International Journal of Cardiology 168 (2013) 427–435

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Influence of platelet reactivity and inflammation on peri-procedural myonecrosis in East Asian patients undergoing elective percutaneous coronary intervention

Young-Hoon Jeong [a,b,*], Udaya S. Tantry [b], Ji Hyun Min [a], Yongwhi Park [a], Eliano Pio Navarese [c], Jin-Sin Koh [a], Jeong Rang Park [a], Seok-Jae Hwang [a], Eun-Ha Kho [d], Kevin P. Bliden [b], Choong Hwan Kwak [a], Jin-Yong Hwang [a], Sunjoo Kim [d], Paul A. Gurbel [b]

[a] Division of Cardiology, Department of Internal Medicine, Gyeongsang National University Hospital, Jinju, Republic of Korea
[b] Sinai Center for Thrombosis Research, Baltimore, MD, USA
[c] Department of Cardiology and Internal Medicine, Ludwik Rydygier Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland
[d] Department of Laboratory Medicine, Gyeongsang National University Hospital, Jinju, Republic of Korea

ARTICLE INFO

Article history:
Received 11 July 2012
Received in revised form 3 September 2012
Accepted 22 September 2012
Available online 12 October 2012

Keywords:
Percutaneous coronary intervention
Myonecrosis
Platelet
Inflammation
Cholesterol

ABSTRACT

Background and objectives: The contribution of multiple risk factors to peri-procedural myocardial infarction (PMI) in East Asians remains controversial. To assess the influence of clinical or laboratory covariates on PMI in these patients.

Methods: Stable patients (n = 341) undergoing elective percutaneous coronary intervention (PCI) were enrolled. Platelet reactivity was measured by conventional aggregometry and VerifyNow. Inflammation markers and lipid profile were determined by standard methods. PMI was defined according to Universal definition (troponin I or CK-MB ≥ 3 times the 99th percentile of the upper reference limit).

Results: PMI (defined by troponin I and CK-MB) occurred in 47 (13.8%) and 30 (8.8%) patients, respectively. There was no significant difference in ADP-induced platelet reactivity between patients with vs. without PMI. Patients with PMI (troponin I) had higher levels of 6 μg/mL collagen-induced platelet aggregation (PA) and VerifyNow 'BASE' compared with those without PMI. The combination of '6 μg/mL collagen-induced PA > 40%' + 'BASE > 318' (odds ratio, 14.08; 95% confidence intervals, 1.68 to 111.11; p = 0.015) or 'WBC > 6550/mm^3' + 'C-reactive protein > 2.3 mg/L' (odds ratio, 7.75; 95% confidence intervals, 2.49 to 24.39; p < 0.001) was associated with an increased risk of PMI (troponin I). The greatest likelihood ratio was observed when cholesterol, inflammation marker and platelet function were combined together.

Conclusion: This is the first study to demonstrate that heightened platelet responsiveness to collagen and thrombin may be a risk factor for myonecrosis in patients undergoing elective PCI. The utility of the combining measures of platelet function, inflammation and cholesterol to enhance risk stratification and thus facilitate personalized therapy deserves further study.

1. Introduction

Advances in technology and adjunctive drug therapy have made percutaneous coronary intervention (PCI) a standard revascularization strategy in symptomatic patients with coronary artery disease (CAD) [1]. However, up to one-third of patients undergoing elective PCI suffer peri-procedural myocardial injury or infarction (PMI) despite the administration of dual antiplatelet therapy [2–4] and the latter events may be associated with increased mortality in selected patients [5,6]. The proximal type of PMI results from mechanical complications such as side branch occlusion, whereas the distal type of PMI accounts for ~75% of all PMIs and is mostly due to distal embolization [2].

It has been reported that the adenosine diphosphate (ADP)–$P2Y_{12}$ receptor interaction plays an important role in the stabilization of thrombus formation and ischemic event occurrence during and after PCI [7]. Multiple studies have indicated that high on-treatment platelet reactivity (HPR) to ADP is a major risk factor for short- and long-term ischemic events occurrence [7]. Compared with Caucasians, East Asians have a higher prevalence of the cytochrome P450 (*CYP*) *2C19 loss-of-function* allele carriage (~65%) and greater platelet reactivity during clopidogrel treatment [8–10]. Nevertheless, the association between ADP-induced platelet reactivity and overall ischemic event occurrence appears weaker in East Asians compared with Caucasian [7–10].

