CASE REPORT

SUSPECTED CLOPIDOGREL RESISTANCE IN PATIENT WITH RECURRENT CORONARY STENT THROMBOSIS

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ABSTRACT

Despite aggressive antiplatelet therapy in the setting of percutaneous coronary intervention, the incidence of stent thrombosis remains approximately 0.5% to 0.8%. We report on a 53-year-old male patient with recurrent coronary stent thrombosis treated by coronary re-interventions and anticoagulation. Initial diagnostic selective coronary angiography revealed 90% proximal circumflex coronary artery stenosis in a patient with 3rd degree of stable angina by Canadian Cardiology Society classification. After premedication with a loading dose of 600 mg clopidogrel, 300 mg aspirin and intravenous enoxaparine 1 mg/kg, a bare-metal stent was implanted. The initial postprocedural course was normal. On the third day after the intervention, the patient was subjected to reintervention because of the stent thrombosis, and on the fifth day after reintervention – to the third percutaneous coronary angioplasty, also because of the stent thrombosis. Clopidogrel resistance was suspected and treatment with warfarin was initiated, after which there were no new cardiac events. Three months later, anticoagulation was discontinued, and as an antiplatelet agent aspirin 100 mg daily remained in therapy. Up to now (one-year), follow-up of the patient has been uneventful. In the case of suspected clopidogrel resistance, alternative therapeutic options have to be considered, like introducing per os anticoagulation (e.g. warfarin), introducing ticlopidin instead of clopidogrel, or, in the near future, possibly introducing prasugrel, a similar agent currently in transition from investigation into clinical use.

Keywords: stent, coronary disease, clopidogrel resistance, thrombosis

INTRODUCTION

Despite aggressive antiplatelet therapy during and after percutaneous coronary interventions (PCI), the incidence of acute stent thrombosis remains to be approximately 0.5-0.8%, according to ISAR trial. Antiplatelet agent clopidogrel is used as the first line in stent thrombosis prevention, together with the standard of antiplatelet therapy (aspirin). Although there are clinical indications and some data from ex vivo research, there’s still no clear definition of clopidogrel resistance. Therefore, in isolated cases, it can only be referred to as a clinical suspicion of clopidogrel resistance. Even today there are no definite recommendations, nor the official guidelines regarding the treatment of choice in the case of suspected clopidogrel resistance, although there is evidence that this condition is linked to an increased risk of adverse thrombotic events. Here we report on a patient with recurrent coronary stent thrombosis treated by percutaneous coronary re-interventions and anticoagulant therapy.

CASE REPORT

We report on a 53-year-old male patient with recurrent coronary stent thrombosis treated by percuta-
neous coronary re-interventions and anticoagulant therapy. By the means of diagnostic selective coronary angiography, in a patient with stable angina pectoris of 3rd degree by Canadian Cardiology Society, we found single-vessel coronary disease with 90% proximal stenosis of circumflex coronary artery (Fig. 1.A, B). After premedication with a loading dose of 600 mg clopidogrel, 300 mg aspirin and intravenous enoxaparine 1 mg/kg, a bare-metal stent (Fig. 1. C) was implanted using 20 atm implantation pressure (Fig. 1. D, E). The initial postprocedural course was uneventful. After the intervention, the patient received 150 mg clopidogrel, 160 mg enoxaparine (in two divided doses), and 300 mg aspirin daily. On the third day after the intervention, the patient reported severe chest pain. In electrocardiogram (ECG) there were horizontal and descending ST-depressions of -3mm with negative T-waves in II, aVL, V4-V6 leads. The patient underwent urgent control coronary angiography, and a thrombotic subocclusion of the treated circumflex artery was found (Fig. 2. A, B), with the beginning at the distal portion of the previously implanted stent. There were no signs of coronary dissection. A re-intervention was performed, with an implantation of the second stent, partially overlapping with the distal portion of the first one (Fig. 2. C, D, E). During the next four days, the patient was clinically and haemodynamically stable. The dose of clopidogrel and aspirin remained unchanged. On the fifth day after re-intervention, the patient was hospitalized again under the clinical pic-

Figure 1. Angiogram of the first intervention.  
A – CX-OM* stenosis (arrow); B – same stenosis enlarged (arrow); C – stent deployment; D – satisfactory result after first intervention (arrow); E – same result enlarged (arrow).  
*CX-OM – obtuse marginal branch of the circumflex coronary artery.

