Journal of Artificial Organs (2019) 22:334–337
https://doi.org/10.1007/s10047-019-01121-7

CASE REPORT

Artificial Heart (Clinical)

Experience of the use of octreotide for refractory gastrointestinal bleeding in a patient with Jarvik2000® left ventricular assist device

Seiko Nakajima-Doi[1] · Osamu Seguchi[1] · Yasuhiro Shintani[2] · Tomoyuki Fujita[3] · Satsuki Fukushima[3] · Yorihiko Matsumoto[3] · Yuka Eura[4] · Koichi Kokame[4] · Shigeki Miyata[5] · Sachi Matsuda[6] · Hiroki Mochizuki[1] · Keiichiro Iwasaki[1] · Yuki Kimura[1] · Koichi Toda[1] · Yuto Kumai[1] · Kensuke Kuroda[1] · Takuya Watanabe[1] · Masanobu Yanase[1] · Junjiro Kobayashi[2] · Norihide Fukushima[1]

Received: 5 January 2019 / Accepted: 16 July 2019 / Published online: 23 July 2019

Abstract

Gastrointestinal bleeding (GIB) is among the major complications affecting implantable continuous-flow left ventricular assist device (iLVAD) recipients and is the major cause of re-hospitalization. GIB in iLVAD recipients is sometimes critical, and controlling bleeding using conventional approaches is difficult. A 35-year-old woman developed refractory GIB from multiple gastric polyps and de novo angiodysplasia after Jarvik2000® iLVAD implantation. Discontinuation of anticoagulation and antiplatelet therapies had little effect on GIB; thus, multiple endoscopic hemostatic therapies were performed. However, bleeding recurred several times, and red blood cell (RBC) transfusion in large volumes was required for progressive anemia. Furthermore, the von Willebrand factor (VWF) multimer analysis revealed loss of the high-molecular weight multimer, which may have resulted from the high-speed rotation of the axial-flow LVAD pump. To supplement VWF, cryoprecipitate was administered, but it was effective for only several days. Finally, the patient was treated with octreotide, a somatostatin analog, on post-operative day 58. After starting octreotide, tarry stool gradually decreased, and progression of anemia slowed down within the first 14 days of treatment; thus, the total RBC transfusion volume was reduced without additional hemostatic interventions, including cryoprecipitate administration. The patient developed mediastinitis on post-operative day 68 and died of sepsis on post-operative day 72. There was no adverse effect associated with octreotide use. Although the observation period was short, octreotide appears to be useful for resolving recurrent GIB after iLVAD implantation and reducing blood transfusions.

Keywords Octreotide · Gastrointestinal bleeding · Angiodysplasia · Acquired von Willebrand syndrome · Ventricular assist device

✉ Norihide Fukushima
nori@ncvc.go.jp

[1] Department of Transplant Medicine, National Cerebral and Cardiovascular Center, 6-1 Kishibe Shin-machi, Suita 564-8565, Osaka, Japan

[2] Department of Cardiovascular Medicine, National Cerebral and Cardiovascular Center, Suita, Japan

[3] Department of Adult Cardiac Surgery, National Cerebral and Cardiovascular Center, Suita, Japan

[4] Department of Molecular Pathogenesis, National Cerebral and Cardiovascular Center, Suita, Japan

[5] Department of Transfusion Medicine, National Cerebral and Cardiovascular Center, Suita, Japan

[6] Department of Pharmacy, National Cerebral and Cardiovascular Center, Suita, Japan

Introduction

Implantable continuous-flow left ventricular assist device (iLVAD) therapy plays an important role in advanced heart failure patients as a bridge to transplantation in Japan. Recently, the number of iLVAD recipients has been rapidly increasing [1], and their ideal clinical management is always pursued. The INTERMACS annual report and previous retrospective studies from western countries have demonstrated that gastrointestinal bleeding (GIB) is among the major complications affecting > 15% of iLVAD recipients and is the major cause of re-hospitalization [2, 3]. Many factors may contribute to iLVAD-related GIB development, with acquired von Willebrand syndrome (AVWS) being among these factors [4]. Moreover, recently, gastrointestinal angiodysplasia has been reported to be a common source of bleeding in iLVAD recipients [5].