Following plaque rupture during PCI, atheromatous debri, tissue factor, and subendothelial matrix proteins (e.g. collagen, von Willebrand

* Corresponding author at: Department of Internal Medicine, Gyeongsang National University Hospital 79 Gangnam-ro, Jinju, Gyeongsangnam-do, 660-702, Republic of Korea. Tel.: +82 55 750 8873; fax: +82 55 750 8150.
E-mail address: goodoctor@naver.com (Y.-H. Jeong).

0167-5273/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijcard.2012.09.132

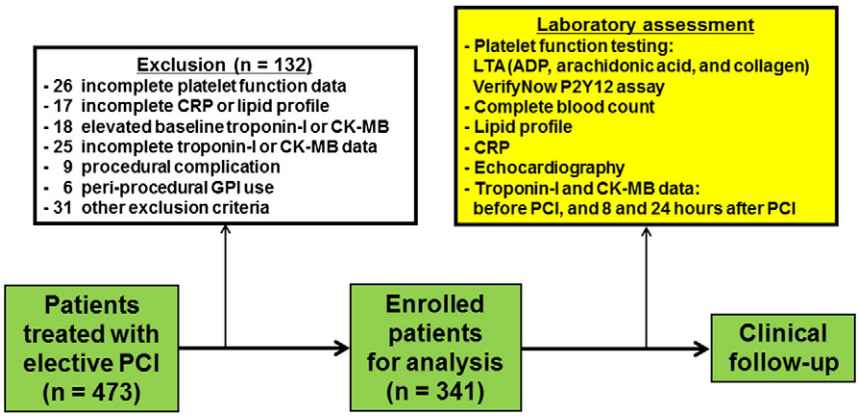

Fig. 1. Flow diagram of the study. CRP indicates C-reactive protein; CK-MB, creatine phosphokinase MB; GPI, glycoprotein IIb/IIIa inhibitor; LTA, light transmittance aggregometry; ADP, adenosine diphosphate; PCI, percutaneous coronary intervention.

factor) are exposed to blood [11]. Under this specific condition, platelets can be activated through various pathways including ADP, thrombin, thromboxane and collagen. However, the relative contribution of each agonist to thrombus generation has not been determined. The relation of pre-procedural ADP-stimulated platelet reactivity to myonecrosis in patients undergoing PCI has been demonstrated in some [12–16], but not all studies [17–20]. Moreover, the relation of platelet reactivity to PMI in East Asians undergoing elective PCI remains controversial [19,20].

Moreover, hemostasis is a complex interplay between blood cells, soluble plasma proteins, and the vessel walls. Therefore, besides platelet activation, inflammation and lipid particle also may participate in thrombus formation after plaque rupture and subsequently influence the occurrence of PMI [2,11,21]. The role of inflammation in PMI occurrence has been demonstrated in Caucasians [3,22,23], but similar findings are not available in East Asians. In addition, there are no data to support the combined influences of these risk factors on peri-procedural myonecrosis.

It remains unclear which myocardial biomarker, troponin (Tn) or creatine phosphokinase-MB (CK-MB) optimally reflects PCI-related myocardial necrosis [24]. Although Tn-I and Tn-T are the preferred biomarkers for myocardial injury due to absolute myocardial tissue specificity, their thresholds may overestimate the risk of peri-procedural necrosis [4,25,26].

We thus performed a prospective, nested case–control study to evaluate the contribution of multiple risk factors (including platelet reactivity, inflammation and lipid particle) to the occurrence of PMI as assessed by Tn-I and CK-MB among East Asians with stable CAD undergoing elective PCI.

2. Methods

2.1. Patient selection

Between July 2009 and December 2010, stable patients with negative myocardial biomarkers (Tn-I and CK-MB) undergoing elective PCI were recruited at the Department of Cardiology of the Gyeongsang National University Hospital (Jinju, Korea). The institutional Ethics Committee approved the study protocol, and the patients provided written informed consent. Patients were eligible for enrollment if they were ≥18 years of age, ingested aspirin (loading dose, 300 mg) and received optimal clopidogrel treatment defined as a maintenance dose of 75 mg/day for ≥5 days or a loading dose of 300 or 600 mg ≥12 h before PCI. After the procedure, patients received aspirin (100 to 200 mg/day) indefinitely and clopidogrel (75 mg/day) for at least 12 months.

