Tibial bypass salvage with eptifibatide in a patient with thrombocythemia

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Early graft failure is a complex and challenging clinical condition faced by vascular surgeons performing infrainguinal bypass surgery. This case describes a patient with undiagnosed thrombocytosis undergoing urgent open revascularization for critical limb ischemia. The operative case was complicated by recurrent on-table acute thrombosis that was successfully managed with intravenous glycoprotein IIb/IIIa antagonism with eptifibatide. This is a novel case of its use for on-table salvage of an infrainguinal bypass graft. This case report outlines this challenging clinical problem and a novel use for glycoprotein IIb/IIIa antagonists. (J Vasc Surg Cases 2015;1:246-8.)

CASE REPORT

A 91-year-old woman was referred emergently to our service from hematology with a short history of rest pain in her left foot, with dry gangrene affecting the first three toes. Consent was obtained from the patient's power of attorney to publish this case report. She had a background history of osteoarthritis, hypertension, and hypercholesterolemia, and she had an initial consultation with a hematologist for an undiagnosed elevated platelet count of 891×10^9/L. Her hemoglobin level was 13 g/dL, and the white blood cell count was 20.7×10^9/L despite absence of infection. Her medications included ramipril, metoprolol, and aspirin. She was noted to have a palpable femoral pulse but no palpable pulses distal to this, and the left foot was cold, with dry gangrene affecting the distal portions of the first three toes. Noninvasive vascular studies revealed an occluded superficial femoral artery with no obtainable pressure at the ankle. Percutaneous diagnostic angiography demonstrated occluded distal superficial femoral, popliteal, and tibial arteries with reconstitution of the posterior tibial artery, which constituted the only patent named vessel crossing the ankle (Fig). Duplex sonography confirmed an excellent left leg long saphenous venous conduit, and echocardiography revealed an ejection fraction of >60%. Given her critical limb ischemia, in consultation with hematology, priority was given to addressing her peripheral vascular disease. Therefore, despite her advanced age, because of her intractable pain and good functional status, a

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femorotibial bypass from her superficial femoral artery to her posterior tibial using a long saphenous venous conduit was performed. She was anticoagulated intraoperatively with intravenous heparin to maintain an activated clotting time of >300 seconds. The inflow and outflow vessels were of excellent quality, and an excellent graft pulse and target vessel pulse/Doppler signal were achieved. Immediately before skin closure, the graft pulse was noted to be absent. A graft thromboembolectomy was performed through a conduit side branch distally. We retrieved a significant amount of white thrombus, and graft flow was restored. A bolus of clopidogrel was administered through nasogastric tube; however, before closing of the wounds, the graft occluded a second time. Another thromboembolectomy again restored graft flow after retrieval of a significant amount of white thrombus. The clinical picture was consistent with recurrent on-table graft occlusion secondary to platelet-rich white thrombus in the setting of an underlying thrombocytosis. Heparin-induced thrombocytopenia was considered unlikely as she had no prior exposure or immediate drop in platelet count. We administered the glycoprotein IIb/IIIa antagonist eptifibatide to suppress platelet function. A bolus of 60 μg/kg was administered, followed by a continuous intravenous infusion rate of 0.7 μg/kg/min while the patient was still on the operating table. To measure response, rotational thromboelastography was used (ROTEM; TEM Systems, Durham, NC) to assess platelet function. Thromboelastography confirmed 82% platelet inhibition. No further on-table thrombosis of the graft occurred, and the surgery was completed successfully. Postoperatively, the patient was continued on an eptifibatide infusion, and hydroxyurea was commenced for a presumed diagnosis of myeloproliferative disorder; her platelet function was monitored by the platelet aggregation assay to ensure that despite her elevated platelet count, her functioning platelet count was suppressed to an acceptable level using eptifibatide. During this period, she was transitioned to warfarin and commenced on clopidogrel 75 mg daily. Subsequent hematologic testing demonstrated a Jak2 mutation consistent with myeloproliferative disorder. Her hydroxyurea was titrated, and on day 9 postoperatively, her platelet count was suppressed to 302×10^9/L and eptifibatide was discontinued. Four months postoperatively,

Fig. Diagnostic angiography of the left leg. **A,** Stenosis in mid superficial femoral artery. **B,** Occluded distal superficial femoral artery with geniculate collaterals. **C,** Occluded tibial vessels. **D,** Reconstitution of distal posterior tibial artery (*arrowhead*), which crosses the ankle joint.

the gangrenous areas on her foot were improving, the graft was patent, and her ankle-brachial indices improved from unmeasurable to 0.72.