Figure 2. Angiogram of the second urgent intervention (first re-intervention).  
A – stent thrombosis (arrow), a hazy-border coronary lesion; B – same lesion enlarged (arrow – stent thrombosis); C – deployment of second stent; D – satisfactory result after re-intervention (arrow shows no thrombosis); E – same region enlarged.
ture of a troponin-negative acute coronary syndrome, with severe chest pain, and ECG finding identical to the one in the first episode of stent subocclusion. A new coronary angiography was performed one more time, finding several small, spherical, hazy-bordered formations in the proximal portion of the first stent, morphologically depicting an intracoronary thrombus (Fig. 3. A, B). The patient was treated by percutaneous transluminal coronary angioplasty (PTCA) using a non-compliant PTCA-balloon (Fig. 3. C) with high inflation pressure (27 atm), which restored normal coronary blood flow (Fig. 3. D, E). Immediately upon re-intervention, ECG was normalized, and the patient reported disappearance of precordial pain. Under the assumption that the recurrent coronary stent thrombosis is a consequence of antiplatelet therapy resistance, primarily clopidogrel resistance, anticoagulant therapy (per os warfarin) was introduced, with recommended INR range of 2-3. This therapy was continued for three months. The patient was advised to also take aspirin 100 mg and clopidogrel 75 mg daily. Clopidogrel was discontinued after one month, and warfarin after three months. Aspirin was continued indefinitely. After introducing warfarin, there were no new cardiac events, nor angina recorded. After the discontinuation of anticoagulation, up to now, in one year follow-up, the patient remained symptom-free.

DISCUSSION

Implantation of coronary stent is the primary means of coronary revascularization. Stent, as a foreign body exposed to bloodflow, in contact with blood provokes thrombosis and blood coagulation. Subtotal thrombosis leads to unstable angina, and total thrombosis, if not urgently treated, leads to an acute myocardial infarction. After the initial treatment of PCI patients only with aspirin, during the era of early PCI which consisted almost exclusively of PTCA, the introduction of thienopyridines (firstly ticlopidine, and later clopidogrel) significantly reduced stent thrombosis rate. But, despite these innovations in adjuvant medical treatment, a small occurrence of acute stent thrombosis of 0.5-0.8% was still evident. Therefore, the concept of antiplatelet resistance was introduced. The time required for a bare-metal coronary stent to be endothelialized is usually 28 days, and according to some recent research up to 3-4 months. Variability in serum concentrations of agents that modulate the platelet response (ADP, nitric oxide - NO, tissue factor, thromboxane A2 – TX A2) also influences the potential resistance to antiplatelet therapy. High doses of clopidogrel were shown to be more efficient in platelet aggregation inhibition, providing a higher concentration of active metabolite. As an alternative in the case of suspected clopidogrel resistance, it is possible to introduce warfarin anticoagulant therapy (the cheapest solution), or bivalirudin as a direct thrombin inhibitor, or eptifibatide as a GP IIb-IIIa inhibitor, which seems to be the most logical choice, knowing its way
of action. One of the novelties in stent manufacturing technology is a stent coated with GP IIb-IIIa inhibitor, shown to be safe in the initial studies, with a possibility to reduce major adverse cardiac events. Due to the misleading definition of resistance and non-standardized method for assessing platelet inhibition, current guidelines do not recommend the use of platelet function assays to monitor the inhibitory effect of antiplatelet drugs. Current guidelines also do not recommend clopidogrel loading doses higher than 300 mg and daily maintenance doses higher than 75 mg, even though a regimen of 600 mg clopidogrel loading dose seems to be preferred for patients undergoing percutaneous coronary interventions.

CONCLUSION

It is important to identify poor responder patients and in the case of suspected clopidogrel resistance alternative therapeutic options have to be considered, like per os anticoagulation, ticlopidin instead of clopidogrel, or, in the near future, possibly introducing prasugrel, a similar agent currently in transition from investigation into clinical use.

REFERENCES