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CASE REPORT

Efficacy of Cangrelor as Bridging Therapy Post PCI

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Abstract: ***Background*:** Dual antiplatelet therapy (DAPT) remains the cornerstone management for the prevention of acute stent thrombosis after percutaneous intervention (PCI). Situations mandating early interruption of DAPT carry a high risk of ischemic complications. Perioperative bridge therapy using Cangrelor, an intravenous P2Y2 inhibitor, may offer a potential solution. Unfortunately, evidence for its use in non-cardiac procedures is limited.

***Methods*:** Our protocol demonstrates successful off-label use of IV Cangrelor bridge therapy in a non-cardiac surgery patient. We describe a case of a 77-year old male; triple therapy with Aspirin, Apixaban, and Ticagrelor for recent drug-eluting stent placement required immediate surgical resection of stage I colonic adenocarcinoma.

***Results*:** Cangrelor bridge therapy was utilized both preoperatively and postoperatively without ischemic or bleeding complications. The patient tolerated exploratory laparoscopic colectomy with minimal bleeding and good post-op recovery.

***Conclusion*:** Minimizing the interruption of DAPT therapy in high-risk patients is achievable. However, careful planning with a team-based approach involving surgeons, cardiologists and pharmacists, along with close clinical follow-up and vigilant management of anti-platelet therapy is recommended.

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1. INTRODUCTION

Current ACC/AHA guidelines recommend the continuation of dual antiplatelet therapy (DAPT) with Aspirin and an ADP receptor antagonist for a minimum of 6-12 months after implantation of a bare-metal stent (BMS) or a drug-eluting stent (DES) following acute coronary syndrome (ACS) [1]. Premature discontinuation of DAPT therapy for a surgical procedure or due to an episode of major bleeding presents as a challenging dilemma for practicing clinicians. Oral P2Y12 inhibitors are often held 5 to 7 days prior to elective non-cardiac surgery in order to diminish the risk of bleeding [2]. Any period of DAPT interruption after recent stent implantation is likely to be associated with an increased risk of stent thrombosis and ischemic complications. Although shorter-duration DAPT can be considered for patients at lower ischemic risk with high bleeding risk, it becomes challenging to manage patients who present an urgent need for surgery within the first 6-month time frame.

Intravenous antiplatelet agents with a short half-life serve as a novel antiplatelet "bridging" option for the management of patients requiring temporary discontinuation of DAPT in the perioperative setting. Cangrelor, approved by the Food and Drug Administration in 2015 as an adjunct to PCI, is an intravenous P2Y12 inhibitor that has previously been used off-label as a bridging agent for coronary artery bypass graft (CABG) surgery [3]. However, limited evidence is currently available supporting antiplatelet bridge therapy with Cangrelor in non-cardiac procedures. We present a case of bridging antiplatelet therapy with Cangrelor in a patient with recent DES placement to the RCA requiring hemicolectomy for colonic adenocarcinoma.

2. CASE DESCRIPTION

A 77-year-old Caucasian male presented to a community hospital complaining of pressure-like chest pain radiating to his left arm and back. He reported additional symptoms of nausea and dizziness whenever he would try to stand up. These symptoms had been persistent for the last 2 days prior to presentation, prompting him to seek further medical attention. His past medical history was also significant which included hypertension, hyperlipidemia, former tobacco use, a prior positive FIT test, a dilated ascending aorta measuring 4.7 cm, and a 5 year agocoronary artery disease with a stent to the right coronary artery. The patient reported no drug allergies and his home medications included Atorvastatin 40

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mg daily, Docusate 200 mg daily, Losartan 25 mg daily, Omeprazole 20 mg twice daily and Zolpidem 5 mg once daily as needed. In the ER, he was noted to be in atrial flutter with rapid ventricular response. Lab tests on admission included Hgb 11.4 g/dl (13.2-17.1 g/dl), HCT 33.3% (38.5-50%) , WBC 5.9 Thousand/uL (3.8-10.8 Thousand/uL), PLT 162 Thousand/uL (140-400 Thousand/uL), Na 134 mmol/l (135-146 mmol/L), K 4.5 mmol/L (3.5-5.3 mmol/L), BUN 16 mg/dl (7-25 mg/dl), Cr 1.0 mg/dl (0.7-1.25 mg/dl), eFGR>60 ml/min/1.73 m^2, Albumin 3.1 g/dl (3.6-5.1 g/dl), Total Protein 5.9 g/dl (6.1-8.1 g/dl), ALT 27 U/L (9-46 U/L), AST 25 U/L (10-35 U/L), Alk Phos 56 U/L (40-115 U/L).