DISCUSSION

Peripheral vascular disease is a significant health problem affecting between 13% and 14% of the elderly population. It is predicted to affect >7 million adults older than 40 years by 2020 in the United States.[1] Critical limb ischemia is its most severe form, and untreated it is associated with a 1-year amputation rate of 44% and 1-year mortality rate of 26%.[2] Despite the improvements in endovascular therapy for patients with critical limb ischemia, in patients suitable for surgery, bypass remains an effective and cost-efficient treatment.[3] Our patient presented emergently with critical limb ischemia and impending limb loss. Despite her thrombocytosis and possible myeloproliferative disorder, the urgent limb-threatening nature of her vascular disease required treatment before definitively diagnosing and addressing her underlying hematologic disorder. In the absence of thrombotic complications, the standard treatment for thrombocytosis in this age group is antiplatelet agents and observation alone. There was significant difficulty with recurrent on-table platelet-type white thrombus. Such patients present a significant clinical challenge in balancing the need for emergency surgery against the risk posed from undiagnosed comorbidities.

Early graft failure requiring reintervention is a significant postoperative complication for vascular surgeons. Studies on data from the National Surgical Quality Improvement Program in the United States demonstrate that early graft failure is associated with an increased mortality rate and overall complications.[4] The incidence at 30 days is between 4.5% and 6.3%. Risk factors associated with early graft failure include female sex (odds ratio, 1.22-1.29) and thrombocytosis (odds ratio, 1.29-1.49).[4,5] Whereas long-term graft patency may be modified by appropriate use of antiplatelet agents and anticoagulation,[6,7] the options for rescue therapy to salvage a failing graft on table have not been studied.

Stimuli that generate platelet-rich thrombi converge on a final pathway involving platelet glycoprotein IIb/IIIa. This receptor mediates interplatelet bridging through fibrinogen. The intravenous glycoprotein receptor antagonists (abciximab, tirofiban, and eptifibatide) are inhibitors with short half-lives that block this final pathway of platelet aggregation. They are used predominantly as adjuncts in the management of myocardial infarction. Intracoronary administration during angiography is described as rescue therapy for thrombus formation.[8] The use of these agents outside the setting of coronary artery disease for acute thrombosis has been described only for endovascular neuro-interventional procedures. On-table arterial thrombosis is a significant complication of endovascular cerebral aneurysm treatment. The use of direct intra-arterial eptifibatide and abciximab has been described in a number of reports with acceptable bleeding rates and good therapeutic success at resolving thrombosis.[9-12] In addition, eptifibatide has been used for perioperative bridging as a short half-life alternative to clopidogrel when the risk of bleeding is a concern.[13,14]

Our patient presented with critical limb ischemia and concomitant leukocytosis and thrombocytosis, which was subsequently diagnosed as a Jak2-positive myeloproliferative disorder. Myeloproliferative disorders arise from a mutation in the Janus family tyrosine kinase Jak2. The Janus family tyrosine kinase is used by the erythropoietin, thrombopoietin, and granulocyte colony-stimulating factor receptors for ligand-stimulated signal transduction. When the Jak2 mutation is activated, it leads to exaggerated clonal hematopoiesis and results in the clinical myeloproliferative syndromes. These are well-defined risk factors for arterial thrombosis.[15] The recurrent acute thrombosis during surgery that we encountered was classic platelet-rich white thrombus. This occurred despite oral aspirin and satisfactory perioperative anticoagulation with heparin. On the basis of the previous history of use in neurointervention procedures for salvage in cases of acute thrombosis and its rapid onset of action, we treated our patient with eptifibatide. The dose chosen in our case was one third of that used in acute coronary syndromes as our patient commenced treatment while on the operating table. This ensured that despite thrombocytosis, the functional platelet counts were suppressed. This enabled successful completion of our surgical bypass until the patient could be transitioned to additional oral clopidogrel and definitive treatment of her myeloproliferation with hydroxyurea.

CONCLUSIONS

We present here a novel case of the use of intravenous platelet inhibition with the glycoprotein IIb/IIIa antagonist eptifibatide for on-table salvage of an infrainguinal bypass graft. This represents an additional therapeutic agent for the vascular surgeon in managing these complex and challenging situations.

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