iLVAD-related GIB prevalence in clinical setting is not common in Japan compared to that in western countries [1]. However, GIB in iLVAD recipients is sometimes critical, since they have to undergo antiplatelet and anticoagulation therapies to prevent iLVAD-related thromboembolic events, and controlling bleeding using conventional approaches is difficult. Therefore, novel therapeutic strategies other than cessation of antiplatelet and anticoagulation therapies, reversal of anticoagulation therapy, and endoscopic procedures are needed.

We herein present a case of refractory GIB from multiple gastric polyps with angiodysplasia in a patient with Jarvik2000® LVAD (Jarvik Heart, Inc., New York, USA) who had been successfully treated with subcutaneous administration of octreotide, a somatostatin analog.

Case report

A 35-year-old woman with a history of malignant lymphoma treated with chemotherapy and radiotherapy, and of bioprosthetic mitral valve replacement for mitral valve regurgitation was referred to our institution for advanced heart failure. Echocardiography showed severe bilateral ventricular dysfunction and coexisting bioprosthetic mitral valve dysfunction and tricuspid regurgitation; thus, both mechanical mitral valve replacement and tricuspid annuloplasty were performed. However, the patient could not be weaned from inotropes, and she underwent biventricular assist device implantation concomitant with tricuspid valve replacement and aortic valvuloplasty as a bridge to transplantation. The Jarvik2000 adjusted for 10,000 rounds/min and extracorporeal membrane oxygenation system followed by durable Nipro-TOYOBO paracorporeal VAD (Nipro; Osaka, Japan) were used for left and right ventricular support, respectively. Despite these complicated surgical approaches, she developed renal failure requiring continuous hemodialysis and suffered from respiratory failure requiring a tracheostomy with ventilator.

The patient had no sign of GIB before VAD implantation, although endoscopic evaluation had revealed multiple gastric polyps without any bleeding. Continuous infusion of unfractionated heparin was started on post-operative day (POD) 2 after VAD implantation, and oral anticoagulation and antiplatelet therapies had not been introduced because of the patient's critical condition. However, she suddenly developed hematemesis and tarry stool with progression of anemia on POD 17. Emergent endoscopy revealed presence of blood oozing around the polyps. Blood coagulation data at that time were as follows: prothrombin time-international normalized ratio (PT-INR) of 1.39, activated partial thromboplastin time (APTT) of 68 s, and platelet count of $11.5 \times 10^4/\mu L$. Although she had not received warfarin, mild PT-INR prolongation was observed, suggestive of liver dysfunction due to surgical invasiveness or prolonged preoperative hepatic congestion. Furthermore, the von Willebrand factor (VWF) multimer analysis showed the severe loss of large molecular weight multimers (Fig. 1a) with the VWF large multimer index (LMI) [6] of 18%, which may have resulted from AVWS caused by high-speed rotation of the LVAD pump. Then, heparin infusion was discontinued, and APTT was shortened to approximately 40 s. Although cryoprecipitate was repeatedly administered in addition to three times of endoscopic hemostasis, this had a limited and short-term effect for controlling bleeding. Ninety-eight units of red blood cell (RBC) have been transfused by POD 47 after VAD implantation.

During repeated endoscopic examinations, angiodysplasia was identified as the etiology of GIB (Fig. 2); therefore, octreotide (100 μg subcutaneous twice a day) was administered on POD 58. Then, the tarry stool gradually disappeared, and the progression of anemia also slowed down. The total RBC transfusion volume was reduced to 6 U in 14 days without additional hemostatic interventions including cryoprecipitate administration. There was no adverse effect, such as bradycardia, anaphylaxis, or digestive symptoms, accompanying octreotide. Although the LVAD was set at a constant speed of 10,000 rpm, VWF multimer analysis at 13 days after starting octreotide revealed a partial recovery of large molecular weight multimers (LMI, 31%) (Fig. 1c). Octreotide was effective for refractory GIB, but the patient developed mediastinitis on POD 68 and died of sepsis on POD 72.

