Scientific letters

Fatal Bleedings With Prasugrel as Part of Triple Antithrombotic Therapy

Hemorragias mortales relacionadas con un tratamiento antitrombótico triple que incluye prasugrel

To the Editor,

Triple antithrombotic therapy with aspirin, clopidogrel, and warfarin is used in about 5% of patients after coronary stent implantation, mostly due to atrial fibrillation and left ventricular thrombosis.[1] This antithrombotic combination has a higher risk of bleeding than dual antiplatelet therapy or warfarin. The third-generation $P2Y_{12}$ inhibitor, prasugrel, has been shown to be more effective that clopidogrel in patients with acute coronary syndromes undergoing angioplasty; however, this drug increased bleeding.[2] A higher risk of bleeding has recently been reported when prasugrel, rather than clopidogrel, was used in patients with coronary stents and an indication for warfarin,[3] although with no fatal cases. We report 2 cases of fatal bleeding in patients undergoing primary angioplasty due to an ST-elevation myocardial infarction, with subsequent initiation of warfarin.

The first case was a 58-year-old male smoker weighing 85 kg who was hypertensive and dyslipidemic and who presented with an anterior ST-elevation myocardial infarction and severe left ventricular dysfunction. Creatinine, hemoglobin, and platelet count on admission were normal. Dual antiplatelet therapy using aspirin and prasugrel was started on admission. Bivalirudin was used during angioplasty, with bailout abciximab and balloon counterpulsation due to no-reflow and no ST-resolution after stent implantation in the left anterior descending artery. On postadmission day 9, revascularization was completed by stenting of a severely narrowed left circumflex artery. During rehabilitation, a left ventricular thrombus was detected on echocardiography and warfarin was added to dual antiplatelet therapy. Four months later, the patient was admitted due to progressive loss of consciousness: a left temporoparietal intraparenchymal hemorrhage was detected on computed tomography scan. The international normalized ratio (INR) was 3.49 (previous values were a maximum of 2.5-3.0). Hemoglobin and platelet count were normal. The patient died despite immediate neurosurgery. Autopsy revealed bleeding from a small arteriovenous malformation.

The second case was a 68-year-old man weighing 96 kg, who was hypertensive and diabetic and who had no history of heart disease or bleeding. He was admitted with an anterior ST-elevation myocardial infarction and severe left ventricular dysfunction. His INR on admission was 1.15. His proximal left anterior descending artery was treated with stenting. Dual antiplatelet therapy was started with aspirin and prasugrel. In the following days, the patient's hemodynamics improved slowly, cardiac rhythm was atrial fibrillation with frequent episodes of ventricular tachycardia: anticoagulation was started with enoxaparin and then with warfarin. On postadmission day 13, the patient had rectal bleeding with a hemoglobin drop to 8.3 g/dL (1U fresh frozen plasma transfused). Colonoscopy showed abundant hematic material, without the possibility of identifying the bleeding source due to patient instability. Warfarin and prasugrel were withdrawn and vitamin K was administered. Twenty-four hours later, the patient had a new episode of melena with hemodynamic deterioration. Colonoscopy showed a bleeding ulcer in the transverse colon, which was treated using a clip. A further 2 h later, the patient had cardiac arrest due to ventricular fibrillation followed by asystole and unsuccessful fluid and cardio-pulmonary resuscitation with exitus.

Upon admission, both patients were at low estimated risk of bleeding: they were relatively young, male, and had normal body weight and no previous bleeding or stroke. ST-elevation myocardial infarction and diabetes were preferential indications to use prasugrel rather than clopidogrel.[4] Finally, the patients' risk of stent thrombosis was higher than average due to severe left ventricular dysfunction. However, later in their clinical course, both patients developed an indication for warfarin. In the patient with intracranial hemorrhage, this complication occurred 3.5 months after the initiation of warfarin and was attributed to an undiagnosed arteriovenous malformation. An additional causative factor for the fatal episode was a higher than optimal INR value at the time of hemorrhage, although previous values were within the guideline-recommended range. In the patient with enteric bleeding, severe hypotension subsequent to massive bleeding in the context of severe left ventricular dysfunction might also have been a causative factor for stent thrombosis, but the same mechanism is more likely to have caused severe myocardial ischemia with ventricular fibrillation.

With regard to anticoagulation, expert recommendations[1] suggest a target INR of 2.0 to 2.5 in the case of triple antithrombotic therapy. Low-dose dabigatran or rivaroxaban, which have been shown to have similar efficacy to warfarin but a lower risk of bleeding, might be possibilities to explore. With regard to the antiplatelet component of the combination, withdrawing aspirin from triple therapy has been associated with less bleeding,[5] and this strategy should be tested for efficacy in larger numbers of patients. For patients already on warfarin at the time of stenting, clopidogrel is the only $P2Y_{12}$ inhibitor empirically recommended by current guidelines. When starting oral anticoagulant therapy in patients like ours, who develop an indication for warfarin after stent implantation and the initiation of dual antiplatelet therapy with either prasugrel or ticagrelor, it seems to be prudent to downgrade the potency of $P2Y_{12}$ inhibition to clopidogrel. Alternative strategies, such as reducing the dosage of prasugrel to 5 mg o.d. should be specifically investigated.

