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Case Report
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Aortic Dissection and Direct Factor Xa Inhibitors: Uncharted Waters

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Abstract

Acute type A aortic dissection is a surgical emergency due to the high mortality in medically treated patients mainly in the first 48 hrs of presentation. The use of factor Xa inhibitors in patients presenting with acute aortic dissection is a challenging situation. Surgical delay has been proposed to mitigate extensive surgical bleeding. We present a case of a patient on Rivaroxaban who could not tolerate delayed surgery and developed massive bleeding despite the use of thromboelastography and specific anti-Xa essay to guide optimal surgical time.

Keywords: Aortic dissection; DOAC; Factor Xa Inhibitors

Introduction

The prescription of Direct Oral Anticoagulants (DOACs) has increased annually, as guidelines favor their use over warfarin in most clinical scenarios. DOAC's include dabigatran, a direct thrombin inhibitor, and the direct activated factor X inhibitors (FXa-inhibitor): rivaroxaban, apixaban, and edoxaban. Only dabigatran has a universally approved reversal agent. While a reversal agent for FXa-inhibitors has been recently approved by the FDA for use [1], it is not widely available and is not currently approved for clinical use in Canada or the EU. While waiting for these reversal agents, cardiac surgeons must occasionally deal with the challenges of emergency operations in patients who take FXa-inhibitors.

Aortic dissection is a surgical emergency where perioperative bleeding is a significant concern. Delayed surgery for aortic dissection has been proposed as an alternative in selected patients on DOAC's [2]. However, clinical acuity may not always allow it. Here we present the case of a patient who underwent aortic dissection repair on Rivaroxaban. Delayed surgery was attempted, but the patient's clinical condition deteriorated and warranted operation. Although pre-operative levels of speficic Rivaroxaban anti-Xa was reassuring, the patient developed extensive post-operative bleeding.

Case Presentation

A 61-year old male presented to a primary hospital with sharp central chest and abdominal pain that radiated to his back, associated with nausea and diaphoresis. His past medical history included hypertension, chronic kidney dysfunction (creatinine 1.4 mg/dL), obstructive sleep apnea and unprovoked recurrent VTE/PE on life-long 20 mg of rivaroxaban, which he took in the morning of the day of the presentation. Computed Tomographic Angiography (CTA) confirmed a Stanford type A aortic dissection, before transfer to our surgical center, the patient was started on a titrated labetalol infusion and received 50 IU/Kg of Octaplex as part of a standardized DOAC reversal protocol. At arrival, he had ongoing chest and abdominal pain as well as coffee ground emesis and hematochezia. Blood pressure was 130/75 and HR 75. IV pantoprazole and nitroprusside infusions were added.

A Rivaroxaban-specific anti-Xa essay showed the absence of clinically relevant anti-factor Xa drug effect (<50 ug/ml). However, Rotational Thromboelastometry (ROTEM) demonstrated a markedly prolonged EXTEM time of 155s (Normal range 43-82) (Figure 1), with normal fibrinogen and platelet function, which suggested the possibility of residual DOAC activity. As his chest pain resolved and there was no pericardial effusion or progression of dissection on repeated CTA, delayed surgery was deemed reasonable. Close ICU monitoring took place.

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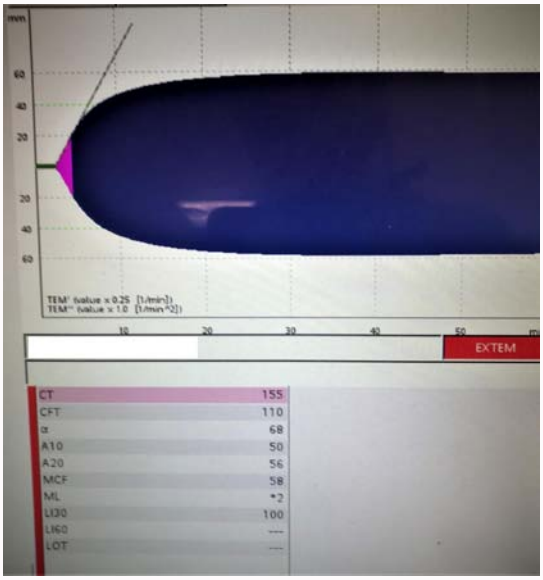

Figure 1: Thromboelastography EXTEM.