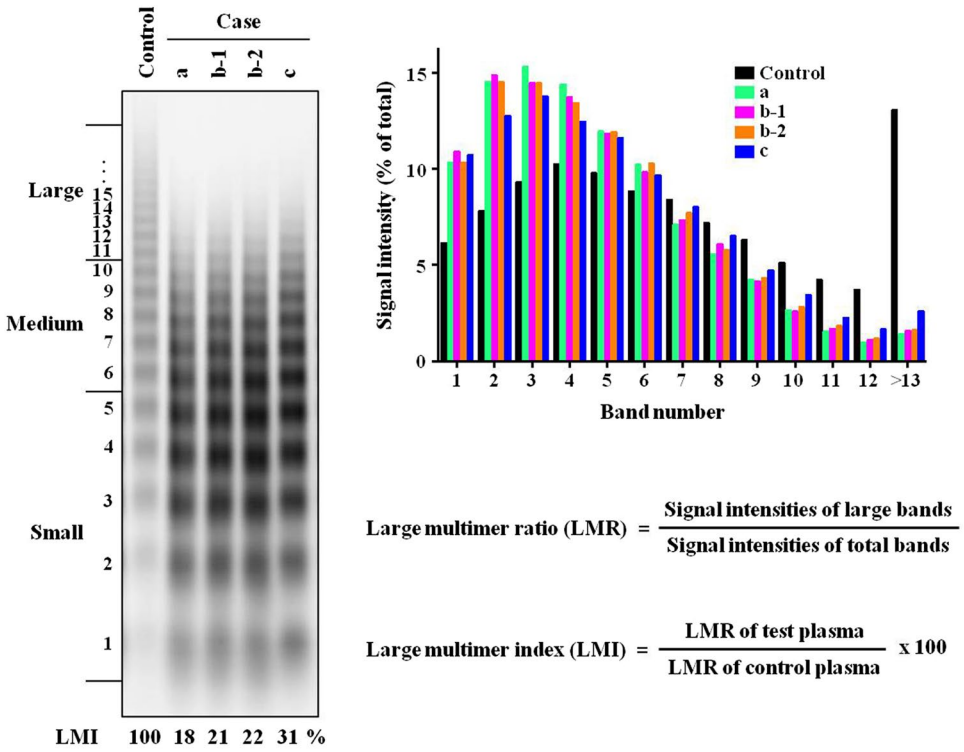

Fig. 1 Blot image of von Willebrand factor (VWF) multimer analysis and calculations of large multimer index (LMI). The LMI values of the patient at each stage (a–c) were calculated from the signal intensities of the VWF multimer bands, as previously described [10]. LMI indicated severe reduction of large-molecular weight multimers; 18% on post-operative day (POD) 27 (a), 21% on POD 71 (pre-cryoprecipitate administration) (b-1), 23% on POD 71 (post-cryoprecipitate administration, before octreotide introduction) (b-2), and 31% on the 14th day after octreotide introduction (c)

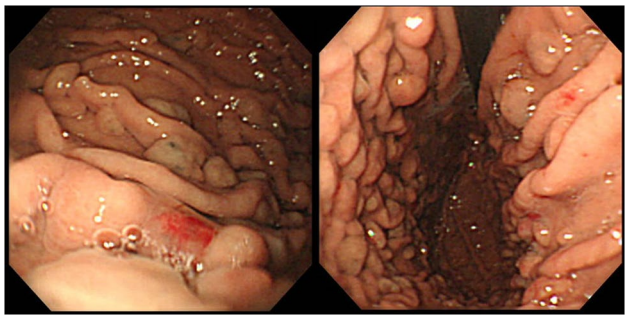

Fig. 2 The result of upper endoscopy performed on POD 41 showing multiple polyps and angiodysplasia around the gastric corpus mucosa

