

Antiplatelet Treatment Guided by Platelet Function Testing After Successful Percutaneous Coronary Intervention

ALFONSINA CANDIELLO¹, FERNANDO CURA^{MTSAC, 1}, MARCELO TRIVI^{MTSAC, 4}, LUCIO T. PADILLA¹, MARIANO ALBERTAL³, GERARDO NAU¹, MARÍA ESTHER ARIS CANCELA², SEBASTIÁN PERALTA¹, FABRICIO TORRENT¹, JORGE A. BELARDI^{MTSAC, 1}

Received: 02/07/2012

Accepted: 04/12/2012

Address for reprints:

Dra. Alfonsina Candiello
Instituto Cardiovascular de Buenos Aires
Servicio de Cardiología
Intervencionista y Terapéuticas Endovasculares
Blanco Encalada 1543
(1428) CABA
Phonenumber +54 (011) 4787-7570
Fax number +54 (011) 4787-7571
e-mail:
alfonsinacandiello@gmail.com

ABSTRACT

Background

Dual antiplatelet treatment with aspirin and clopidogrel is an essential therapy to prevent ischemic events in patients undergoing percutaneous coronary intervention (PCI). However, there is a significant interindividual variability in response to clopidogrel treatment, which is responsible for failure of its therapeutic effect with high residual platelet reactivity (HRPR). Prasugrel could reduce this prothrombotic state.

Objectives

To evaluate: 1) the antiaggregant response in clopidogrel or prasugrel pretreated patients undergoing successful PCI, and 2) the response to prasugrel loading in patients with HRPR on clopidogrel therapy.

Methods

Eighty three patients without high hemorrhagic risk were prospectively included in the study. They underwent successful PCI under dual antiplatelet treatment: aspirin plus clopidogrel (600 mg loading dose or 75 mg maintenance dose for more than 7 days; n=42) or prasugrel (60 mg loading dose or 10 mg maintenance dose for more than 7 days; n=41). The selection of thienopyridine was left at the discretion of the treating physician. Patients with high hemorrhagic risk were excluded. Platelet function was tested 12-24 hours after PCI with the VerifyNowTMP2Y12 Assay. HRPR was defined as P2Y12-reaction units (PRU) ≥ 230 . In case of HRPR, patients received a loading dose of 60 mg prasugrel and platelet function was reassessed 2 hours later.

Results

Baseline characteristics did not differ in patients who initially received clopidogrel or prasugrel. At 12-24 hours post PCI, patients treated with prasugrel presented significantly less PRU compared with the clopidogrel cohort (median 49 (9-78) vs. 160 (82-224), $p < 0.001$). HRPR was observed in 24% of the patients in the clopidogrel group and in no patients in the prasugrel cohort ($p < 0.001$). All patients with HRPR on clopidogrel therapy corrected this value after the prasugrel loading dose.

Conclusions

After successful PCI, prasugrel treatment achieved greater platelet aggregation inhibition (PAI) compared to clopidogrel. Moreover, in patients with HRPR on clopidogrel therapy, optimal PAI was obtained by additional prasugrel administration.

REV ARGENT CARDIOL 2012;80. <http://dx.doi.org/10.7775/rac.v80.i5.870>

Key words > Balloon Coronary Angioplasty- Stents - Platelet Aggregation Inhibitors

Abbreviations >

ADP	Adenosine diphosphate	AMI	Acute myocardial infarction
PCI	Percutaneous coronary intervention	PAI	Platelet aggregation inhibition
Hb	Hemoglobin	ACS	Acute coronary syndrome
HRPR	High residual platelet reactivity	PRU	P2Y12 reaction unit

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Instituto Cardiovascular de Buenos Aires (ICBA)

^{MTSAC} Full Member of the Argentine Society of Cardiology

¹Department of Interventional Cardiology and Endovascular Therapeutics

²Department of Hematology

³Research Department

⁴Department of Clinical Cardiology

BACKGROUND

Platelet activation and aggregation play a key role in the development of ischemic events during and after acute coronary syndromes (ACS) and percutaneous coronary interventions (PCI). Dual antiplatelet therapy with aspirin and clopidogrel constitutes an essential treatment to prevent thrombotic events in these patients. (1-3)

However, there is a significant interindividual variability in the pharmacodynamic response to clopidogrel, which is responsible for the development of resistance or high residual platelet reactivity (HRPR). (4-5) Several studies have demonstrated the impact of HRPR, measured with different laboratory tests, in the development of thrombotic complications, as acute myocardial infarction (AMI) and intrastent thrombosis during follow-up (6-7).

