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Full Length Article

Impact of pre-procedural dual antiplatelet therapy on periprocedural myocardial infarction in patients undergoing percutaneous coronary interventions with adjunctive tirofiban

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ABSTRACT

Background: Recent trials have failed to demonstrate any clinical benefit from pre-treatment with dual antiplatelet therapy (DAPT) in patients undergoing percutaneous coronary interventions, (PCI), even in the setting of acute coronary syndrome. However, suboptimal platelet inhibition during (PCI) has been shown to enhance the risk of acute ischemic complications, such as stent thrombosis and periprocedural myocardial infarction (PMI), thus raising the attention on the potential advantages of adjunctive glycoprotein IIbIIIa inhibitors to obviate to the delayed onset of action of oral antiplatelet drugs. The aim of the present study was then to evaluate the impact of platelet reactivity and pre-procedural DAPT on PMI in patients undergoing PCI with adjunctive tirofiban.

Methods: In a consecutive cohort of patients undergoing PCI with tirofiban (intracoronary/intravenous ± prolonged infusion), periprocedural myonecrosis was defined as troponin I increase by 3 times the ULN or by 50% of an elevated baseline value, whereas PMI as CKMB increase by 3 times the ULN or 50% of baseline. Platelet function was assessed by impedance aggregometry.

Results: A total of 168 patients were included, 77 (45.8%) of whom were on DAPT at the time of PCI. Patients on DAPT had more often a history of previous PCI ($p = 0.03$), higher ACS at admission ($p < 0.001$) and creatinine levels ($p = 0.03$). Coronary calcifications and type C lesions were more frequent in patients without DAPT ($p = 0.02$ and $p = 0.03$, respectively), as much as TIMI flow < 3 ($p = 0.03$), while procedural characteristics were comparable. Baseline platelet reactivity was significantly reduced in DAPT treated patients ($p < 0.001$ for ASPI, COL and ADP tests). However the rate of periprocedural myonecrosis did not differ according to pre-procedural DAPT (68.4%vs 67%, $p = 0.87$; adjusted OR[95%CI] = 1.34[0.71–2.53], $p = 0.36$) and neither the occurrence of PMI (13.3% vs 12.6%, $p = 0.99$; adjusted OR[95%CI] = 1.24[0.51–3.1], $p = 0.64$). Furthermore, baseline platelet reactivity was similar in patients with and without PMI/myonecrosis with no relationship between platelet function and Troponin I peak.

Conclusion: In patients undergoing PCI with adjunctive GP IIb-IIIa inhibitors, preprocedural DAPT and baseline platelet reactivity are not associated to the risk of periprocedural myocardial infarction or myonecrosis. These data further support the role of periprocedural Gp IIb-IIIa inhibitors in order to overcome any suboptimal inhibition of platelet aggregation at the time of the procedure due to drug-resistance or delayed (downstream) administration of ADP antagonists, especially in complex high-risk procedures.

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1. Background

Platelet inhibition represents a crucial therapeutic point in patients undergoing percutaneous coronary interventions (PCI), for the prevention of periprocedural complications as acute stent thrombosis, or periprocedural myocardial infarction (PMI) [1–3]. In fact, 5–30% of PCI procedures is weighted by the occurrence of PMI, and microvascular thrombotic obstruction has certainly been claimed for explaining myocardial damage in apparently uncomplicated procedures [4,5].

Previous studies, have pointed at the suboptimal effectiveness of antiplatelet drugs, conditioning the occurrence of periprocedural thrombotic events, PMI and worse outcomes. In particular, such risk could be even enhanced in patients treated with Clopidogrel, in consequence of its delayed onset of action and complex metabolic activation [6]. However, still the majority of elective patients receive Clopidogrel after PCI. Indeed, newly developed oral antiplatelet drugs have allowed to achieve a more potent platelet inhibition and faster onset of action, therefore showing no benefit from early pretreatment before PCI, even in the context of acute coronary syndromes [7,8]. Therefore, DAPT administration prior to PCI is not mandatory, according to current guidelines [9]. Nevertheless, only about half of the patients quickly achieves an effective platelet inhibition after loading dose of Prasugrel or Ticagrelor, especially in the context of STEMI [10].

Adjunctive periprocedural tirofiban administration has been suggested to abolish this residual platelet reactivity, offering protection from thrombotic complications in the early phases of PCI [11]. However, even GPIIbIIIa inhibitors may suffer from some interindividual variability [12]. Therefore, it might be argued that the use of pre-procedural dual antiplatelet therapy (DAPT) could offer potential advantages in optimizing platelet inhibition and reducing the risk of PMI in patients undergoing PCI, that was therefore the aim of the present study.