Discussion

Our patient with biventricular support including axial-flow LVAD, Jarvik2000®, developed refractory GIB. Despite cessation of anticoagulation therapy, and multiple endoscopic interventions, she still developed recurrent GIB, and large amount of RBC was transfused for progressive anemia. Cryoprecipitate administration to supply coagulation factors, including VWF, had only a limited short-term effect on GIB, which could only slow down the transfusion frequency. Therefore, octreotide was used to treat GIB by stabilizing the altered angiogenesis, resulting in amelioration of tarry stool and marked reduction in RBC transfusion volume.

Historically, bleeding is among the major complications occurring in LVAD patients. Various non-surgical bleeding mechanisms, such as AVWS, have been presented for second-generation LVADs driven by continuous-flow pumps. More recently, angiodysplasia has attracted attention as the etiology of GIB, and specific intracellular signals have been reported to be associated with altered angiogenesis. It is thought that elevated tumor necrosis factor-α (TNF-α) in LVAD recipients is a central regulatory mechanism of altered angiogenesis, inducing endothelial tissue factor and endothelial angiopoietin-2 (Ang-2) expressions and generating thrombin. TNF-α and Ang-2 promote endothelial proliferation. Contrarily, TNF-α also induces pericyte apoptosis, leading to decreased Ang-1 expression and endothelial destabilization. This mechanism may contribute to the development of angiodysplasia [7]. In this case, the preexisting gastric polyps and de novo gastric angiodysplasia were origins of GIB, and the presence of AVWS must have exacerbated the bleeding. Despite her critical condition after iLVAD implantation, there might be no direct relationship between GIB and multiple organ failure and infection. The laboratory data obtained before her death still did not fulfil the diagnostic criteria of disseminated intravascular coagulation, and no obvious bleeding symptoms were observed in the other organs.

Regarding treatments, there has been no specific therapeutic option for GIB other than cessation or reversal of antithrombotic therapy and conventional endoscopic interventions. However, recently, there have been several reports

showing the effectiveness and safety of octreotide, a somatostatin analog, on iLVAD-related GIB [8, 9], and it is becoming widely used as a secondary prophylaxis for GIB. Octreotide is also used in domestic facilities for esophageal varices, peptic ulcers, and tumor bleeding; however, its use for GIB is not currently approved in Japan.

The pharmacological mechanism of octreotide's effect on GIB has not been fully elucidated. Octreotide is proposed to produce vasoconstriction of the splanchnic artery, decrease splanchnic blood flow, and inhibit angiogenesis at the bleeding site by suppressing secretion of various growth factors, which may contribute to the control of angiodysplasia-related GIB [10]. Moreover, octreotide has been reported to improve platelet aggregation and has been used in patients with von Willebrand disease (VWD) [11]. Although its mechanism of action for VWD is unknown, the patients displayed an increase in baseline VWF while being treated with octreotide. In fact, in our case, the LMI increased from 18 to 31% after starting octreotide, but it was still low; thus, we should still be very careful to ensure that the LMI will sufficiently recover by the effect of octreotide.

Our patient died 2 weeks after starting octreotide; thus, only the short-term effect of octreotide on GIB was evaluated. However, it is certain that the tarry stools were reduced and the frequency of RBC transfusion dramatically decreased after starting octreotide. Furthermore, it is unlikely that octreotide exacerbated the infection, considering the action mechanism of the drug. The patient's general condition had already been poor and compromised when octreotide was started.