Initial cardiac enzymes were negative; however, given the presence of high-risk features concerning unstable angina, he was placed on intravenous heparin. Echocardiogram reported a left ventricular ejection having a fraction of 50-55% with a dyskinetic inferior wall, mild bi-leaflet prolapse of the mitral valve, mild mitral regurgitation, and mild left atrial enlargement. The patient underwent a stress test, which revealed reversible inferior, inferoapical and apical ischemia. Diagnostic coronary angiogram indicated an 80% in-stent restenosis in the proximal right coronary artery (RCA). This was followed by a successful percutaneous transluminal coronary angioplasty (PTCA) and DES placement to the RCA lesion. He developed normal sinus rhythm after an initiation of Carvedilol 12.5 mg BID. The patient was discharged on triple therapy with Aspirin, Ticagrelor and Apixaban for 30 days, followed by discontinuation of Aspirin after a month. Discharge instructions also included obtaining a CT Angiogram in 3 months for the assessment of aortic root dilatation and repeating his CBC in 3 weeks given a previously positive FIT test.

The patient presented 1 day after hospital discharge complaining 3 episodes of bright red blood per rectum associated with sharp intermittent abdominal pain. Diagnostic workup included an unremarkable esophagogastroduodenoscopy and a 5 cm ulcerating polyp in the transverse colon on colonoscopy. CT scan of the chest, abdomen and pelvis revealed a few hilar nodes considered to be a benign finding and a 15 mm sacral sclerotic lesion. A follow-up bone scan was unremarkable. Biopsy fragments of colonic mucosa were positive for an adenocarcinoma invading into at least the lamina propria with a desmoplastic stromal response. General surgery was consulted and immediate surgical resection was recommended. However, the risk of ischemic complications had to be assessed given the recent DES placement and interim discontinuation of antiplatelet agents prior to surgery. Ultimately the multidisciplinary team involving Cardiology and General surgery decided to postpone the surgery and use IV Cangrelor bridging therapy.

Five days prior to the scheduled procedure, the patient was admitted to the cardiac care unit of the hospital. Approximately 12 hours after the patient's last dose of Ticagrelor, the Cangrelor intravenous infusion was started at a rate of 0.6 mcg/kg/min based on actual body weight. Each Cangrelor intravenous infusion contained 50,000 mcg of Cangrelor in 250 mL of normal saline. Daily P2Y12 levels were checked and Cangrelor infusion rate adjusted to maintain platelet reactivity (PRU) levels between 80 and 180 units. Total IV Cangrelor infusion time was 5 days, and the infusion was stopped 2 hours prior to surgery. Laparoscopic right hemicolectomy with colo-enteric anastomosis was performed on Day 5 of admission with no complications and minimal blood loss. IV Cangrelor was resumed 2 hours after

