Perspective Piece

Continuation of Dual Antiplatelet Therapy in a Patient with a Coronary Artery Stent with Dengue Hemorrhagic Fever: A Clinical Conundrum

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Abstract. Severe thrombocytopenia with impairment of the activity of platelets and impairment of blood clotting occurs in dengue hemorrhagic fever (DHF). Continuation of dual antiplatelet therapy in such patients can result in life-threatening hemorrhages. On the other hand, withholding of antiplatelets in a patient undergone coronary stenting lately can lead to stent thrombosis, resulting in myocardial infarctions and sudden cardiac death. There are no guidelines on management of DHF in patients with coronary stents. Here, we discuss about several divergent factors that need to be considered and balanced when managing such patients. We describe a case as an example to illustrate how we balanced the risk of serious bleeding versus the risk of stent thrombosis successfully according to evolution of the disease process, by temporary withholding of antiplatelets in such a patient.

INTRODUCTION

Dengue is an emerging mosquito-borne viral hemorrhagic fever.^{1–3} Thrombocytopenia with impairment of function of the remaining platelets is a characteristic feature of dengue hemorrhagic fever (DHF).^{1,3} In different case series, 20–60% of hospitalized dengue patients had evidence of bleeding.⁴ Continuation of platelet aggregation inhibitors aspirin and clopidogrel (dual antiplatelet therapy [DAPT]) for DHF can lead to fatal hemorrhages and that may amount to medical malpractice. On the other side, patients with coronary stents depend on platelet aggregation inhibitors for the prevention of stent thrombosis. According to several studies, the single most important predictor of stent thrombosis (ST) is termination of antiplatelets.^{5,6} Coronary stent thrombosis can occur swiftly and can lead to ST elevation myocardial infarction and associated complications.^{5,6} Therefore, withholding of antiplatelets in a patient with a coronary stent also may amount to medical malpractice. Bleeding risk rises to an acme and then decreases during the course of DHF.^{1,2} Balancing the risk of serious bleeding versus the risk of stent thrombosis according to evolution of the disease process of dengue/DHF is challenging and crucial in managing a patient with a coronary stent on DAPT, developing dengue. Lately, we faced such a situation. We did not find any guidelines but only a case report and a “point of view” article on management of DHF in a patient with a coronary stent in the English medical literature.^{7,8} We illustrate the divergent factors that clinicians have to consider when dealing with this clinical conundrum, giving the case we managed as an example.

A CLINICAL SCENARIO WE MANAGED

A 47-year-old man was presented to us on the third day (D3) of a febrile illness. He had undergone percutaneous angioplasty of the left proximal anterior descending coronary artery with a drug-eluting stents (DES) 6 months before. He was advised to take aspirin 150 mg at night for the rest of his life and clopidogrel 75 mg at night for 1 year by the cardiology

team. On the same day, his platelet count has dropped from $125 \times 10^9/L$ to $90 \times 10^9/L$ and other findings were unremarkable. Our working diagnosis was dengue. Considering the declining trend of his platelet count and because we have no means to predict the nadir, we decided to withhold DAPT, to do serial counts until we see an upswing of the platelet count and then to restart aspirin followed by clopidogrel. We relied on already low and dropping platelet counts, irreversible inhibition of most existing platelets because of DAPT (that lasts > 7 days), and impairment of platelet activity by dengue to protect him against ST. He developed DHF, after a nadir of $6 \times 10^9/L$ on D6 of the illness, platelet count showed a rising trend. On D8 of the illness, the diagnosis was confirmed by positive IgM (IgM antibody capture-ELISA) test. On D9 of the illness, platelet count raised to $77 \times 10^9/L$ and we restarted aspirin. As the patient clinically improved, he was sent home and asked to come back on D11. However, he came back on D13 of the illness. His platelet count had risen to $355 \times 10^9/L$ and, hence, immediately clopidogrel was also restarted. He never had any clinical bleeding or angina during this whole episode.

