Rev Esp Cardiol. 2014;67(1):22–27

Original article

Effect of an Optimized Treatment With Insulin on Platelet Reactivity After Discharge in Patients With an Acute Coronary Syndrome and Hyperglycemia

David Vivas,[a,*] Juan C. García-Rubira,[a] Esther Bernardo,[a] Dominick J. Angiolillo,[a] Patricia Martín,[b] Alfonso Calle,[b] Iván Núñez-Gil,[a] Carlos Macaya,[a] and Antonio Fernández-Ortiz[a]

[a] *Instituto Cardiovascular, Hospital Clínico San Carlos, Madrid, Spain*
[b] *Servicio de Endocrinología, Hospital Clínico San Carlos, Madrid, Spain*

Article history:
Received 8 May 2013
Accepted 10 May 2013
Available online 3 October 2013

Keywords:
Platelets
Acute coronary syndrome
Diabetes mellitus

ABSTRACT

Introduction and objectives: Intensive glucose control with insulin in patients with an acute coronary syndrome reduces platelet reactivity during hospitalization, compared to conventional control. However, the effect of strict, long-term glucose control on platelet reactivity in these patients remains uncertain.
Methods: This is a prospective, randomized trial evaluating the effects of optimized glucose control (target glucose, 80-120 mg/dL) with insulin, compared with conventional control (target glucose, <180 mg/dL), on platelet reactivity after hospital discharge in patients with an acute coronary syndrome and hyperglycemia. The primary endpoint was assessment of platelet aggregation after stimulation with adenosine diphosphate 20 μM at 12-month follow-up.
Results: One hundred four patients were randomized to optimized management (n=53) or conventional management (n=51). There were no differences between groups in baseline characteristics or platelet function. After 12 months of follow-up, blood glucose levels were significantly lower in the optimized treatment group (104 vs 119 mg/dL; *P*<.001). However, platelet aggregation following adenosine diphosphate 20 μM stimulation showed no differences between the groups (54.2% [14.3%] vs 55.1% [18.3%] respectively; *P*=.81). There were no significant differences for other platelet function tests.
Conclusions: Long-term optimized glucose control with insulin in patients with an acute coronary syndrome did not result in a reduction in platelet reactivity compared to conventional control.

Efecto del tratamiento optimizado con insulina en la reactividad plaquetaria tras el alta de pacientes hiperglucémicos con síndrome coronario agudo

Palabras clave:
Plaquetas
Síndrome coronario agudo
Diabetes mellitus

RESUMEN

Introducción y objetivos: El control intensivo con insulina de la glucemia de pacientes con un síndrome coronario agudo reduce la reactividad plaquetaria durante la fase hospitalaria en comparación con un tratamiento convencional. Sin embargo, se desconoce el efecto en la reactividad plaquetaria con un control estricto de la glucemia a largo plazo.
Métodos: Ensayo prospectivo y aleatorizado que evaluó el efecto de un tratamiento optimizado para el control de la glucemia (objetivo, 80-120 mg/dl) con insulina comparado con un tratamiento convencional (objetivo, < 180 mg/dl) en la reactividad plaquetaria al alta hospitalaria de pacientes con un síndrome coronario agudo e hiperglucemia. El objetivo primario es la valoración de la agregación plaquetaria tras estímulo con adenosina difosfato 20 μM a los 12 meses de seguimiento.
Resultados: Se incluyó a 104 pacientes (53 al tratamiento optimizado y 51 al convencional). No se encontraron diferencias en las características basales de ambos grupos, incluida la función plaquetaria. A los 12 meses de seguimiento, las cifras de glucemia eran significativamente menores en el grupo de tratamiento optimizado (104 frente a 119 mg/dl; p < 0,001). Sin embargo, la agregación plaquetaria tras estímulo con adenosina difosfato 20 μM no mostró diferencias significativas entre los grupos (tratamiento optimizado frente a convencional, 54,2 ± 14,3% frente a 55,1 ± 18,3%; p = 0,81). Tampoco se objetivaron diferencias significativas con los otros tests de función plaquetaria evaluados.
Conclusiones: El control optimizado de la glucemia con insulina a largo plazo en pacientes que han sufrido un síndrome coronario agudo no reduce la reactividad plaquetaria en comparación con un tratamiento convencional.

SEE RELATED ARTICLE:
http://dx.doi.org/10.1016/j.rec.2013.08.011, Rev Esp Cardiol. 2014;67:3–5

* Corresponding author: Instituto Cardiovascular, Hospital Clínico San Carlos, Prof. Martín Lagos s/n, 28040 Madrid, Spain.
E-mail address: dvivas@secardiologia.es (D. Vivas).

1885-5857/$ – see front matter
http://dx.doi.org/10.1016/j.rec.2013.05.020

Abbreviations

ACS: acute coronary syndrome
ADP: adenosine diphosphate

INTRODUCTION

Patients with an acute coronary syndrome (ACS) and hyperglycemia have an increased risk of experiencing new cardiovascular events at both the long and short term.[1–4] Greater platelet reactivity has been documented in patients with hyperglycemia,[5] and it has been proposed that, among other factors, platelet activation could play a fundamental role in this clinical context.

