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Two case of preoperative bridging therapy for patients undergoing non-cardiac surgery after coronary stent implantation

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It has been reported that up to 12% of patients underwent non-cardiac surgery or invasive procedures within the first year after the coronary stent implantation.[1] Premature discontinuation of antiplatelet therapy is associated with a significant increase in mortality and major adverse cardiac events, in particular, stent thrombosis.[2] Thus, postponement of elective surgery is advocated during the first year after the coronary stent implantation.[3] However, if non-deferrable surgery is required within this 12-month period, recommendations are less clear. For such patients, preoperative administration of a short-acting intravenous agent has been proposed to reduce the risk of perioperative stent thrombosis.[4]

Tirofiban is a low-molecular weight, competitive and short-acting GPIIb/IIIa receptor inhibitor. After stopping administration of tirofiban, platelet aggregation recovers to 50% of the baseline value within 4 h.[5] This letter introduces two cases underwent non-cardiac surgery with the bridging therapy of tirofiban when oral antiplatelet agents were temporally withdrawn.

The first patient is an 81-year-old female, who presented with non-ST-elevation myocardial infraction (NSTEMI). The dual antiplatelet therapy of aspirin and ticagrelor was administered immediately. Coronary angiography revealed a long and heavily calcified lesion with severe stenosis involving the mid-left anterior descending artery (LAD), (Figure 1). A drug-eluting stent (DES, 2.75 mm × 36 mm, Partner stent, Lepu medical, China) was successfully inserted in the LAD. During hospitalization, the patient accidentally fell down, causing right distal femoral fracture. Her hemoglobin level dropped from 105 g/L to 75 g/L considering the hematoma of the thigh. Ticagrelor was withdrawn because of the aggravated swelling of the right limb. Aspirin

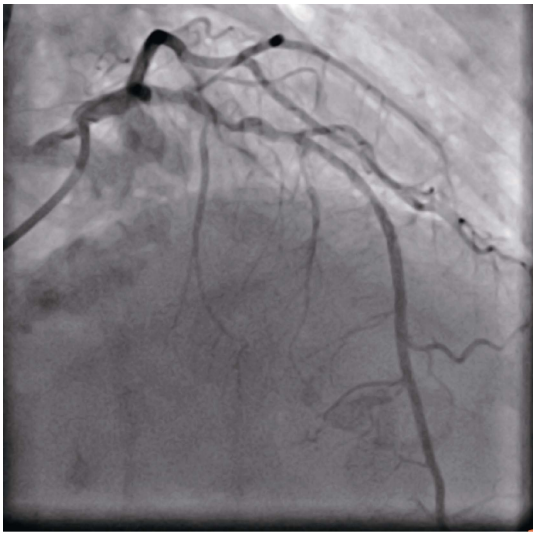

Figure 1. Coronary angiography in an 81-year-old female revealed a long lesion with severe stenosis involving the mid-left anterior descending artery.

was continued, and a low-molecular-weight heparin (LMWH) enoxaparin 6000 U/d [0.5 U/kg, since her creatinine clearance rate (CCR) = 23.24 mL/min] was used to prevent deep venous thrombosis (DVT). Conservative treatment of femoral shaft fracture may cause fracture nonunion or malunion, accompanied with bedsore, pulmonary embolism or DVT. Thus, an open reduction and internal fixation (ORIF) was planned. Three days before the surgery, aspirin was also withdrawn in order to minimize the risk of bleeding during the surgery. The infusion of tirofiban was immediately started as a bridge therapy from the day aspirin was stopped, at half dose (0.05 μg/kg per minute) considering her low CCR (23.24 mL/min), and was maintained till 6 h prior to the surgery. Enoxaparin was stopped 12 h prior to the surgery. ORIF was successfully performed. She was given clopidogrel 24 h after the surgery with a loading dose

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of 300 mg. Enoxaparin was also started at the same time to prevent DVT and was maintained till 14 days after the surgery. Then dual antiplatelet therapy of aspirin and clopidogrel was resumed on that day. The patient was discharged 21 days after the surgery without complications.

The second patient is a 67-year-old male, who presented with exertional angina for one month. The dual antiplatelet therapy including aspirin and ticagrelor was administered. Coronary angiography revealed an 80% stenosis of the proximal LAD (Figure 2). A DES (3.5 mm × 33 mm XIENCE Prime stent, Abbort) was successfully inserted in LAD. On the following day, the patient passed reddish brown stools once, and the stool occult blood was positive. Aspirin was withdrawn while ticagrelor was continued after weighing the risks of stent thrombosis and bleeding. CT scan revealed a mass at hepatic flexure of the colon. Colonoscopy and biopsy were needed for further diagnosis. Gastrointestinal consultant suggested that all antiplatelet agents should be stopped at least three days prior to the colonoscopy in order to reduce the perioperative risk of bleeding. Thus, ticagrelor was also withdrawn and then the infusion of tirofiban was administered as a bridge therapy at the dose of 0.1 μg/kg per minute till 4 h prior to the colonoscopy. Colonoscopy and biopsy were successfully preformed without overt blood loss. Histology and colonoscopy confirmed a middle differentiated adenocarcinoma at hepatic flexure of the colon. The dual antiplatelet therapy of aspirin and ticagrelor was resumed 24 h after colonoscopy considering the high risk of stent thrombosis. The surgical resection of the carcinoma was planned after consultation with the treating cardiologist, anesthesiologist, and surgeon.