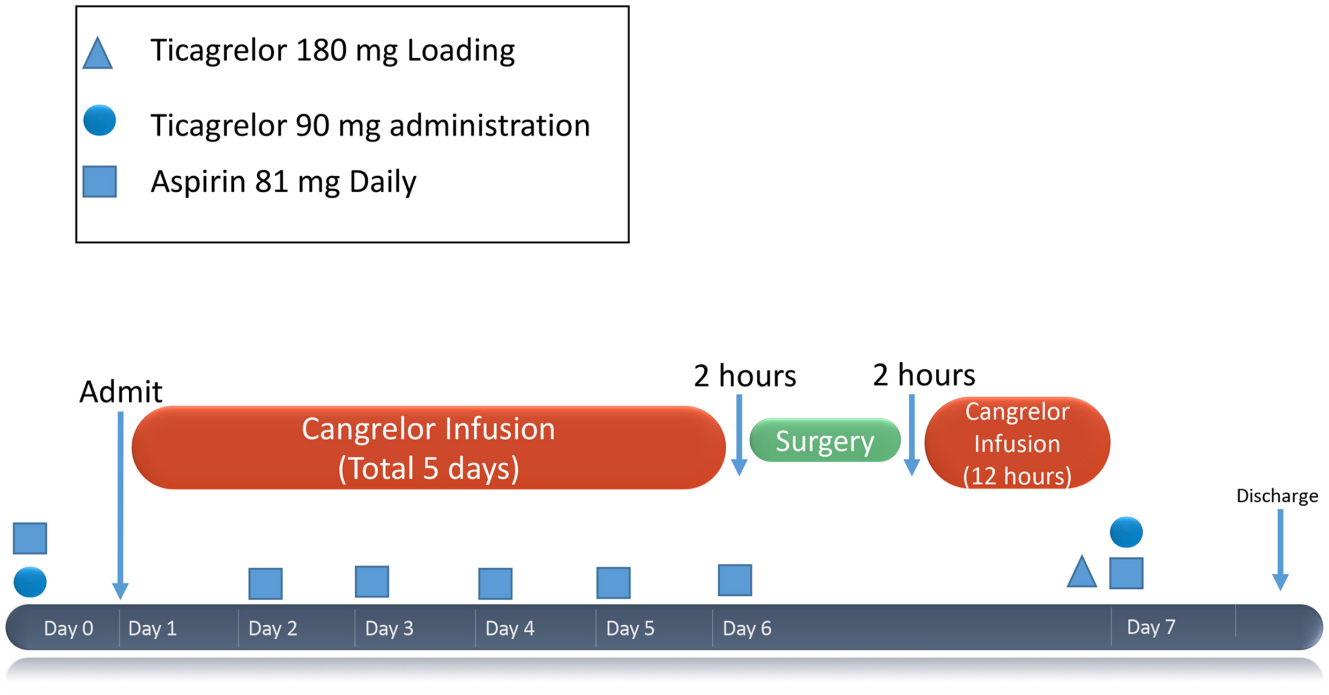

Fig. (1). Antiplatelet therapy administration in the perioperative setting. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

surgery at the same titrated rate (0.48 mcg/kg/min) prior to the operation and continued for another 12 hours to allow for rapid discontinuation in case, early surgical re-exploration was warranted. A Ticagrelor 180 mg loading dose was given 1 hour prior to discontinuation of the Cangrelor infusion with the plan to resume Ticagrelor 90 mg twice daily 12 hours later (Fig. **1**). Throughout the preoperative period, the patient received Aspirin 81 mg daily with the last dose given 4 hours before the procedure.

His hospital course was complicated by a post-surgical ileus, pneumonia, mild congestive heart failure and atrial flutter. He was ultimately discharged 2 weeks later without any incidence of bleeding or signs of ischemic complications. At a 2-month follow-up visit, the patient stated no new complaints and was tolerating dual antiplatelet therapy with Apixaban and Ticagrelor without bleeding complications.

3. DISCUSSION

Premature interruption of DAPT following PCI remains a challenge. Approximately, 51.8% of patients undergo non-cardiac surgery within twelve months of DES implantation [4]. The 2016 ACC/AHA guidelines recommend against performing elective non-cardiac surgery within 1 month of bare metal stent (BMS) implantation and six months of DES implantation in stable angina patients. The 2017 European Society of Cardiology guidelines, however, maintain that elective surgery requiring interruption of DAPT may be considered in as little as one month after BMS/DES if Aspirin can be continued peri-operatively. Nevertheless, there are no consensus guidelines for peri-procedural antiplatelet management in patients for whom surgery cannot be deferred. A team-based approach to evaluate and reduce the risk of thrombotic events and surgical bleeding is required when surgery is deemed urgent.