Thus, the bioavailability of a faster and stronger thienopyridine as prasugrel not only allows to predict the level of platelet aggregation inhibition (PAI) but also to reduce HRPR rate, thus decreasing the incidence of ischemic events compared to clopidogrel (8)

The Verify Now™ (Accumetrics Inc., San Diego, California) system is a novel method to estimate platelet P2Y₁₂ receptor thienopyridine-mediated inhibition. Several studies have suggested that the degree of PAI evaluated by the Verify Now™ system has an independent prognostic value. (9) Beyond the information provided by the literature, there are no publications in our environment evaluating the level of platelet aggregation with this method after a successful PCI.

The goals of the present study were to evaluate: 1) the antiaggregant response measured by the Verify Now™ system in clopidogrel or prasugrel pretreated patients undergoing successful PCI and, 2) the response to prasugrel loading in patients with HRPR on clopidogrel therapy.

METHODS

Study population

Consecutive patients undergoing successful PCI with stent implantation were prospectively included in an open-label, observational, comparative study. An informed consent form was signed by all the participants and approved by our Ethics Committee.

All patients received aspirin 325 mg as loading dose plus a thienopyridine before PCI: clopidogrel (600 mg loading dose or 75 mg daily maintenance dose for more than 7 days; n = 42) or prasugrel (60 mg loading dose or 10 mg daily maintenance dose for more than 7 days, n = 41), and continued with aspirin 100 mg daily indefinitely. The selection of thienopyridine was left at the discretion of the treating physician. All patients with high risk of bleeding (>75 years, weight <60 kg, history of stroke, platelet count <100,000/mm³, history of bleeding disorders and use of glycoprotein IIb/IIIa inhibitors) were excluded.

Although the safety evaluation of both drugs was not the primary objective of this study, the TIMI definition of major bleeding (any intracranial hemorrhage or any clinically overt bleeding, including bleeding evident on imaging

studies, associated with a decrease in hemoglobin (Hb) \geq 5 g/dl) and minor bleeding (any clinically overt bleeding, including bleeding evident on imaging studies, associated with a decrease in Hb between 3 - 5 g/dl) was used.

Evaluation of platelet function

Blood samples (2 ml) were obtained between 12 and 24 h after PCI and collected in tubes containing 3.2% sodium citrate (Vacuette™, Greiner Bio-One, Monroe, North Carolina) to analyze platelet function using the Verify Now™ system (Accumetrics Inc., San Diego, California) 15 to 60 minutes after sample withdrawal. Briefly, the Verify Now™ assay is based on the interaction between platelet receptors and fibrinogen-coated beads that induce agglutination. Light absorbance of the sample is measured as a function of time and the rate of agglutination is quantified as P2Y₁₂ reaction units (PRUs). The correlation between the results obtained with this system and those obtained with optical platelet aggregometry is excellent.

Specific P2Y₁₂ kits are used to determine the effect of clopidogrel and prasugrel. Platelet reactivity unrelated to the effect of thienopyridines (baseline reactivity) is measured with the first channel; the platelet activity remaining after inhibition of the clopidogrel or prasugrel-mediated P2Y₁₂ receptor is then measured with the second channel (values expressed in PRUs).

HRPR (lack of adequate antiaggregation) was defined as PRU \geq 230. Patients with HRPR received 60 mg of prasugrel and the platelet aggregation test was repeated 2 h later.

Statistical analysis

Continuous variables with normal and non Gaussian distribution were expressed as mean and standard deviation, or median and interquartile range, respectively. Comparison between two groups was performed using Student's t test or the Wilcoxon test, according to parametric or non-parametric distributions, respectively. Medians were compared using the Kruskal Wallis test. Categorical variables were expressed as percentages and were compared using the chi square test. The Wilcoxon test for paired samples was used to evaluate PRU in patients with HRPR before and after the administration of the loading dose of prasugrel. A p value < 0.05 was considered statistically significant.

