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Dengue fever, thrombocytopaenia and management issues in post-coronary stenting patients

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Severe thrombocytopaenia is a rare finding, particularly in patients with coronary artery disease. Percutaneous coronary intervention (PCI) is best avoided in such patients because of the increased risk of bleeding complications that may result due to the mandatory use of periprocedural anticoagulation and post-procedural antiplatelet therapy. This concern is reinforced by data which has revealed an inverse relation between in-hospital death, major adverse cardiac events and major bleeding rates in PCI patients and platelet counts[1].

However, when faced with such a rare situation, there are no definite guidelines on how to address such tough calls. One such situation is where dengue fever along with thrombocytopaenia complicates periprocedural or post-procedural PCI settings.

The dengue virus is a single-stranded RNA arbovirus of the Flaviviridae family and is transmitted by the bite of the female mosquito of the genus Aedes (most commonly Aedes aegypti). Dengue fever has a wide clinical spectrum ranging from a mild self-limiting febrile illness (classic dengue) to life-threatening dengue haemorrhagic fever and dengue shock syndrome (DHF/DSS) which has ravaged mankind for centuries. Currently, the disease is endemic in all continents (especially tropical and subtropical countries) except Europe[2]. From a clinical point of view, it is not possible to distinguish those patients who will progress to the haemorrhagic form of the disease from those with the self-limiting illness. It is estimated that there are currently 50-100 million cases of dengue every year worldwide, including more than 500,000 reported cases of DHF/DSS[3]. In recent times, India has seen a major spurt in dengue, causing widespread panic, and this has stretched the medical services to their fragile limits.

One of the most dreaded features of dengue is thrombocytopaenia (TCP) which is usually seen between the 4th and 7th days of the illness, during the phase of defervescence when the fever is subsiding. The platelet counts may decline to alarmingly low levels. This is mentioned in the WHO guidelines of 2009 as a potential indicator of clinical severity[4]. In adults, a platelet count of 5,000/mm^3 and packed cell volume >50 are significantly associated with bleeding manifestations. Various mechanisms have been proposed in the pathogenesis of thrombocytopaenia in dengue, namely:

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– Bone marrow suppression by the virus. In the early phase of the disease marrow hypocellularity and retardation of megakaryocyte maturation have been documented[5].

– Increased platelet destruction is seen, which may be a part of an ongoing consumptive coagulopathy, secondary to complement system activation[6] or peripheral sequestration[7].

– Besides platelets counts, the functional disruption of these cells is seen[8]. Platelet function resumes its normal conditions two to three weeks after the initial convalescence period.

Also during the febrile period, variable reductions are observed in the different coagulation factors, such as fibrinogen, factor V, factor VIII, factor IX and factor X, besides antithrombin and alpha 2-antiplasmin. These changes explain the prolongation in prothrombin time and activated partial thromboplastin time. Elevations in the concentrations of fibrinogen/fibrin degradation products (FDP) and d5-dimer have also been described[9].

Taken together, these may have significant clinical implications due to altered haemostasis.

In the light of these facts, a great therapeutic dilemma may arise if a patient with dengue fever with thrombocytopaenia develops an acute coronary syndrome (ACS) or a patient who has undergone PCI in the recent past develops dengue fever with thrombocytopaenia, as antiplatelet therapy constitutes one of the cornerstones of therapy in ACS or post-PCI settings.

Possible implications of cessation of antiplatelet therapy in dengue complicated by TCP in patients who have undergone PCI

One of the most dreaded and catastrophic complications after PCI and stenting is stent thrombosis (ST). Acute ST (occurring 0-24 hours after stent implantation) carries mortality and myocardial infarction rates of 20-45% and 50-70%, respectively[10]. Although multifactorial in aetiology, the cessation of antiplatelet therapy is an important cause. Trials such as PCI CURE[11], TRITON-TIMI 38[12] and PLATO[13] have established the efficacy of dual antiplatelet therapy (aspirin in combination with oral $P2Y_{12}$ receptor inhibitors also called thienopyridines) in:

– Reducing rates of ST.

– Showing that ticagrelor and prasugrel in a situation of ACS are better than clopidogrel in reducing ischaemic events and ST but with a higher bleeding risk.

In PLATO, ST rates for ticagrelor and clopidogrel were 1.3% and 1.9%, respectively (p=0.009), while in TRITON-TIMI 38 the prasugrel group had lower rates of myocardial infarction, urgent target vessel revascularisation, and ST (2.4% versus 1.1% for the clopidogrel group; p<0.001).