Although it has not been established that intensive treatment to reduce glucose levels results in a decrease in cardiovascular events,[6–11] our group recently demonstrated that rigorous control with insulin in ACS patients with hyperglycemia decreases platelet reactivity during the hospitalization phase.[12] Furthermore, the poorer the patients' glucose control had been before the coronary event, the greater the reduction was seen to be.[13]

Outside the acute phase, studies that have evaluated protocols for strict glucose control at long term have yielded discordant clinical results.[14–19] For that reason, the current clinical practice guidelines recommend a less rigorous target for blood glucose control (HbA_{1c}<7%).[20] Patients with chronic ischemic heart disease and hyperglycemia also show increased platelet reactivity, which is associated with a poorer prognosis.[21] Nonetheless, the effect of strict glucose control on platelet reactivity is uncertain.

In this study, the impact on platelet reactivity of implementing an optimized protocol for glucose control with insulin is compared with that of a conventional protocol.

METHODS

Study Design

The CHIPS[12] (Management of Hyperglycaemia and Platelet Activity in Patients With Acute Coronary Syndrome) study is a randomized, single-center trial that evaluated the impact of allocation to an intensive protocol with intravenous insulin for blood glucose control on platelet reactivity in ACS patients with hyperglycemia. The details and results of the first randomization phase of this trial were recently published.[12,13]

For the present long-term study, at the time of hospital discharge patients were again randomized 1:1 to an optimized treatment protocol for glucose control (target glucose value, 80-120 mg/dL) or to conventional treatment (target glucose value, <180 mg/dL). The optimized management consisted of follow-up in the hospital diabetes mellitus unit by endocrinologists with expertise in diabetes mellitus. Patients in this group received ultra-slow insulin by protocol, together with rapid-acting insulin with meals. Conventional management consisted of follow-up by primary care physicians, who sent patients to a general endocrinologist or not, at their discretion. Glucose levels were measured with the capillary blood glucose test (Accu-Chek Sensor®; Roche, Mannheim, Germany).

As to the management of ACS, all participants received the treatment currently recommended in clinical practice guidelines, except when there were contraindications.[20,22,23] The study was carried out in accordance with the Declaration of Helsinki and was approved by the ethics committee of our hospital. All patients gave written consent for participation in the study.

The primary endpoint of the study was defined as the reduction in platelet aggregation following stimulation with 20 μM adenosine diphosphate (ADP), evaluated at 12 months after ACS. Secondary endpoints were the reductions in platelet function occurring with other parameters of aggregation and activation, and the incidence of cardiovascular events.

Platelet Function Analysis

For the study of platelet function, blood samples were collected by forearm venipuncture. A total blood volume of approximately 30 mL was extracted at baseline (at the time of hospital discharge and before randomization) and at 12 months after treatment. The first 3 mL of sample was discarded to avoid spontaneous platelet activation. All samples were analyzed within 1 h after collection by investigators blinded to the assigned intervention group.

Platelet Aggregation

Platelet aggregation was assessed by turbidimetric light transmission aggregometry using platelet-rich plasma[24] on a dual-channel instrument (IZASA, Chrono-Log, Model 490). Various platelet agonists were used as stimuli: ADP at 5 and 20 μM (primary endpoint of the study), collagen at 6 μg/mL, epinephrine at 20 μM, and thrombin receptor activating peptide at 25 μM. Platelet-rich plasma was obtained by centrifuging citrated blood at 800 rpm for 10 min and was kept at 37 °C for 20 min before use. Platelet-poor plasma was obtained by a second centrifugation of the remaining blood at 2500 rpm for 10 min. When platelet count in platelet-rich plasma was outside the desired range, it was adjusted to 250 000/μL by dilution with autologous plasma. Analysis of aggregation was performed by adjusting the aggregometer with platelet-rich plasma as the reference of 0% light transmission (0% aggregation) and platelet-poor plasma as the reference of 100% transmission and measuring the increase in light transmission through a platelet-rich plasma suspension during 5 min with constant shaking, then incubation at 37 °C in the presence of a platelet agonist.

Platelet Reactivity Index

Activation of platelet receptor $P2Y_{12}$ was analyzed using the platelet reactivity index, which was determined by evaluation of the intracellular platelet protein according to previously reported protocols.[25] Briefly, vasodilator-stimulated phosphoprotein phosphorylation was measured by flow cytometry (Coulter EPICS XL- MCL™ and System II™ software; Coulter, Miami, Florida, United States) using a monoclonal antibody-labeled commercial kit (Biocytex Inc.; Marseille, France). The platelet reactivity index was calculated after adding prostaglandin E_1 (PGE_1) and PGE_1+ADP, then measuring the mean fluorescence intensity of vasodilator-stimulated phosphoprotein phosphorylation. PGE_1 increases vasodilator-stimulated phosphoprotein phosphorylation through adenylate cyclase stimulation, while ADP binding to purinergic receptors leads to its inhibition. Thus, addition of ADP to PGE_1-stimulated platelets reduces the concentration of PGE_1-induced phosphorylated vasodilator-stimulated phosphoprotein. On this basis, elevation of the platelet reactivity index indicates upregulation of the activating mechanisms of $P2Y_{12}$ receptors.

P-selectin Expression and IIb/IIIa Glycoprotein Activation

Activated glycoprotein (GP) IIb/IIIa receptor expression on the platelet surface was evaluated using PAC-1 antibodies (conjugated PAC1-FITC, Becton Dickinson; Rutherford, New Jersey, United