thrombotic risk at the time of PCI, which can be closed by immediate GPI bolus administration.

Intracoronary (i.c.) administration of the abciximab bolus has been shown to be superior to the intravenous (i.v.) route, with improvements in short-term mortality [9]. The recent (2012) randomised, large-scale, multicentre AIDA STEMI (Abciximab Intracoronary versus intravenous Drug Application in ST-Elevation Myocardial Infarction) trial failed to confirm these findings, but showed that i.c. administration of abciximab is both safe and related to lower rates of congestive heart failure [10].

Numerous studies including more than 13,000 PCI patients revealed the significant association of a high residual ADP-induced platelet reactivity during therapy with clopidogrel and thrombotic risk at follow-up [11,12]. Especially in the acute setting where patients with increased thrombus burden predominate, high residual platelet reactivity seems predictive of acute intra- and periprocedural thrombotic events, even under prasugrel therapy [13], underlining the importance of the GPI bolus administration for immediate platelet inhibition in addition to oral ADP receptor antagonist loading.

Thrombin receptor-activating peptide (TRAP)-induced platelet aggregation serves as a positive control to judge overall platelet aggregability in newer generations of point-of-care platelet reactivity assays, including the multiple electrode aggregometry (MEA, Multiplate® Analyzer) [14]. Like thrombin, TRAP exerts its actions via platelet protease-activated receptor-1 (PAR-1) [15], which is not blocked by P2Y12-inhibiting ADP receptor antagonists. Therefore, combining measurements of TRAP- and ADP-induced platelet aggregation allows monitoring of overall GPI induced, as well as ADP receptor antagonist-induced platelet inhibition.

This study sought to evaluate the "blocking and bridging strategy" in high-risk ACS patients (STEMI and NSTEMI with visible thrombus) undergoing PCI by evaluating the time course and extent of platelet inhibition by i.c. bolus-only administration of abciximab and the relationship to co-medication with clopidogrel or prasugrel.

Methods

Patient Population and Study Design

Fifty-six consecutive high-risk ACS patients (STEMI or NSTEMI patients with visible thrombus burden) who were referred for acute PCI and received an i.c. abciximab (Reopro®) bolus (0.25 mg/kg) at the Kaiser Franz Josef Hospital were included in this analysis. As a local laboratory rule, patients with occluded infarct-related arteries or visible thrombus received abciximab via the i.c. route. STEMI patients accounted for 70% of the subjects, and NSTEM patients accounted for 30% of the subjects. Primary PCI was performed in STEMI patients within 3 hours of pain onset. Urgent PCI was performed in NSTEMI within 2 hours of presentation at the hospital. All patients received i.v. unfractionated heparin (70 IU/kg) before PCI. Aspirin-naive patients received i.v. aspirin at a dose of 500 mg before PCI, whereas patients on chronic aspirin therapy received i.v. aspirin at a dose of 250 mg. The i.c. GPI bolus was given prior insertion of the guide wire into the culprit vessel. Oral loading with either 600 mg clopidogrel (Plavix®) or 60 mg prasugrel (Efient®) was performed according to a local standard operating procedure (SOP) as part of the "Individualizing Dual Antiplatelet Therapy After Percutaneous Coronary Intervention - The IDEAL-PCI Registry" phase 3 trial (ClinicalTrials.gov identifier: NCT01515345). Briefly, STEMI patients without history of stroke, age below 75 years or weight above 60 kg received 60 mg prasugrel prior to PCI, while all other patients received 600 mg clopidogrel (either in the emergency room, the coronary care unit or the catheter laboratory). Intubated patients in cardiogenic shock received the loading dose of the appropriate drug via a nasogastric tube after PCI in the intensive care unit. The type of stent implantation was at the discretion of the interventional cardiologist. In cases of clopidogrel nonresponse at follow-up, patients without contraindications were switched to prasugrel.

The local Ethics Committee approved the study protocol in accordance with the Declaration of Helsinki. Informed consent was obtained after PCI, either from the patient or from the guardian in cases of critically ill conditions. Follow-up information was obtained by either direct patient or telephone contact at 30 days. The clinical efficacy endpoints were death, repeat myocardial infarction or stent thrombosis. The safety end point was the incidence of thrombolysis in myocardial infarction (TIMI) major or minor bleeding [16].

Impedance Aggregometry

Whole blood aggregation was determined using MEA, a new-generation impedance aggregometer (Multiplate® Analyzer, Roche, Munich, Germany). The system detects the electrical impedance change due to the adhesion and aggregation of platelets on two independent electrode-set surfaces in the test cuvette, with a low rate of intra-and interassay variability [14]. TRAP-6 and ADP were used as agonists. A 1:2 dilution of whole blood anticoagulated with hirudin and 0.9% NaCl was stirred at 37 °C for 3 min in the test cuvette. ADP (6.4 μM) and TRAP-6 (32 μM) were added, and the increase in electrical impedance was continuously recorded for 6 min. The mean values of the two independent determinations were expressed as the area under the curve (AUC) of the aggregation tracing. AUC is reported herein in units (U), as described previously [17]. On-treatment platelet reactivity was measured at 4 h (range: 3–7 hours), 24 h (range: 18–36 hours), 3 days (range: 2–4 days) and 6 days (range: 5–7 days), after GPI bolus administration. The oral loading dose of ADP was given prior cardiac catheterization in non-shock patients (15–40 minutes prior in STEMI patients, 60–120 minutes in NSTEMI patients), and immediately after PCI in shock patients via a nasogastric tube. In case of high on-treatment platelet reactivity to ADP (>49 U) [18], patients were classified as clopidogrel nonresponders and were reloaded with 60 mg prasugrel in the absence of contraindications (i.e., a history of stroke). TRAP values below 84 U were classified as indicative of reduced overall platelet aggregation (according to the Multiplate® reference values).

Statistical Analysis

Data are expressed as the mean ± the SD or the standard error of mean (SEM), where indicated. Statistical comparisons were performed with the Mann Whitney U test, the unpaired Students t-test, the chi-squared test or a one way analysis of variance followed by the Bonferroni post hoc test. All statistical calculations were performed using commercially available statistics analysis software (SPSS Version 11.5; Chicago).

Sample Size

Based on a 50% difference in the effect of abciximab on TRAP-induced platelet aggregation (baseline: 90 ± 26 U vs. abciximab bolus: 45 ± 17 U), a sample size of 54 patients was calculated to provide 100% power to detect a significant difference between conditions (two-sided alpha value of < 0.05).