2. Methods

We included patients undergoing coronary angioplasty at Ospedale "Maggiore della Carità" from May 2010 to January 2013 for both elective indication or acute coronary syndrome (UA/NSTEMI). NSTEMI patients were defined by the presence of chest pain and cardiac biomarkers elevation > ULN (respectively 0,04 μg/l for Troponin I and 5,00 μg/l for CK-MB) undergoing elective coronary angiography after pharmacological stabilization, but not STEMI and unstable patients requiring urgent angioplasty. All patients were treated with ASA. In patients with a history of ASA allergy, a desensitization protocol was applied as previously described [13].

All patients received, according to guidelines [9], a bolus of an antiplatelet ADP antagonists (Clopidogrel 600 mg, prasugrel 60 mg or Ticagrelor 180 mg) according to clinical presentation, at the time of hospitalization or during angioplasty (in particular, elective patients were generally not pre-treated prior to PCI -if not already on DAPT for a previous PCI-, while ACS patients usually received a complete antiplatelet therapy at the moment of the first medical contact or at admission). All included patients received before starting the procedure intracoronary or intravenous tirofiban (25 μg/kg bolus followed or not by subsequent 0,1 μg/kg/min infusion according to the operator's discretion). Infusion was started immediately after bolus, lasting at least 4 h. No exclusion criteria were applied except patient's refusal or clinical contraindications to GpIIbIIIa inhibitors such as severe thrombocytopenia or history of major bleeding. Medical history and blood chemistry parameters were obtained for each patient.

Diabetes mellitus was defined for one of the following: 1) previous diagnosis, 2) specific treatment administration (oral or insulin), 3) fasting glycemia > 126 mg/dL in at least 2 repeated determinations or random values > 200 mg/dl 4) HbA1C > 6.5%. Hypertension was defined as systolic pressure > 140 mm Hg and/or diastolic pressure was > 90 mm Hg or if the individual was taking antihypertensive medications.

The study was approved by our local Ethical Committee. Patients were clinically followed up to hospital discharge.

2.1. Biochemical measurements

Blood samples were drawn at admission in patients undergoing elective (following a fasting period of 12 h) or urgent coronary angiography. Glucose, creatinine, HbA1c and lipid profile were determined by standard methods. White blood cells count and formula was measured in a blood sample collected in tripotassium EDTA (7.2 mg) tubes. These blood samples were analyzed within 2 h of venipuncture by automatic blood counter (A Sysmex XE-2100) used for whole blood analysis. Cardiac biomarkers (Troponin I and CK MB) were measured at baseline, before coronary revascularization, and later 6, 12, 24 and 48 h after PCI.

2.2. Coronary angiography and PCI

Coronary angiography was routinely performed by the Judkins technique using 6-French catheters. Quantitative coronary angiography was performed by experienced interventional cardiologists by an automatic edge-detection systems (Siemens Acom Quantcor QCA, Erlangen, Germany) [14]. Coronary angioplasty was performed with standard techniques. Use of stents, type of stents and stent implantation techniques, as much as the use of directional or rotational atherectomy, IVUS, glycoprotein IIb-IIIa inhibitors, was left at the discretion of the operators.

2.3. Study endpoints

Primary study endpoint was periprocedural MI defined as CK-MB mass release ≥3 times the upper limit normal (ULN) or an increase by 50% of baseline if already elevated, but stable or falling, at the time of the procedure. Secondary study endpoint was periprocedural increase in troponin $I \geq 3 \times$ ULN or an increase by 50% of the pre-procedural value, if > 0.04 ng/ml.

2.4. Platelet aggregation tests

Platelet function was assessed by whole blood impedance aggregometry (Multiplate®- multiple platelet function analyser; Roche Diagnostics AG) at baseline and after 10 min, 1 h and 4 h from GPI bolus administration. A blood sample was obtained from every patient and stored in Vacutainer standard lithium heparin tubes and analyzed within 1 h from collection. For each sample, different agonists were used as activating stimulito evaluate platelet function: arachidonic acid, collagen, ADP and prostaglandin E1 and thrombin receptor activating peptide (TRAP-6). The results were considered as AUC (area under the curve) [15].

2.5. Statistical analysis

Statistical analysis was performed using SPSS 22.0 statistical package. Continuous data are expressed as mean ± SD and categorical data as percentage. Analysis of variance and the chi-square test (or Fisher-test) were used for continuous and categorical variables, respectively. Pearson's correction was applied in case of $n < 5$ in one of the study subgroups. Multiple logistic regression analysis was performed to evaluate the relationship between pre-procedural DAPT and periprocedural myocardial necrosis or infarction, after correction for clinical and angiographic significant differences, that were entered in the model in block.

3. Results

A total of 168 patients were included, 77 (45.8%) of whom were on