DIVERGENT FACTORS TO BE CONSIDERED AND BALANCED

Drug-eluting stents continuously release drugs that discourage cell proliferation.^{5,6,9} This dampens the formation of a new endothelium inside their lumen and resulting in narrowing but keeps the stent exposed to circulating platelets, increasing the risk of stent thrombosis.⁶ Therefore, continuation of antiplatelets is especially important in patients with DES compared with patients with bare metal stents.^{5,6} According to recent review articles, other stent characteristics such as the material, strut thickness, coatings applied, and the count of stents in the patient influence risk of ST.^{5,6,9} Stent deployment factors such as malpositioning, under expansion and lesion characteristics such as the position and length, and presence of a necrotic core in the atheroma also have an impact.^{5,6,9} Presence of comorbidities such as diabetes, end-stage kidney diseases, and smoking were demonstrated to increase the risk of ST.^{6,9} There are patients resistant to antiplatelet agents, and they are at higher risk of ST.⁹ Patients with poor left ventricular functions are at a greater risk of ST.^{6,9} A few past studies have demonstrated ventricular dysfunction

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in DHF, although we underdiagnose that in clinical practice.⁸ When the risks of ST versus bleeding were weighed, dual antiplatelets are most beneficial up to a year after the stenting.⁶ DHF disease process has subsequent febrile, critical, and recovery phases. In dengue fever, there is no critical phase.^{1,2} At present, there is no generally accepted way to reliably forecast whether a patient will develop DHF or another severe form of dengue at the onset of symptoms. During the course of illness of dengue, platelet count drops to a nadir and then starts to rise over a few days.^{1,2} There is no reliable way yet to predict the level of this nadir. Platelet activity also gets impaired in dengue.^{1-3,8} In DHF patients, platelet activity recovery time is 2 days slower than the platelet count recovery time.¹⁰ According to some authors, this recovery takes 2-3 weeks.⁸ In healthy people, it takes 4 days or more for platelet activity to get normalize after aspirin withdrawal.¹¹ Corresponding time lag is 7-10 days after withdrawal of clopidogrel.^{11,12} Thrombocytosis can rarely occur immediately after recovery of dengue and that might contribute to precipitation of myocardial infarctions in patients with stents.^{3,13} Past studies give conflicting results regarding the platelet count below which there is a significant risk of bleeding in dengue patients.^{3,4} Blood clotting also gets impaired in DHF by several mechanisms. Excessive fibrinolysis, rise of D5 D-dimer levels, and reduced thrombin formation were demonstrated in dengue patients.^{1,8,14} Lengthening of thrombin time, prothrombin time, and activated partial thromboplastin time due to reduction in coagulation factors I, V, VIII, IX, X, antithrombin, and α 2-antiplasmin, with capillary leakage (hallmark of DHF), happens in dengue.^{4,8} Nonstructural protein 1 on the surface of dengue virus leads to generation of antibodies that cross react with human plasminogen and activate it.¹⁵ Continuations of aspirin in patients with viral fevers including dengue make them susceptible to Reye's syndrome with a high case fatality rate.⁸ Reye's syndrome usually affects children but adults are not spared.⁸ Bridging therapy with heparin is used when patients with coronary stents undergo surgery because of heparins' shorter duration of action.⁵ Heparin can induce two types of thrombocytopenia: type 1 could onset within 2 days.¹⁶ Bridging therapy with short-acting antiplatelet agents such as eptifibatide may also be used, but to our best knowledge that drug is unavailable in most hospitals of dengue-endemic countries. A more feasible alternative is bridging therapy with a short-acting oral non-steroidal anti-inflammatory drug (NSAID) such as ibuprofen, which reversibly inhibits platelet action (by contrast, effects of aspirin and clopidogrel last for the lifetime of affected platelets).¹⁷ Nonetheless, the WHO guidelines (2009) says "aspirin and NSAIDs are not recommended" in dengue.¹ There is a "point of view" article (2007) dealing with this issue recommending continuation of DAPT in patients with coronary stents until the platelet count drops below $50 \times 10^9/L$, unless there is bleeding or shock.⁸ Continuation of DAPT and if any bleeding manifestations ensue stopping DAPT and treating with blood products is another potential way of management.

CONCLUSION

There is a necessity to generate evidence-based guidelines regarding the best time to withhold antiplatelets and to resume it, place for a bridging therapy etc. The need is acute because coronary stenting is one of the most frequently executed

therapeutic procedures in medicine and it is estimated 3.9 billion people, in 128 countries (mostly in developing countries), are at risk of infection with dengue viruses.^{1,3,18,19} Developing countries contribute to 82% of the total disability-adjusted life years due to coronary heart diseases.²⁰ Consequently, already large and a growing population with coronary stents lives in dengue-endemic developing countries and are at risk of contracting dengue. As explained earlier, the ST risk varies widely from patient to patient among patients with coronary stents, and the spectrum of clinical dengue is also broad.^{1,2,5,6} Hence, generating guidelines applicable to the whole spectrum of such patients will be challenging. Until evidence-based guidelines are available, tailoring the management considering divergent risk factors of that individual patient according to the evolution of the phases of the DHF is the best option available.

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