Treatment of recurrent GIB in patients with iLVAD implantation is essential for preventing re-hospitalization, reducing blood transfusions, improving prognosis and quality of life, and improving cost-effectiveness of LVAD therapy. Moreover, patients undergoing a large amount of transfusion can develop anti-human leukocyte antigen antibodies, which could have negative effects on donor-recipient matching during heart transplantation. Finally, the destination therapy will be approved in Japan at an early date, and it is expected that the number of patients with GIB will increase as the iLVAD population ages. Octreotide will be a promising treatment for refractory GIB, but we should carefully select the cases and increase our experience in the use of octreotide from now on.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

References

1. Nakatani T, Sase K, Oshiyama H, Akiyama M, Horie M, Nawata K, Nishinaka T, Tanoue Y, Toda K, Tozawa M, Yamazaki S, Yanase M, Ohtsu H, Ishida M, Hiramatsu A, Ishii K, Kitamura S, J-MACS investigators. Japanese registry for mechanically assisted circulatory support: first report. J Heart Lung Transplant. 2017;36:1087–96.
2. Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, Myers SL, Miller MA, Baldwin JT, Young JB. Seventh INTERMACS annual report: 15,000 patients and counting. J Heart Lung Transplant. 2015;34:1495–504.
3. Mehra MR, Naka Y, Uriel N, Goldstein DJ, Cleveland JC Jr, Colombo PC, Walsh MN, Milano CA, Patel CB, Jorde UP, Pagani FD, Aaronson KD, Dean DA, McCants K, Itoh A, Ewald GA, Horstmanshof D, Long JW, Salerno C, MOMENTUM 3 Investigators. A fully magnetically levitated circulatory pump for advanced heart failure. N Eng J Med. 2017;376:440–50.
4. Uriel N, Pak SW, Jorde UP, Jude B, Susen S, Vincentelli A, Ennezat PV, Cappleman S, Naka Y, Mancini D. Acquired von Willebrand syndrome after continuous-flow mechanical device support contributes to a high prevalence of bleeding during long-term support and at the time of transplantation. J Am Coll Cardiol. 2010;56:1207–13.
5. Eckman PM, John R. Bleeding and thrombosis in patients with continuous-flow ventricular assist devices. Circulation. 2012;125:3038–47.
6. Tamura T, Horiuchi H, Imai M, Tada T, Shiomi H, Kuroda M, Nishimura S, Takahashi Y, Yoshikawa Y, Tsujimura A, Amano M, Hayama Y, Imamura S, Onishi N, Tamaki Y, Enomoto S, Miyake M, Kondo H, Kaitani K, Izumi C, Kimura T, Nakagawa Y. Unexpectedly high prevalence of acquired von Willebrand syndrome in patients with severe aortic stenosis as evaluated with a novel large multimer index. J Atheroscler Thromb. 2015;22:1115–23.
7. Tabit CE, Coplan MJ, Chen P, Jeevanandam V, Uriel N, Liao JK. Tumor necrosis factor-α levels and non-surgical bleeding in continuous-flow left ventricular asist devices. J Heart Lung Transplant. 2018;37:107–15.
8. Shah KB, Gunda S, Emani S, Kanwar MK, Uriel N, Colombo PC, Uber PA, Sears ML, Chuang J, Farrar DJ, Brophy DF, Smallfield GB. Multicenter evaluation of octreotide as secondary prophylaxis in patients with left ventricular assist devices and gastrointestinal bleeding. Circ Heart Fail. 2017;10:e004500.
9. Malhotra R, Shah KB, Chawla R, Pedram S, Smallfield MC, Priday AG, DeWilde CT, Brophy DF. Tolerability and biological effects of long-acting octreotide in patients with continuous flow left ventricular assist devices. ASAIO J. 2017;63:367–70.
10. Sieg AC, Moretz JD, Horn E, Jennings DL. Pharmacotherapeutic management of gastrointestinal bleeding in patients with continuous-flow left ventricular assist devices. Pharmacology. 2017;37:1432–48.
11. Bowers M, McNulty O, Mayne E. Octreotide in the treatment of gastrointestinal bleeding caused by angiodysplasia in two patients with von Willebrand's disease. Br J Haematol. 2000;108:524–7.