Major exclusion criteria were baseline elevated myocardial biomarkers or acute coronary syndrome (ACS), procedural failure, hemodynamic instability, active bleeding or history of bleeding diatheses, oral anticoagulation therapy with warfarin, use of peri-procedural glycoprotein IIb/IIIa inhibitors, contraindication to antiplatelet therapy, left ventricular ejection fraction <30%, leukocyte count <3000/mm^3, platelet count <100,000/mm^3, aspartate aminotransferase or alanine aminotransferase levels ≥3 times upper normal, stroke within 3 months, and non-cardiac disease with a life expectancy <1 year.

Before PCI, all patients received a 70 IU/kg intravenous bolus of unfractionated heparin. Stent type was chosen by the operator after coronary angiography, and all interventions were conducted according to the current standard guidelines [1]. Procedural success was defined as a reduction in % diameter stenosis to below 30% in the presence of Thrombolysis In Myocardial Infarction (TIMI) flow grade 3 in the main vessel and all side branches ≥2 mm in diameter without procedural complication [1].

2.2. Biomarkers

Fasting blood samples were obtained before the procedure to determine baseline complete blood count, and lipid profile; high sensitivity C-reactive protein (hs-CRP) was determined using a UniCel® DxC 800 Synchron® Clinical System (Beckman Coulter, Inc., Brea, CA). Tn-I (normal range: ~0.04 ng/mL) and CK-MB (normal range: ~6.3 ng/mL) were determined using the Access® Immunoassay System (Beckman Coulter, Inc., Brea, CA) before PCI and 8 and 24 h after PCI. PMI was defined as a post-procedural increase in cardiac biomarker ≥3 times the 99th percentile of the upper reference limit according to Universal definition [24].

2.3. Platelet function testing

Blood samples for platelet reactivity were obtained immediately after insertion of the arterial sheath using the double-syringe technique. The first 2 to 4 mL of blood was discarded to avoid spontaneous platelet activation. The protocol and validation data for light transmittance aggregometry (LTA) and the VerifyNow P2Y12 assay (Accumetrics, San Diego, CA) were described in detail elsewhere [27]. For LTA, blood samples were drawn into Vacutainer tubes containing 0.5 mL of sodium citrate 3.2% (Becton-Dickinson, San Jose, CA). Platelet-rich plasma was obtained after centrifuging blood samples at 120 *g* for 10 min. The remaining blood was further centrifuged at 1200 *g* for 10 min to recover platelet-poor plasma. Platelet-rich plasma was adjusted to a platelet count of 250,000/mm^3 by adding platelet-poor plasma if needed. Maximal platelet aggregation (PA) was evaluated for 10 min at 37 °C using an AggRAM™ aggregometer (Helena Laboratories Corp., Beaumont, TX) after the addition of ADP (5 and 20 μM), arachidonic acid (0.5 mg/mL) and collagen (6 μg/mL).

The VerifyNow P2Y12 assay is a whole-blood, point-of-care turbidimetric assay that measures the responsiveness to $P2Y_{12}$ antagonists [28]. Blood samples were collected in 3.2% citrate Vacuette tubes (Greiner Bio-One Vacuette® North America Inc., Monroe, NC). The cartridge consists of 2 channels; one channel contains fibrinogen-coated polystyrene beads, 20 μM ADP and 22 nM prostaglandin E_1; its optical signal is reported as 'P2Y12 reaction units' (PRU). The second channel contains fibrinogen-coated polystyrene beads, 3.4 μM iso-thrombin receptor activating peptide [iso-TRAP: protease-activated receptor (PAR)-1 agonist] and PAR-4 activating peptide [28], and the readings are defined as 'BASE'. The instrument reports 'percent inhibition' to indicate the extent of $P2Y_{12}$ blockade by $P2Y_{12}$ inhibitors: percent inhibition = [(BASE − PRU)/BASE] × 100 (%).

2.4. End points

The primary end point was 20 μM ADP-induced PA. Secondary end points were 5 μM ADP-, arachidonic acid- and collagen-induced PAs, and values of the VerifyNow P2Y12 assay. We also evaluated the relationship of PMI to clinical, laboratory and procedural characteristics.