Successful Use of Fondaparinux for Perioperative Bridging in a Patient with a Mechanical Heart Valve and Heparin-induced Thrombocytopenia

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Abstract:
The mechanical heart valve prosthesis is a thrombotic state requiring anticoagulation at therapeutic doses. Heparin-induced thrombocytopenia (HIT) is both a thrombotic and bleeding state which has a high chance of recurrence when heparin is reinitiated. Unfractionated heparin and low molecular-weight heparin are the standard of care for bridging therapy that are on anticoagulation with warfarin for various reasons. However, perioperative bridging in patients having a prior history of HIT is often elusive. We successfully used fondaparinux as a bridging agent for warfarin in a mitral valve replacement patient with a history of HIT.

Keywords:
Bridging anticoagulation, fondaparinux, heparin-induced thrombocytopenia, mitral valve replacement

Introduction
Mechanical prosthesis in the mitral valve position is a high risk for thrombosis warranting therapeutic doses of anticoagulation. Unfractionated heparin (UFH) and low molecular-weight heparin (LMWH) are the standard of care in case of perioperative bridging of anticoagulation. However, in the case of a history of heparin-induced thrombocytopenia (HIT), the usage of UFH and LMWH may further exacerbate thrombosis and their usage is unwarranted. We have successfully used fondaparinux in the case of mitral valve replacement (MVR) patient with prior HIT for perioperative bridging of anticoagulation.

Case Report
A 70-year-old female with a mechanical prosthesis at the mitral valve (CarboMedics 29 prostheses) in 2014 was on long-term anticoagulation with warfarin. She had HIT during the valve replacement surgery. She was referred to our center for perioperative bridging anticoagulation for her left eye vitrectomy. Echocardiography showed a well-functioning mechanical mitral valve prosthesis without any signs of thrombosis with normal ejection fraction. Her laboratory results on the admission day showed a platelet count of 234 × 10^9/l and an international normalized ratio (INR) of 3.52; her liver and renal functions were within the normal limits. In preparation for the left eye vitrectomy, it was decided to stop warfarin 5 days before the vitrectomy and to commence bridging therapy with fondaparinux at 7.5 mg subcutaneously once daily before surgery, considering her history of HIT in March 2014 during her hospitalization for mechanical MVR. On withdrawal of warfarin, her INR decreased to 1.38 on the day of surgery which ensured that the operation can be performed safely. The patient successfully underwent...
the left eye pars plana vitrectomy as planned after discontinuation of warfarin for 5 days and fondaparinux for 24 h. Her postoperative INR was 1.33, platelet count was 198 × 10^9/l, and hemoglobin level was 150 g/l. Fondaparinux was resumed 24 h postoperatively at 7.5 mg subcutaneously once daily. The treatment was bridged to warfarin on the 2nd postoperative day. The patient was discharged home receiving warfarin on the 3rd postoperative day. The two drugs were concomitant for 5 days until the patient’s INR was projected to be within the therapeutic range of 2.5–3.5. Her anticoagulation protocol throughout the hospitalization is shown in Table 1.

She followed up in our outpatient clinic regularly for her further management of anticoagulation. No evidence of thromboembolic events was encountered throughout the hospitalization and later. She showed neither any signs and symptoms of thrombosis nor any signs and symptoms of bleeding. The baseline hemoglobin was 142 g/l before the initiation of fondaparinux and ranged from 142 to 150 g/l for the remainder of the hospitalization. On follow-up on the postoperative day 30, the patient continued to have no evidence of thrombosis or bleeding. Due to the restriction of the assay method, fondaparinux levels by anti-Xa activity assay were not monitored during the hospitalization.

**Discussion**

UFH and LMWH are the standard of care for bridging to warfarin in patients with MVR. The safety and efficacy of UFH and LMWH as perioperative bridging have been confirmed in patients with mechanical heart valves on long-term oral anticoagulant therapy. However, the issue of perioperative anticoagulation in patients with MVR and a history of HIT remains elusive.

We report for the first time a case where fondaparinux was used as a perioperative bridging agent in a patient with MVR and a history of HIT undergoing vitreoretinal surgery for retinal detachment.

Mechanical prosthesis at the mitral position is a moderate-to-high risk for any surgery if anticoagulation has to be discontinued. Since this patient had a documented history of HIT, after reviewing the literature and going through case reports, we decided for the use of fondaparinux in this patient. Fondaparinux was started as soon as the INR fell below 2.0; it was stopped 24 h before surgery and was started immediately once the risk of intracocular bleed was less after a thorough discussion with the ophthalmology team. Warfarin was added subsequently to reach a therapeutic INR.

Two experimental investigations demonstrated the efficacy of fondaparinux in preventing thrombus formation on mechanical heart valves. The rate of thrombosis was, respectively, tested in an in vitro “thrombosis tester” and an experimental ex vivo rabbit model with similar outcomes compared to UFH and LMWH. However, there are only six case reports described the successful use of fondaparinux in patients with MVR. The characteristics of these reports are shown in Table 2.