RESULTS

Eighty-three consecutive patients undergoing successful PCI were included in the study from March to May 2001. Mean age was 60 \pm 8 years, 94% were men and 20.4% had diabetes. Forty two patients were pretreated with clopidogrel and 41 patients with prasugrel.

The baseline characteristics were similar in both groups, though there was a trend towards a greater proportion of diabetics and patients with ACS in the prasugrel group (Table 1).

Twelve to 24 h after PCI, patients treated with prasugrel presented significantly lower PRU values compared to those treated with clopidogrel [median 49 (9-78) vs. 160 (82-224) respectively, p < 0.001; Figure 1]. None of the patients in the prasugrel group presented HRPR compared to 24% (n = 10) of the patients in the clopidogrel group (p < 0.001). In the 10 patients with HRPR on clopidogrel therapy, median PRU was 279 (262-322), with a significant reduction

to 49 after the administration of 60 mg of prasugrel (7-104), $p < 0.001$ (Figure 2). Thus, the level of achieved after correcting with prasugrel was similar to the one initially obtained in patients treated with prasugrel (49 (7-104) in the initial prasugrel group vs. 49 (9-78) in the prasugrel group in clopidogrel-resistant patients, $p = ns$).

No major bleeding events were reported in any of both groups. Two patients with HRPR on clopidogrel therapy presented hematoma at the puncture site (radial artery in one patient and femoral artery in the other).

DISCUSSION

Several studies have confirmed the role of dual antiplatelet therapy with aspirin and clopidogrel in reducing the incidence of short and long-term ischemic events in patients with ACS undergoing PCI. (1, 2)

Dual antiplatelet treatment should achieve a strong inhibition of platelet aggregation to be effective.

The degree of platelet inhibition by clopidogrel varies from one patient to another with a bell-shaped normal distribution, and is time and dose-dependent.

HRPR during treatment with clopidogrel has been evaluated with different methods and reported to be between 4 and 68%. (10) The rate of HRPR previously reported with the VerifyNow™ system 24 h after 300 mg clopidogrel loading dose is about 30% and is lower after one month treatment or with 600 mg loading dose. (11)

The present study shows that 24% of patients treated with clopidogrel presented HRPR or resistance to treatment after PCI, a rate similar to the one previously reported in the literature. This is mainly due to the fact that clopidogrel is a prodrug that needs to be activated in the liver to an active metabolite in a two-step, cytochrome P450-dependent process. Approximately 85% of absorbed clopidogrel is hydrolyzed by esterases into an inactive form, and only 15% is converted into an active metabolite that inhibits ADP-dependent platelet aggregation.

Multiple lines of evidence strongly suggest that insufficient active metabolite generation is the

primary explanation for clopidogrel interindividual variability. Among other reasons, this is due to the functional variability in P450 isoenzyme activity which is influenced by interaction with drugs and by polymorphism of genes that encode enzymes of this enzymatic system. (11)

In our study, HRPR on clopidogrel therapy (24%) was corrected in all cases with prasugrel without increasing bleeding rates.

Unlike clopidogrel, prasugrel, a third generation thienopyridine is also a prodrug that is rapidly hydrolyzed to its active metabolite by carboxylesterases located mainly in the intestine. This intermediate metabolite undergoes subsequent activation in the liver by a single cytochrome P450-dependent step which explains the greater bioavailability and makes the antiaggregant effect more efficient. Prasugrel has a more rapid onset of action, with lower interindividual variability and greater PAI induced by ADP.

Several studies have demonstrated an association between HRPR on clopidogrel therapy and the development of future ischemic events. Most of these studies have been based on light transmission aggregometry or flow cytometry. As these techniques are complex and require training, they result expensive and impractical. The evaluation of PAI by the VerifyNow™ system is a novel, rapid and simple method that would allow treatment guided by the degree of PAI.

However, there is no agreement about which method is the best to quantify platelet reactivity or which cutoff point defines the presence of HRPR. We used a value of ≥ 230 PRUs measured by the VerifyNow™ system to define HRPR, a value that according to the meta-analysis by Brar et al. was associated with greater mortality, AMI and stent thrombosis compared with patients without HRPR. (7)

Currently, no clinical studies have demonstrated that personalized antiplatelet treatment guided by platelet function tests improves the outcome. Yet, it is an attractive option, especially in patients undergoing complex and high-risk PCI.