The following day, patient had recurrent chest and abdominal pain and increasing creatinine (3.2 mg/dL). Due to persistent pain and possible signs of hypo perfusion, emergency surgery was performed slightly after 24 hours of the last dose of rivaroxaban. A second Rivaroxaban-specific anti-Xa essay was performed just before the operation in case the first test reflected trough concentrations and because of increased renal dysfunction [3]. The repeat level was less than 50 ng/mL. A supra-coronary ascending aorta and hemiarch replacement were performed under DHCA (22°C). Bypass, aortic cross-clamp,and circulatory arrest were 181, 34 and 27 min respectively. The patientdeveloped severe coagulopathy intraoperatively requiring massive blood transfusion- 10 FFPs, 4 adult platelets, 1000 IU of Octaplex® and 100 units of cryoprecipitate. There was no intraoperative difficulties or surgical bleeding. Eventually, bleeding was controlled by surgical means and blood product transfusion and the sternum was closed. Chest tube output was 550 ml in the first 24 hrs. The patient's lactate quickly normalized postoperatively and his clinical abdominal exam was reassuring. No laparotomy was needed. He developed AKI and fluid overload, requiring hemodialysis for three days. The patient was extubated on the postoperative day 3 and was discharged from the ICU on day 7. He spent a total of 13 days in hospital prior to discharge without the need for ongoing dialysis.

Four-month follow-up CTA showed near complete remodeling of the thoracoabdominal aorta. Although this patient is high risk for recurrent VTE/PE, thrombosis and cardiac surgery have decided to keep him off anticoagulation until aorta remodeling has been stable. The patient has returned to his routine activities.

Comment

Type A Aortic dissection is a medical emergency with 50% mortality in 30 days in medically treated patients [4]. Most of the death happens during the first two days. Emergency surgery is the treatment of choice. Operative bleeding is a significant concern because of fragile tissues and the use of hypothermia for the surgical repair. Patients on anticoagulation benefit from anticoagulation reversal before the operation which is not currently available in most centers, being recently approved for clinical use only in the USA. Our patient did well despite massive transfusion. However, reviewed published cases of acute aortic dissection on FXa-inhibitors are not encouraging. To our knowledge, this is the first report to survive during the full scope of medication. Three cases have been reported. One patient died of postoperative complications [5]. Other died of cardiac tamponade after an attempt of delayed surgery [6]. The third case who survived had a delayed surgery [2]. However, the later patient went to the operating room after 60 hrs delay with no likely residual effect of the anticoagulant based on the calibrated anti-Xa essay and thromboelastography. Interestingly, the 60 hrs delay is close to the recommended time off FXa-inhibitors before elective cardiac operations, which is to have the last dose three days before the procedure [7]. Hamad et al. [2] have proposed delayed operation for patients on DOAC's and the use of thromboelastometry and drug-specific anti-Xa essay for monitoring drug effect [2]. However, a thorough analysis of risk and benefits of delayed surgery is necessary due to the deadly natural history of aortic dissection.

We attempted the delayed approach in the hope of full clearance of the medication. Recurrent abdominal and chest pain and kidney function deterioration led us to intervene earlier despite an abnormal ROTEM EXTEM value. Our patient developed severe coagulopathy, requiring massive transfusion which may have been reflective of residual DOAC activity despite an anti-Xa value lower than 50 ng/mL.

Intriguingly, our rivaroxaban-specific anti-Xa test was negative on two occasions. Arguably, the level might have been between 30 ng/mL and 50 ng/mL, which may have contributed to the coagulopathy in addition to other factors associated with coagulopathy post DHCA. The subcommittee on control of anticoagulation of the International Society on Thrombosis and Haemostasis currently recommend DOAC antidote administration if the level is greater than 50 ng/mL and consideration of antidote if greater than 30 ng/mL if there is a high risk of bleed [3]. Hamad *et al.* [2] suggest delaying the operation until the rivaroxaban-specific anti-Xa essay and thromboelastography are normal. However, FXa-inhibitor-specific anti-Xa essays have variability and reduced accuracy at upper and lower limits of quantification, misleading interpretation. Thereforethe judicious use of them is warranted until accurate and standardized tests are available [8]. Thromboelastography may be helpful to clarify coagulation abnormalities in those scenarios.

In the case presented, we tried to delay operation, but had to change strategies when faced with the possibility of ongoing dissection and regional hypo perfusion. Surgeons are left to navigate the delicate balance of delaying surgery and massive bleeding. Delayed operation is quite concerning in aortic dissection and may be beneficial only in the seamlessly selected patient. The perioperative teamshould be prepared for severe coagulopathy and the potential consequences of massive transfusions. Until anti-Xa reversal agents are approved for use in all jurisdictions, treating these patients with require a multidisciplinary approach involving input from cardiac anesthesia, cardiac surgery, and thrombosis-specialists to optimize patient outcomes.

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