Assessment of Platelet Function in Acute Ischemic Stroke Patients Previously Treated with Aspirin

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Background: Platelet inhibition measured by platelet function tests could be critical to understand the reasons for early recurrence and to guide therapeutic recommendations. We assess the platelet function during the acute phase of ischemic stroke in patients pretreated with aspirin who continue their treatment with aspirin only, are started on clopidogrel only, or add clopidogrel to aspirin. *Methods:* Sixty-four patients were taking aspirin before the stroke. Depending on the administered antiplatelet, 3 groups were defined: ASA: patients who continued on aspirin orally or intravenous acetylsalicylate of lysine, n = 30; CLO: patients who discontinued aspirin and were started on clopidogrel, n = 16; and ASA + CLO: patients who were prescribed both aspirin and clopidogrel, n = 10. Collagen-induced thromboxane A_2 (TXA_2) synthesis, ADP (adenosine diphosphate)-induced aggregation, and occlusion time (PF-100) were measured. *Results:* CLO group only had a marked elevation of TXA_2 (17.44 ± 15.62 ng/mL, $P = .000$) and a shortening of the platelet function analyzer (PFA)-100 closure time (157.13 ± 88 seconds, $P = .047$) compared with the other 2 groups (ASA: TXA_2, .62 ± 1.59 ng/mL; ASA + CLO: TXA_2 1.79 ± 4.59 ng/mL). They achieved a small (13%) but significant reduction of ADP-induced aggregation (87.00 ± 23.06 mm, $P = .008$) compared with the ASA group (102.82 ± 22.38 seconds). *Conclusions:* Stopping aspirin intake within the first 72 hours of the acute stroke drastically increases TXA_2 synthesis. During the same time window, the freshly prescribed clopidogrel manages to reduce the ADP-induced aggregation only slightly (13%). This study offers analytic proof that the common practice of replacing aspirin with clopidogrel does not leave stroke patients fully protected during the first days after an ischemic stroke. Possible solutions could be to preserve aspirin during a few days or to use loading doses of clopidogrel at hospital admission. **Key Words:** Antiplatelet—ischemic stroke—aspirin—clopidogrel.

Introduction

Platelet inhibition is important not only in the chronic phase; it must be ensured in the acute phase of brain ischemia as well, to prevent early vascular recurrence, because the early vascular risk after a stroke/transient ischemic attack (TIA) is not small.[1] Studies on platelet function during the acute phase of stroke are scarce compared with studies on myocardial infarction, although their number is slowly growing.[2-6]

Altered platelet aggregation has been linked to vascular recurrence[6-8] and stroke severity,[9,10] and some authors have advocated for the use of quantitative assessments of platelet function for early detection of platelet resistance.[2,11]

No clinical trials have directly addressed the topic of acute phase therapy for patients who experience brain ischemia while taking aspirin. Aspirin remains the most evaluated antiplatelet agent in the acute phase of ischemic stroke, producing a modest but clear benefit,[12] so that it

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remains the only clinically proven antiplatelet in the setting of acute stroke.[13] Although the administration of clopidogrel alone or in combination with aspirin is not recommended for treatment of acute ischemic stroke,[13] many clinicians choose to substitute aspirin for an alternative antiplatelet drug.[14] The measurement of platelet inhibition through platelet functional tests could be critical to understand the reasons for early recurrence and to guide therapeutic recommendations.

We studied a series of patients who presented with ischemic stroke/TIA while on aspirin, examining their subsequent antiplatelet medication and assessing their level of platelet inhibition.

Methods

An observational study was undertaken: 269 patients with TIA or ischemic stroke consecutively enrolled in platelet function studies during the acute phase of brain ischemia at the University Hospital la Fe between March 2008 and March 2010 were assessed.

Sixty-four patients (24%) who were taking 100-300 mg of aspirin daily before their ischemic event were included in this study. Because there were no clear protocols on further antiplatelet treatment in those cases, antiaggregation on admission was always left at the discretion of the neurologist.