Table 1. Baseline characteristics of the population by treatment group

	Clopidogrel (n = 42)	Prasugrel (n = 41)	p
Age (years \pm SD)	60 \pm 9.8	59 \pm 8.5	0.19
Male gender, %	93	93	1
Hypertension, %	78	88	0.25
Diabetes Mellitus, %	12	29	0.06
Dyslipidemia, %	83	85	0.77
Previous PCI, %	39	34	0.82
Previous CABGS, %	10	12	0.73
CLINICAL PICTURE			
Stable chronic angina, %	40	29	0.35
Unstable angina, %	45	52	0.51
Non-STEMI, %	5	7	0.67
STEMI, %	10	12	0.73

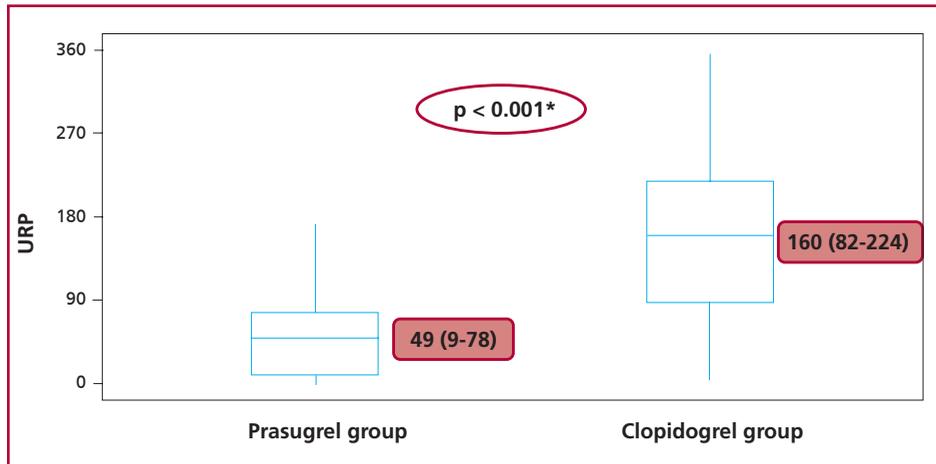


Fig. 1. Median (25-75%) PRU by treatment group. * Kruskal-Wallis test.

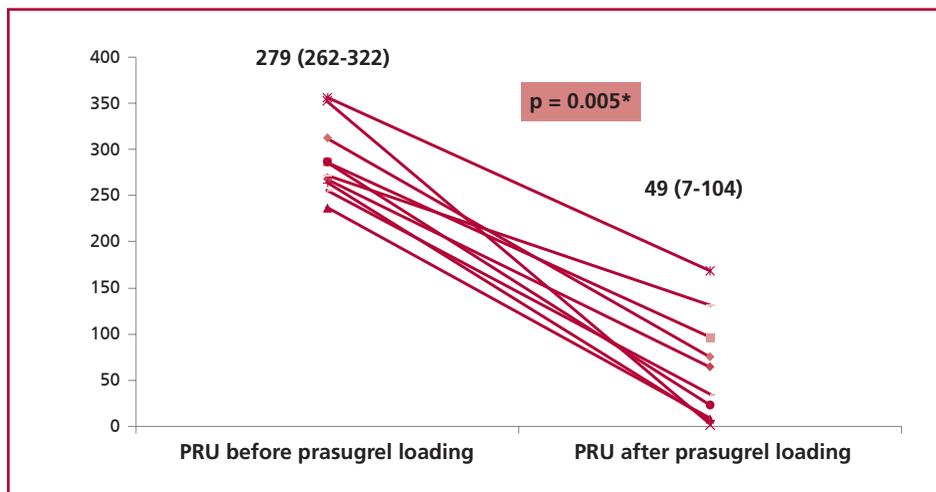


Fig. 2. Response to prasugrel in patients with HRPR on clopidogrel therapy. Median PRU at baseline and after prasugrel loading dose in patients with HRPR on clopidogrel therapy (n = 10). * Wilcoxon test.