Thus, the use of DAPT after PCI and stent placement seems imperative. Aspirin is an integral part of DAPT and should be continued indefinitely as one of the agents. On the basis of the available data, the optimal range of aspirin dose in patients treated with DAPT that provides maximal protection from ischaemic events and minimises bleeding risk appears to be 75 mg to 100 mg. The current recommendations[14] advocate the use of ticagrelor or prasugrel over clopidogrel for at least 12 months after PCI and stent (BMS/DES) implantation in ACS settings. If patients have tolerated the therapy well with no bleed or they are not at high risk of bleeding events, the DAPT may be continued beyond 12 months. If need be (e.g., patient develops a high risk of bleeding such as concomitant use of an oral anticoagulant, a major bleed occurs or the risk of bleeding is high such as needing intracranial surgery), the $P2Y_{12}$ inhibitor may be discontinued at six months. In the subgroup of patients with stable ischaemic heart disease (patients with a history of ACS >1 year prior who have since remained free of recurrent ACS are considered to have transitioned to stable ischaemic heart disease) who have undergone stent implantation, DAPT should be continued for at least six months when a DES was used and for at least one month if a BMS was used. If well tolerated, the therapy may be continued beyond these time frames or else, in case of DES use when faced with a situation where the drugs need to be discontinued, they may be withheld at three months. These guidelines are applicable to newer-generation DES which are less thrombogenic than first-generation DES[14]. The decision to discontinue antiplatelet therapy should be taken after carefully weighing the risks and benefits associated with the discontinuation of therapy.

It is also important to understand the association between the stent type and rates of ST. Overall, the rates of ST are highest in first-generation DES (sirolimus-eluting and paclitaxel-eluting stents). ST with BMS usually occurs within the first 30 days of implantation, when these stents are prone to thrombus formation[15]. Conversely, with first-generation DES, the greatest concerns are late ST (LST) (30 days to one year) and very late ST (VLST) (beyond one year). Second-generation DES, such as the zotarolimus-eluting stent and everolimus-eluting stents, demonstrate a decreased risk of LST and VLST. In a recent paper, Tada et al[15] reported the cumulative incidence of definite ST at three years to be 1.5% with BMS, 2.2% with first-generation DES, and 1.0% with second-generation DES. On multivariate analysis, the first-generation DES showed a significantly higher risk of stent thrombosis than the BMS, while second-generation DES were associated with a similar risk of ST when compared with the BMS. This goes to show that better technology and pharmacotherapy is available which can reduce the chances of ST.

Recommendations

– In all patients with dengue fever, antiplatelets should be avoided as they carry the risk of triggering Reyes syndrome apart from the worsening of thrombocytopaenia. Reyes syndrome is a rare condition characterised by hepatitis and encephalopathy and triggered by the use of aspirin in patients with viral infections such as varicella, influenza and dengue[8].

– If a patient with dengue fever develops an ACS, chart out a conservative approach and avoid interventional therapy. Antiplatelet drugs (aspirin along with clopidogrel rather than ticagrelor or prasugrel) should be used with caution and platelet counts monitored. In case PCI becomes imperative:

- Use the radial route.
- Use a BMS.
- For periprocedural anticoagulation use bivalirudin rather than heparin as the latter carries the risk of heparin-induced thrombocytopaenia (HIT) which may worsen an already complicated interventional scenario.
- Do not use GP IIb/IIIa inhibitors which are also known to cause thrombocytopaenia.
- The prophylactic use of platelet transfusions in dengue fever has been recommended when platelet counts are below 10-20,000/mm^3 without overt bleed or haemorrhage and below 50,000/mm^3 with bleed or haemorrhage in some guidelines. However, these are highly controversial and may increase hospital stay and increase the risk of pulmonary oedema, thus best avoided[16].

– Stent thrombosis after platelet transfusion has been documented. Cornet et al reported three cases where stent thrombosis occurred within six to 17 hours after platelet transfusion for bleeding or anticipated bleeding[17]. In fact, they proposed that transfusion of platelets be considered a risk factor for thrombotic stent occlusion. Donor thrombocytes may not be inhibited by antiplatelet drugs in the blood stream. The thrombogenic surface of a recently inserted stent may attract and activate donor platelets, resulting in thrombotic occlusion[18].
– In patients at high short-term risk of thrombosis, including those who have undergone PCI with stenting (received BMS within the past one month or DES in past zero to six months), it would be wise to continue DAPT while closely monitoring platelet counts. Switch over from prasugrel or ticagrelor to clopidogrel and maintain use of aspirin at 75-100 mg. If platelet counts fall below 50,000/mm^3, one may strongly consider discontinuation of DAPT or continuation with one antiplatelet agent.
– In patients with dengue and low short-term risk of thrombosis, including patients with stable ischaemic heart disease (SIHD), interrupt the use of DAPT while carefully monitoring the platelet counts and reintroduce one and then the second agent once platelet counts begin to rise.
– Patients with DHF/DSS represent perhaps the most catastrophic situation characterised by alteration in capillary permeability and significant capillary leakage of plasma into extravascular spaces, along with immune activation and high serum levels of tumour necrosis factor (TNF) receptor, interleukin (IL)-8, and other factors. This causes intravascular hypovolaemia and shock. DAPT should be interrupted immediately[8]. This condition not only requires a significant volaemic expansion, but also evaluation and treatment of the accompanying ventricular dysfunction, as in the current treatment of sepsis.

Conclusions

In the light of a paucity of data in the literature, the decision to discontinue antiplatelet therapy in a patient with dengue fever with thrombocytopaenia in peri- and post-PCI settings needs to be based on the evaluation of the patient's risk of bleeding and ischaemic complications. Each case must be decided individually. Discontinuation of antiplatelet therapy appears to carry real challenges, and continuation of antiplatelet therapy should be the rule when the risk of bleeding is low or haemostasis is achievable.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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