CONFLICTS OF INTEREST

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Stefano Savonitto,[a,*] Marco Ferri,[a] and Elena Corrada[b]

[a]*Division of Cardiolgy, IRCCS Arcispedale S. Maria Nuova, Reggio Emilia, Italy*
[b]*Cardiovascular Department, Humanitas Clinical and Research Center, Rozzano, Italy*

[*] Corresponding author:
E-mail address: stefano.savonitto@asmn.re.it (S. Savonitto).

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Histologic and Angiographic Imaging of Acute Shock Dengue Myocarditis

Imagen histológica y angiocardiográfica de miocarditis aguda por dengue

To the Editor,

A 65-year-old woman, resident of Mexico City, began to complain of myalgia, headache, general malaise, and fever 3 days after returning from a 5-day stay in Acapulco. Two days later, she experienced syncope and was taken to hospital. She was conscious, her blood pressure was 70/30 mmHg, respiratory rate was 24 per minute, and her temperature was 38.6°C; no skin lesions or edema where seen, heart sounds were normal, and lung fields clear.

Her electrocardiogram showed sinus rhythm; chest x-ray was normal. A complete blood count revealed normal hemoglobin, normal white blood cells with 90% neutrophils, and mild thrombocytopenia. Blood urea nitrogen and creatinine were normal; hyponatremia and hypokalemia were also present (126 and 3.6 mEq/L, respectively).

Volume replacement was started with saline and norepinephrine infusion was also required. Clarithromycin, cefepime, and oseltamivir were started. The patient continued to have a fever of 38.7°C and increased hemoglobin and hematocrit (17.9 g/dL and 53%) and leucopenia (3000/mL^3 with 71% neutrophils, 17% lymphocytes, and 12% monocytes) were observed. All culture samples were negative.

On the sixth hospital day, she suddenly developed oppressive chest pain and dyspnea. Heart sounds revealed S3 gallop rhythm and generalized lung rales. An electrocardiogram showed sinus tachycardia, new ST depression in V_1 through V_3, and ST elevation in aVR and aVL. Chest x-ray revealed an enlarged cardiac silhouette and pulmonary edema. Creatine kinase-MB fraction was elevated (38 mg/dL), while troponin I was normal (1.6 μg/L).

The patient was started on noninvasive ventilation, digoxin, furosemide and ivabradine. Six hours later she developed bidirectional ventricular tachycardia, sustained monomorphic ventricular tachycardia, and polymorphic ventricular tachycardia, which were attributed to digitalis intoxication and were resolved with diphenylhydantoin. Endotracheal intubation was required and cardiac catheterization was performed. Left ventricular end-diastolic pressure was 38 mmHg, left ventriculography demonstrated severe diffuse hypokinesis with an ejection fraction of 14% and grade II mitral regurgitation (Figure 1). Coronary angiography revealed normal coronary arteries; left ventricular endomyocardial biopsy shows necrosis of myocardial fibers (Figure 2).

Dengue virus-specific IgM and IgG antibodies were positive. Oseltamivir was replaced with ribavirin. A diagnosis of severe dengue myocarditis was made and steroid treatment was initiated with methylprednisolone (500 mg i.v. bolus followed by 250 mg tid for 3 days).

On the tenth day, her electrocardiogram showed sinus rhythm, giant T wave inversion, and prolonged QT interval; chest x-ray showed reduction of cardiac silhouette and a marked decrease of pulmonary interstitial edema. Catecholamine infusion was stopped on the eleventh day. On the following day, the

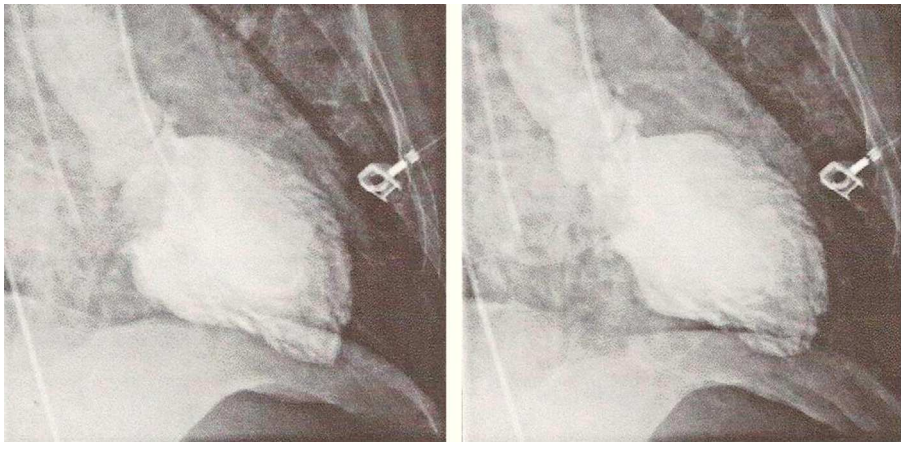

Figure 1. Clear furrowing of the left ventricle border, a peculiar striation known as "myocardial waffling", which is more apparent in anteroapical segments and is considered a sign of myocardial necrosis.