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Peer-Reviewed Case Series

Fondaparinux as an Alternative Anticoagulant Treatment in Patients with Left Ventricular Assist Devices and Recurrent Gastrointestinal Bleeding: Case Series

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Abstract

Gastrointestinal bleeding (GIB) can occur in patients after left ventricular assist device (LVAD) implantation. In cases of recurrent GIB, the management of anticoagulation treatment represents a challenging situation in which the risk of bleeding recurrence and the need for long-term anticoagulation must be balanced. This case series describes the successful management of anticoagulation in three patients with recurrent GIB using fondaparinux.

To our knowledge, these are the first reported cases of recurrent GIB in which a single dose of subcutaneous fondaparinux was used instead of oral anticoagulation. None of the patients presented with signs of pump thrombosis or arterial embolism.

If confirmed by larger studies, the substitution of oral anticoagulation with subcutaneous, single-dose fondaparinux could represent a safe alternative treatment in a select group of patients with recurrent GIB.

Background

Gastrointestinal bleeding (GIB) is a major complication after continuous-flow left ventricular assist device (LVAD) implantation. Despite the technological innovations of more recent devices, GIB still occurs in almost 25% of patients.[1] Its multifactorial etiology includes anticoagulation therapy, development of vascular malformations from an LVAD's continuous flow function, and acquired Von Willebrand factor deficiency. In about 30% of cases, the location of the bleeding is not diagnosed, and the GIB is attributed to vascular malformations at the level of the ileum and jejunum.[2] It has been reported that after a GIB episode, about 40% of patients with an LVAD experience relapsing episodes (recurrent GIB).[3] In this subset of patients, management of the anticoagulation treatment represents a challenge for the clinician, who must balance the risk of recurrent GIB and the need for long-term anticoagulation. We describe the successful management of anticoagulation in three patients with refractory GIB using fondaparinux.

Fondaparinux can be administered via subcutaneous or intravenous routes. The bioavailability is 100% after subcutaneous administration, and the mean maximum plasma concentration is achieved at 1.7 h. The long half-life of 17.2 h allows for once-daily dosing.[4] When compared to low molecular weight heparins, fondaparinux sodium has no effect on fibrinolytic activity or bleeding time, thereby promoting hemostasis with a favorable bleeding risk profile. Fondaparinux does not bind to or interact with other plasma proteins or cellular elements, such as platelets or platelet factor 4; therefore, it does not cause heparin-induced, thrombocytopenia-like syndrome.[5]

Institutional Experience

At our institution, 82 patients underwent surgical intervention for advanced heart failure from 2009 to 2021. Of these 82 patients, 71 underwent LVAD implantation (51% as a bridge to transplantation with a mean follow-up of 2 years), and 11 patients underwent biventricular VAD implantation (all of them as a bridge to transplantation). Our anticoagulation protocol is based on the type of device implanted and the presence of concomitant atrial fibrillation (AF). Patients with a Jarvik 2000 (Jarvik Heart, Inc., New York, NY) are discharged with warfarin only (International Normalized Ratio [INR] target of 1.8-2.2 if AF is not present or 2.0-2.5 with concomitant AF). Patients with a HeartWare VAD (HVAD, Medtronic, Minneapolis, MN) or a HeartMate3 (Abbott Laboratories, Chicago, IL) are discharged with warfarin (INR target of 2.0-3.0) and aspirin titrated on an ASPItest.

Of the 71 patients implanted with an LVAD, 12 (17%) experienced GIB. Aspirin therapy was discontinued, and all patients underwent a colonoscopy and esophagogastroduodenoscopy (EGD) to treat any identified lesions. Oral anticoagulation treatment was tailored to achieve INR values between 1.5 and 2.0 in 55% of cases and was discontinued, in favor of enoxaparine 100 IU/kg twice/day, in the remaining 45%. Oral anticoagulation was resumed when hemoglobin levels

remained stable for at least one week. Subcutaneous, low-molecular-weight heparin was administered when the INR was lower than 1.5.

Among patients who experienced GIB, 3 (40%) were affected by relapsing episodes of bleeding and were effectively treated using fondaparinux.

Case Report

Case One

A 76-year-old male received a Jarvik 2000 LVAD for ischemic cardiomyopathy. The patient was discharged on the following medical regimen: aspirin (100 mg/day) and warfarin (5mg/day) with an INR target between 1.8 and 2.2. Three months after device implantation, the patient was readmitted because of severe anemia that required blood transfusions. Despite positive fecal occult blood (FOB) tests, the EGD and colonoscopy were unable to detect the source of bleeding. Antiaggregant treatment was suspended, and a strict follow-up with weekly control of hemoglobin (Hb) levels was planned. In the following year, the Hb levels continued to decrease, and FOB tests were persistently positive. At 1-year post-implantation, the patient was readmitted. Since the EGD confirmed the absence of bleeding sites, we assumed that the GIB could be the consequence of a small bowel vascular malformation. Treatment with octreotide (0.1 mg/three times per day) and propranolol (40 mg/twice per day) was started to induce splanchnic vascular constriction and down signaling of the vascular endothelial growth factor pathway. However, due to the persistent anemia, we suspended oral anticoagulation after 4 months of treatment and started fondaparinux (2.5 mg/day). This treatment was controlled with anti-X coagulation factor (Xa) activity dosage (targeting levels between 0.6 and 1.0 IU/ml and eventually modified two years later when the patient suffered a second transient ischemic attack). During the follow-up, the patient suffered from 2 episodes of transient ischemic attack for which we safely augmented fondaparinux to 5 mg/day with an anti-Xa activity of 1.8 U/mL. At the one-year follow-up, a computed tomography scan showed no signs of pump or outflow thrombosis, and levels of device consumption remained stable. At four years of follow-up, no new GIB or pump thrombosis events occurred.