Fondaparinux has a low propensity to form complexes with PF4 and therefore has scarce antigenic properties. Although several isolated cases raised the probability of fondaparinux inducing HIT derived from fondaparinux-dependent platelet activation, more reports suggest that it can be used safely in the case of HIT. Despite fondaparinux is not approved for the treatment of HIT, the current ACCP guidelines have recommended it as first-line therapy for the treatment of acute thrombosis (unrelated to HIT) in patients with a history of HIT. Nevertheless, large randomized clinical trials are lacking to examine the use of fondaparinux in patients with MVR.

Despite fondaparinux safe administration in our patient, there are still several arguments for using this agent as a perioperative bridging after MVR. First, the optimum perioperative dosage of fondaparinux for such patients remains to be determined. Although a therapeutic dose (7.5 mg) is recommended for patients after MVR, prophylactic regimen (2.5 mg) also has been used in some case reports in patients with a high risk of bleeding. Second, because of fondaparinux’s extended half-life, we also focused on the ideal interval of this drug surrounding the surgery. Data supporting the preoperative use of fondaparinux are limited to one study of surgical (Venous thromboembolism) VTE prophylaxis.

| Date                  | Hemoglobin (g/l) | Platelets (×10^9/l) | INR     | Warfarin | Fondaparinux |
|-----------------------|------------------|---------------------|---------|----------|--------------|
| July 26, 2017         | -                | -                   | 2.80    | Stopped  | -            |
| July 28, 2017         | 142              | 234                 | 2.2     | -        | -            |
| July 29, 2017         | -                | -                   | 1.6     | -        | 7.5 mg started|
| July 30, 2017         | -                | -                   | 1.52    | -        | 7.5 mg       |
| August 1, 2017 (day of surgery) | 145              | 213                 | 1.38    | -        | -            |
| August 3, 2017        | 150              | 198                 | 1.33    | 4 mg     | 7.5 mg       |
| August 4, 2017        | -                | -                   | 1.56    | 5 mg     | 7.5 mg       |
| August 7, 2017        | -                | -                   | 2.56    | 5 mg     | Stopped      |

INR=International normalized ratio
and two case reports. Based on the available data, we recommend that the last dose of fondaparinux should be administered no later than 24 h before surgery. Unfortunately, due to the restriction of the assay method, we did not obtain any fondaparinux-specific anti-factor Xa levels in our patient. However, for safety reasons, monitoring may have been considered before surgery and in long-term therapy.

**Conclusion**

We present a successful case of perioperative bridging with fondaparinux in a patient with MVR and a history of HIT. Fondaparinux may provide an option of bridging for such patients, but further clinical investigations are warranted to identify the role of this agent for the prophylaxis of thrombus formation in patients with MVR.

**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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**Table 2: Case reports of fondaparinux in anticoagulation after the mitral valve replacement**

| Characteristic                  | Corbett et al.[5] | Asghar and Vidovich[8] | Nagler et al.[6] | Perissinotti et al.[7] | Willenborg[9] | Wei et al.[9] |
|---------------------------------|-------------------|------------------------|------------------|------------------------|---------------|---------------|
| Position of the valve           | Aortic valve      | Aortic and mitral valves | Aortic valve     | Aortic and mitral valves | Aortic valve  | Mitral valve  |
| Concomitant with HIT            | Confirmed HIT     | Suspected HIT           | No               | Suspected HIT           | Confirmed HIT | Confirmed HIT |
| Surgery/procedure               | Haemoperitoneum evacuation | Intracranial hematemesis evacuation | NR              | AVR + MVR + TVP + CABG | AVR          | Radical resection of esophageal cancer |
| Protocol of anticoagulation     | FOND bridging to WAR | FOND bridging to WAR | FOND + ASA      | FOND + ASA bridging to WAR + ASA | FOND + ASA bridging to WAR + ASA | FOND bridging to WAR |
| Postoperative timing and dose of FOND (FOND along) | 1st day, 7.5 mg QD SC | 1st day, 2.5 mg QD SC | NA, 10 mg QD SC | 8th day, 7.5 mg QD SC | 2nd day, 2.5 mg SC then 5 days (0) | 1st day, 2.5 mg QD SC |
| Duration of treatment (FOND along) | At least 14 days (2 days) | 1 month (3 months) | 30 months (0) | 8 days (0) | 5 days (0) | 28 days (24) |
| Anti-Xa level (µg/ml)           | 0.71=1.141        | NR                     | −1.0            | 0.62=1.53             | NR            | NR            |

ASA=Acetylsalicylic acid/aspirin; AVR=Aortic valve replacement; CABG=Coronary artery bypass graft surgery; FOND=Fondaparinux; HIT=Heparin-induced thrombocytopenia; MVR=Mitral valve replacement; TVP=Tricuspid valve prostheses; WAR=Warfarin; NR = Not recorded; NA = Not available.

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