Factors associated with increased risk of thrombotic event after percutaneous intervention (PCI) include recent acute coronary syndrome, age>65 years, prior stent thrombosis, peripheral arterial disease, chronic kidney disease, angiographic factors (multiple lesions, small vessels, long stents, suboptimal stent deployment, *etc*.), multi-vessel coronary artery disease, particularly in diabetic patients [5]. Premature discontinuation of antiplatelet therapy remains the strongest predictor of stent thrombosis for both bare-metal and drug-eluting stents. In one study, premature discontinuation of antiplatelet therapy resulted in a 29% thrombosis rate and 45% mortality for patients with stent thrombosis [6]. Our patient was deemed high risk for stent thrombosis in case temporary discontinuation of antiplatelet therapy was pursued due to advanced age, recent ACS and history of in-stent restenosis.

The assessment of bleeding risk in gastrointestinal surgery is contentious. There are no firm recommendations regarding cessation or continuation of antiplatelet therapy in the elective or urgent perioperative setting [7]. Studies of bleeding risk have provided conflicting information. A recent systematic review assessing continued antiplatelet therapy and the risk of bleeding in gastrointestinal procedures found no difference in the overall incidence of bleeding in gastrointestinal surgery [8]. The largest study included in this review involved 1075 general surgery patients and similarly did not find a significant difference in the probability of bleeding related to ongoing use of single antiplatelet agents following various laparoscopic operations [9]. However, the use of dual antiplatelet agents was associated with a higher rate of hemorrhage in multivariable analysis.

Cangrelor is the only intravenous $P2Y_{12}$ inhibitor available for clinical use. Its quick onset and offset make it an ideal agent for bridge therapy. Blockade is direct, reversible, and competitive [10]. Cangrelor has a 3-6-minute plasma half-life with rapid platelet function recovery within 30-60 minutes after discontinuation of the infusion. A phase II, randomized, double-blind, placebo-controlled (BRIDGE) trial [11] evaluated Cangrelor as a bridging agent. Enrolled patients (n=210) required thienopyridine in the setting of recent acute coronary syndrome (ACS) or recent PCI while awaiting CABG surgery. Thienopyridines were stopped and patients were administered Cangrelor 0.75 mcg/kg/min or placebo for at least 48 hours, which was discontinued 1 to 6 hours before CABG surgery [12, 13]. A higher percentage of patients in the Cangrelor group achieved the primary end-point of platelet reactivity <240 PRU (98.8% *vs*. 19%, $P < .001$) with no differences in major bleeding. It is pertinent to note that this study was small and underpowered for Major adverse Cardiac events such as death, MI, or stent thrombosis. This trial supported the hypothesis that intravenous Cangrelor is a feasible management strategy in patients who require discontinuation of thienopyridine before surgery. However, Cangrelor is not currently FDA approved for this indication.

Until 2016 through 2017, the peri-procedural management of atrial fibrillation in the setting of recent coronary stenting often involved the use of an oral anticoagulant in addition to two antiplatelet agents for some period after stenting. This approach has been termed “triple anti-thrombotic therapy” or triple therapy. While the use of three antithrombotic agents reduces the rate of ischemic events, the risk of bleeding is significantly increased compared with one or two antithrombotic agents. This approach has been discounted in a number of recent randomized controlled trials comparing two or three of these antithrombotic combinations [14, 15]. A recent meta-analysis involving 4 RCTs noted that the use of OAC plus one $P2Y_{12}$receptor blocker, compared with triple therapy, led to a similar rate of major adverse cardiac events (10.4 *versus* 10.0 percent; HR 0.85, 95% CI 0.48-1.29) and a lower rate of TIMI major or minor bleeding (4.3 *versus* 9.0 percent; HR 0.53, 95% CI 0.36-0.85) [16]. Given the fact our patient was at increased risk of peri-operative bleeding, he was discharged home on Apixaban and Ticagrelor combination therapy.

To the best of our knowledge, this is the first case report describing the use of IV Cangrelor in the setting of major gastrointestinal surgery shortly after percutaneous coronary intervention with a drug-eluting stent.

CONCLUSION

Minimizing the interruption of DAPT therapy in high-risk patients is achievable. However, careful planning with a

team-based approach involving surgeons, cardiologists and pharmacists, along with close clinical follow-up and vigilant management of anti-platelet therapy is recommended.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

No Animals/Humans were used for studies that are basis of this research.

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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