Case Two

A 74-year-old male was implanted with a Jarvik 2000 LVAD for ischemic cardiomyopathy. Due to the presence of concomitant AF, he was discharged on warfarin (5mg/day) with an INR goal of 2.0-2.5. In the first year following device implantation, the patient was readmitted to the hospital three times for severe anemia and positive FOB tests. Both EGD and colonoscopy were negative for bleeding, and the attempts at medical treatment with octreotide (0.1 mg/three times per day), propranolol (40 mg/twice per day), and intermittent suspension of warfarin failed. Therefore, we decided to withhold warfarin and start treatment with

fondaparinux (2.5 mg/day), ensuring an anti-Xa assay of 0.6-1.0 U/mL. After this therapeutic modification, the patient was readmitted two more times. The first readmission was for anemia caused by iron depletion, and the second one was for GIB relapse (2 years after device implantation). However, in the two years following the relapse, the patient remained stable with no signs of pump thrombosis or anemia.

Case Three

A 64-year-old male was implanted with an HVAD for ischemic cardiomyopathy as a bridge to heart transplantation. His postoperative course was characterized by a single episode of melena. The patient was discharged on warfarin (5mg/day; target INR of 2.0-3.0) and aspirin (100 mg/day). He was readmitted for GIB 11 months after discharge. EGD and colonoscopy were negative for bleeding. A contrast computed tomography scan revealed a bleeding focus at the ileum level, and an attempt at arterial embolization was ineffective. Aspirin and warfarin therapy was promptly suspended, and treatment with fondaparinux (2.5 mg/day) and octreotide (0.1 mg/three times a day) was started. During the one-year follow-up appointment, the fondaparinux dosage was increased to 5 mg/day to reach the target anti-Xa level. At the 2-year follow-up, the patient showed no signs of hemolysis or VAD thrombosis.

Discussion

The 2013 International Society for Heart and Lung Transplantation guidelines on mechanical circulatory support provide several recommendations for the management of GIB in patients with LVADs.[6] These include cessation of anticoagulant/antiaggregant therapy until bleeding resolves and resumption of antiplatelet and anticoagulation therapy after resolution of the first episode of GIB. For recurrent GIB without a source or with a source not amenable to treatment, it is recommended that the dose, intensity, or even the use of antiplatelet drugs or warfarin should be re-evaluated.[6] The updated 2019 guidelines note that reducing the LVAD speed to induce pulsatility may decrease GIB risk.[7] In this series, all the patients exhibited well-defined arterial pulsatility at discharge and during GIB episodes; thus, pump speed levels remained unchanged.

Pharmacological adjunctive therapies aim to induce splanchnic vascular constriction (octreotide[8]) and downregulate the vascular endothelial growth factor signaling that leads to arteriovenous malformations (ACE-Inhibitors,[9] beta-blockers,[10] and inhaled desmopressin[11]). Our institutional policy utilizes such pharmacological treatment after GIB whenever possible. However, in the case of recurrence of GIB, suspension of oral anticoagulant treatment is to be considered.

In this case series, two patients were implanted with the Jarvik 2000, and one patient received an HVAD. It has been reported that the axial flow, compared to the centrifugal flow, is responsible for greater shear stress that results in a reduction of platelet count.[12] Thus, patients with Jarvik 2000s may be less affected by device thrombosis with sub-therapeutic INR levels or after suspension of aspirin when compared to patients with the HVAD that was associated with a hypercoagulable state.[12] Given the limited number of patients, no decisive conclusions can be drawn.

The management of anticoagulation in patients with LVADs and recurrent GIB requires a balance between the thromboembolic and hemorrhagic risks. Different anticoagulation protocols have been proposed, including the use of enoxaparin[13] and dabigatran.[14] However, a randomized controlled trial showed an excess of thromboembolic events in dabigatran-treated patients when compared to anti-vitamin K-treated patients.[15] Fondaparinux has been used in patients with LVADs with heparin-induced thrombocytopenia;[16] it is rapidly and completely absorbed after subcutaneous administration and is distributed mainly in the blood. Furthermore, fondaparinux's activity can be monitored with an anti-Xa assay. A meta-analysis of seven studies (mainly enrolling patients affected by acute myocardial infarction) compared enoxaparin with fondaparinux and showed similar rates of mortality and major cardiovascular complications.[17] However, at the midterm follow-up, major, minor and total bleeding were significantly lower with fondaparinux when compared to enoxaparin (OR: 0.50, 95% CI: 0.28–0.89; P = 0.02, OR: 0.51, 95% CI: 0.31–0.84; P = 0.009 and OR: 0.48, 95% CI: 0.34–0.69; P = 0.0001, respectively).[17] This finding may explain why fondaparinux proved to be effective in our patients, where the selective action on factor X and the lower impact on other coagulation components may have prevented the recurrence of gastrointestinal hemorrhage.

To our knowledge, these are the first reported cases of long-term follow-up of recurrent GIB managed by withholding oral anticoagulation and administering a single dose of subcutaneous fondaparinux, with a target anti-Xa activity range of 0.6-1.0 U/mL. Only Patient 2 presented with relapses of anemization after initiation of fondaparinux treatment with the first relapse correlated to iron deficiency. None of the patients presented with signs of pump thrombosis.

Conclusion

Based on our experience, the substitution of oral anticoagulation with subcutaneous single-dose fondaparinux could be an alternative treatment in a select group of patients with recurrent GIB, where no clinical foci of bleeding are found and other medical options have failed.

In these high-risk patients, it is mandatory to monitor kidney function and routinely test the efficacy of this innovative approach by evaluating anti-Xa activity levels in order to titrate the drug dose and prevent possible side effects.

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