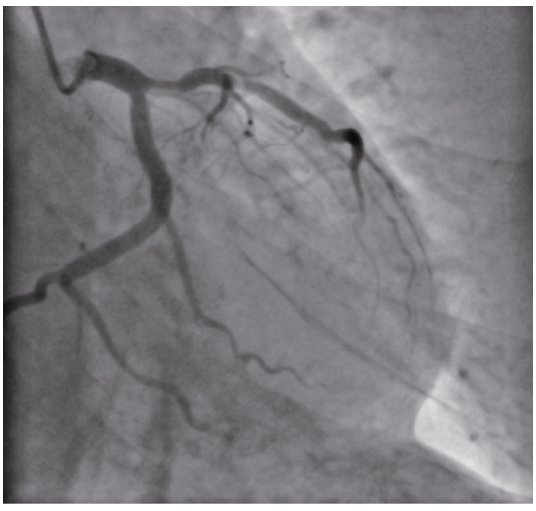

Figure 2. Coronary angiography in a 67-year-old male revealed a 80% stenosis of the proximal left anterior descending artery.

Aspirin was continued during the perioperative period. Ticagrelor was discontinued five days prior to surgery, and bridging therapy with tirofiban was started 48 h later till 4 h prior to the operation. Right hemicolectomy was successfully performed with only 100 mL blood loss during the operation. The patient was given clopidogrel 48 h after the operation, discharged five days later.

Both patients mentioned above were in urgent need of surgical operations just several days after the DES implantation. The risk of bleeding and thrombosis should be considered in the perioperative management of antiplatelet therapy in these patients.[3] Whenever possible, efforts to continue dual antiplatelet therapy (or at least aspirin) should be made. If the risk of bleeding in the procedure is low while the risk of thrombosis is high, dual antiplatelet therapy is suggested to continue. If the risk of bleeding is intermediate or high, P2Y12 receptor inhibitors should be discontinued five days before the procedure, while aspirin is recommended to be continued. If the risk of thrombosis is high, glycoprotein IIb/IIIa inhibitors could be used as a bridge therapy when P2Y12 receptor inhibitors are discontinued.[6]

Recent studies[4,7] indicate that bridging therapy with intravenous antiplatelet, including glycoprotein IIb/IIIa inhibitors during temporary withdrawal of oral agents might be a possibly effective and safe replacement option. In a retrospective analysis of patients who underwent urgent surgeries after coronary stenting,[7] Eighty seven patients received bridging therapy with tirofiban, whereas 227 were treated with other treatment options (the control group). There were no stent thrombosis cases in the bridging therapy group and three (1.3%) in the control group. Bridging therapy was associated with a decreased 30-day net adverse clinical event rate compared to patients in the control group (8% *vs*. 22.5%, $P < 0.01$). A recent meta-analysis collected the data of 280 patients from eight studies, showing that patients who received preoperative bridging therapy with glycoprotein IIb/IIIa inhibitors have an incidence of stent thrombosis and major bleeding at 1.3% and 7.4%, respectively.[4] A consensus from Italian cardiological, surgical and anaesthesiological societies recommended that glycoprotein IIb/IIIa inhibitors infusion should start three days prior to surgical intervention whereas clopidogrel and ticagrelor should be discontinued five days prior to the surgery.[6] Glycoprotein IIb/IIIa inhibitors should be stopped at least 4 h prior to the surgery (8 h for patients with creatinine clearance < 30 mL/min). P2Y12 inhibitors should be resumed within 24 to 48 h after the intervention with a loading dose.

In clinical practice, the management of antiplatelet ther-

apy should be formulated after consultation with the cardiologist, anesthesiologist, and surgeon, on a case-by-case basis, considering not only the existing guidelines but also the experts' experience. In case one, the risks of both bleeding and stent thrombosis during the perioperative period were high. The patient also had hemotoma and was in high risk of developing DVT. Ticagrelor and aspirin were stopped respectively before the surgery. Although the ACC/AHA guideline on the duration of dual antiplatelet therapy in patients with coronary artery disease recommends that aspirin should be continued for as long as possible,[3] surgeons are still worried about the hemorrhagic risk during the surgery. In a 2010 survey, only 64% surgeons were willing to follow the recommendation as they perceived the risk of bleeding to be greater.[8] Tirofiban infusion was given immediately after aspirin withdrawn to prevent stent thrombosis in this case. LMWH was used during the perioperative period in order to prevent DVT. After the surgery, only clopidogrel, rather than dual antiplatelet therapy, was administered. Considering the combination of aspirin, clopidogrel and LMWH may increase the risk of bleeding, especially for a senior female with renal insufficiency. Aspirin was resumed until 14 days after surgery when LMWH was stopped. In case two, the risks of bleeding in colonoscopy and colectomy were low. Aspirin was withdrawn because of intestinal hemorrhage. British Society of Gastroenterology and European Society of Gastrointestinal Endoscopy guidelines suggest that enteroscopy with or without biopsy is a low-risk endoscopic procedure. They also recommended continuing P2Y12 receptor inhibitors as single or dual antiplatelet therapy. However, the class of recommendation is low with few evidence on the safety of P2Y12 receptor inhibitors in colonoscopy.[9] Thus, ticagrelor was also withdrawn and tirofiban was used as bridging therapy before colonoscopy. After colonoscopy, both aspirin and ticagriler were resumed, considering the high risk of stent thrombosis while intestinal hemorrhage was not severe. And then before surgery, tirofiban was administered again as a bridging therapy when ticagrelor was withdrawn. Considering the relatively low risk of bleeding in colectomy, aspirin was continued during the perioperative period.

In conclusion, bridging therapy with glycoprotein IIb/IIIa inhibitors during temporary withdrawal of oral agents for operation might be an effective and safe replacement option. However, it should be noted that this bridging therapy does not abolish the risk of perioperative stent thrombosis and may carry an increased risk of bleeding. Controlled clinical studies are still insufficient.

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