We defined 3 groups (all patients were on previous aspirin treatment): ASA: patients who continued on 100-300 mg of aspirin daily (alternatively in those incapable of oral intake, 450 mg of intravenous acetylsalicylate of lysine daily); CLO: patients who discontinued aspirin on admission and were started on clopidogrel 75 mg daily; and ASA + CLO: patients who were prescribed both aspirin and clopidogrel in the previously mentioned doses.

Out of the antiaggregation drug of choice, all patients were treated according to the universally accepted stroke guidelines.[13]

For the study of platelet function, citrate-anticoagulated venous blood was collected into siliconized glass tubes (Vacutainer; Becton Dickinson, Madrid, Spain) within the first 72 hours after onset of cerebral symptoms, after an overnight fast and before the daily intake of antiplatelet drug. Blood collection took place within 4 and less than 24 hours after the last dose of antiplatelet agent.

Antithrombotic protection provided by aspirin was assessed by means of collagen-(1 μg/mL)-induced thromboxane A_2 (TXA_2) levels and arachidonic acid–induced aggregation (arachidonic acid, 1 mM), measured as previously described.[10,15,16] Antithrombotic protection provided by aspirin was assessed by means of collagen-induced TXA_2 levels, measured as previously described.[15,16] Antithrombotic protection provided by clopidogrel was gaged by studying ADP (adenosine diphosphate)-induced aggregation (ADP, 3 μM) evaluated in platelet-rich plasma by optical aggregometry (Chrono-Log 540; Chrono-Log, Havertown, PA), and the occlusion time was assessed in the PF-100 system (Dade PFA collagen/Epi test cartridge; Siemens Healthcare, Madrid, Spain).

The study protocol was approved by the Hospital la Fe Ethics Committee. All patients or their proxy gave their written informed consent.

Their clinical data were included in the Stroke Data Bank of the Spanish Neurological Society, BADISEN,[17] recording demographic data, risk factors, previous medication, initial modified Rankin Score, time of stroke, wake-up stroke, Canadian scale and National Institutes of Health scale at entry and at discharge, and modified Rankin Score at discharge. Patients were also classified using Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.

Statistical analysis: categorical variables are presented as percentages and compared using chi-square tests. Continuous variables are presented as mean ± standard deviation, using Kruskal–Wallis nonparametric test for comparison. P less than .05 was considered significant.

Results

Sixty-four consecutive aspirin-pretreated patients with stroke/TIA, with a mean age of 73.6 years (range, 55-93), 33% female, were studied.

Eight patients were excluded: in 5 cases aspirin was suspended, and no new antiplatelet drug was started during the first 24 hours because of the use of alteplase, 1 patient was started on anticoagulation, and 2 patients received triflusal. Therefore, a group of 56 patients conformed the study population. Of these 56 patients, 48 (85.7%) had ischemic stroke and 8 (14.3%) had TIA. At discharge, TOAST classification of ischemic stroke was: 15 patients (31.25%) atherothrombosis, 13 patients (27.08%) cardioembolic, 6 patients (12.5%) lacunar, 1 patient (2.08%) others, and 13 patients (27.08%) undetermined.

In 18 patients, platelet function studies were performed after administration of the first dose of antiplatelet, whereas in 28 and 8 patients, they were performed after the second and third doses of antiplatelet administration, respectively.

Of the 56 patients included, 30 were in group ASA, 16 in group CLO, 10 in group ASA + CLO. Patients remained on antiplatelet treatment during hospitalization.

Thirty patients were in the ASA group: 3 patients (10%) took 100 mg aspirin, 23 patients (77%) took 300 mg aspirin, 4 patients (13%) 450 mg of intravenous acetylsalicylate of lysine.

Series characteristics are listed in Table 1. Substitution of aspirin by clopidogrel was significantly more frequent in patients with concomitant peripheral arteriopathy, $P = .015$. Eighty percent of ASA + CLO had a history of previous stroke before being hospitalized for the current one, statistically significant. Active smokers were more