The GRAVITAS (Gauging Responsiveness With a VerifyNow Assay Impact on Thrombosis and Safety) study reported that after 600 mg prasugrel loading dose, the increase in the maintenance dose to 150 mg daily during 6 months compared with the standard dose of 75 mg daily in patients with HRPR defined by $PRU \geq 230$, provided a variable and modest pharmacodynamic effect without reducing the incidence of death from cardiovascular causes, AMI, or stent thrombosis after PCI, or increasing bleeding events. (12)

On the other hand, the TRIGGER-PCI (Testing Platelet Reactivity in Patients Undergoing Elective stent Placement on Clopidogrel to Guide Alternative Treatment With Prasugrel) trial that compared prasugrel 60 mg followed by 10 mg daily vs. clopidogrel 75 mg in patients with HRPR on clopidogrel therapy (defined by $PRU \geq 208$) after elective PCI with drug-eluting stents, was prematurely terminated due to the relatively few events in both arms, but with greater bleeding events in the prasugrel arm.

Probably, in low-risk patients with chronic stable angina as those included in the TRIGGER-PCI trial who undergo PCI with drug-eluting stents,

the incidence of events is low independently of the response to antiplatelet therapy, and thus it might be difficult to reduce. In addition, a great number of patients would be needed in both arms to demonstrate significant differences.

Further studies are needed to evaluate the role of antiplatelet therapy adjusted for high-risk patients as those with ACS undergoing high-risk PCI.

Study limitations

Firstly, this non-randomized open-label study included a small sample of patients. Secondly, the target of this study was to evaluate the antiaggregant response to both antiplatelet drugs; therefore it was not designed to determine whether correction with prasugrel of HRPR on clopidogrel therapy might impact on the development of future thrombotic events.

CONCLUSIONS

In patients undergoing PCI, the administration of prasugrel achieves greater PAI compared to clopidogrel. Moreover, in patients with HRPR on clopidogrel therapy optimal platelet inhibition is accomplished by additional prasugrel administration.

RESUMEN

Tratamiento antiagregante guiado por pruebas de función plaquetaria en pacientes sometidos a angioplastia coronaria exitosa

Introducción

El tratamiento antiagregante dual con aspirina y clopidogrel constituye un tratamiento esencial para la prevención de eventos isquémicos en pacientes sometidos a angioplastia transluminal coronaria (ATC). Sin embargo, existe alta variabilidad interpaciente en la respuesta al clopidogrel, condicionando la falla en su efecto terapéutico, que se manifiesta como hiperreactividad plaquetaria residual (HPR). El prasugrel podría reducir este estado protrombótico.

Objetivos

1) Evaluar la respuesta antiagregante en pacientes sometidos a ATC exitosa pretratados con clopidogrel o prasugrel y 2) evaluar la respuesta a una carga de prasugrel en pacientes con HPR bajo tratamiento con clopidogrel.

Material y métodos

Se incluyeron en forma prospectiva y consecutiva 83 pacientes sin riesgo hemorrágico alto sometidos a ATC exitosa bajo tratamiento antiagregante dual: aspirina más clopidogrel (600 mg de carga o mantenimiento de 75 mg/día por más de 7 días; n=42) o prasugrel (60mg de carga o mantenimiento de 10 mg/día por más de 7 días, n=41). La selección de la tienopiridina quedó a cargo del médico tratante. La función plaquetaria se evaluó a las 12-24 horas pos-ATC con el método VerifyNow®. Se definió HPR a la presencia de ≥ 230 unidades de reactividad plaquetaria (URP). Los pacientes con HPR recibieron una dosis de carga de prasugrel de 60 mg y se repitió la evaluación de la función plaquetaria a las 2 horas.

Resultados

No hubo diferencias significativas en las características basales de ambos grupos. A las 12-24 horas pos-ATC, los pacientes tratados con prasugrel presentaron menos URP en comparación con el grupo clopidogrel [mediana 49 (9-78) vs. 160 (82-224); $p < 0,001$]. Se observó HPR en el 24% de los pacientes del grupo clopidogrel y cero en el grupo prasugrel ($p < 0,001$). Todos los pacientes con HPR bajo tratamiento con clopidogrel lograron corregirla luego de la carga de prasugrel.

Conclusiones

En pacientes sometidos a ATC exitosa, el tratamiento con prasugrel logró una mayor inhibición de la agregación plaquetaria (IAP) en comparación con la administración de clopidogrel. Por su parte, los pacientes con HPR bajo tratamiento con clopidogrel lograron alcanzar una IAP óptima con la administración adicional de prasugrel.

Palabras clave > Angioplastia coronaria con balón -Stents Antiagregantes de plaquetas

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