Long-acting Octreotide Reduces the Recurrence of Gastrointestinal Bleeding in Patients with a Continuous-Flow Left Ventricular Assist Device

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Abstract

Background—Recurrent gastrointestinal bleeding is one of the most significant adverse events in patients with left ventricular assist devices (LVAD).

Methods—We enrolled LVAD patients who had received an intramuscular injection of 20 mg of octreotide LR every 4 weeks as secondary prevention for recurrent gastrointestinal bleeding despite conventional medical therapies and repeated transfusions. The frequency of gastrointestinal bleeding and other associated clinical outcomes before and during octreotide therapy were compared.
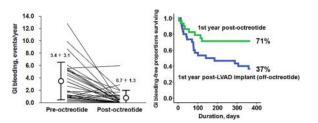
Results—Thirty LVAD patients (66.4 ± 8.8 years old and 16 male [53%]) received octreotide therapy for 498.8 ± 356.0 days without any octreotide-associated adverse events. The frequency of gastrointestinal bleeding was decreased significantly during octreotide therapy (from 3.4 ± 3.1 to 0.7 ± 1.3 events/year, p <0.001), accompanied by significant reductions in red blood cell and flesh frozen plasma transfusions, days in hospital, and need for endoscopic procedures (p <0.05 for all).

Conclusions—Octreotide therapy reduced the frequency of recurrent gastrointestinal bleeding and may be considered for secondary prevention.

Graphical abstract

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INTRODUCTION

Left ventricular assist device (LVAD) therapy has improved long-term survival rates in patients with stage D heart failure,[1, 2] but gastrointestinal (GI) bleeding remains a significant adverse effect and a major cause of readmissions following LVAD implantation.[3, 4] GI bleeding occurs more frequently with continuous-flow devices than the previous pulsatile devices.[5–7] The site of bleeding varies among each patient and occurs similarly from both upper and lower GI sources.[8]

Several factors are believed to contribute to GI bleeding. Originally, acquired von Willebrand disease, characterized by low levels of high molecular weight von Willebrand factor[7], was thought to be induced by continuous-flow LVADs and linked to the high GI bleeding rate. However, our understanding today has shifted to the concept that GI arteriovenous malformations (AVMs)[3] render patients susceptible to bleeding, particularly in the context of required continuous antiplatelet and anticoagulant therapy.[9] We demonstrated recently that thrombin-induced angiopoietin-2 expression in LVAD patients leads to increased angiogenesis *in vitro* which may contribute to AVM formation *in vivo*.[10]

Conservative therapies for GI bleeding include temporary discontinuation of anticoagulant and antiplatelet therapy, intravenous administration of proton pump inhibitors, invasive endoscopic cauterization[3] and, only in extreme cases, administration of vitamin K and/or flesh frozen plasma (FFP). These latter strategies should be used cautiously to prevent acute pump thrombosis. GI bleeding refractory to the aforementioned therapies is often encountered in the real-world setting.[4]

In non-LVAD patients, octreotide, a somatostatin analog, has been used to manage recurrent GI bleeding particularly due to vascular malformations.[11] Favorable effects of octreotide have been reported in a small number of case reports and in a phase I study in LVAD patients.[12–16] However, these previous studies were underpowered to statistically assess the efficacy of octreotide. In this study, we describe the clinical effects of octreotide therapy in a moderate-sized cohort of continuous-flow LVAD patients with refractory GI bleeding.

METHODS

Patient selection

Patients with continuous-flow LVADs who were hospitalized for treatment of GI bleeding refractory to conventional therapies were enrolled in the octreotide clinic. GI bleeding was defined per INTERMACS as any clinically suspected or documented bleeding from the GI tract as indicated by a new drop in hemoglobin and/or the appearance of melena, hematochezia, hematemesis, or guaiac-positive stool. Validity of the definition of GI bleeding was confirmed by two independent researchers for all events.

All patients received standard guideline-directed medical therapy for LVADs including antiplatelet therapy, proton pump inhibitor, and warfarin with dosing to achieve an international normalized ratio (INR) between 2.0 and 3.0 for HVAD LVAD and between 2.0–2.5 for HeartMate II LVAD, unless recurrent GI bleeding occurred.[17] Patients were followed until death, transplant or LVAD explant for any other reason.

Management of GI bleeding

When patients were admitted to the hospital due to GI bleeding, anticoagulants and antiplatelet agents were discontinued. Transfusions of red blood cells (RBC) were performed to a minimum target hemoglobin level of 7.0 g/dL or 8.0 g/dL per the physician's discretion. Vitamin K and/or FFP were considered when continued bleeding was present in the context of an elevated INR. All patients received proton pump inhibitor therapy by intravenous infusion. Invasive upper and/or lower endoscopy was performed in most cases, along with capsule endoscopy, push eneteroscopy and mesenteric angiography when needed.

After active GI bleeding resolved, anticoagulation was reintroduced using the previous INR target, which is device-dependent. Antiplatelet therapy was typically held or reintroduced at a reduced dose. With repeat bleeding, the INR target could be reduced or warfarin could be discontinued at the discretion of each patient's physician. Octreotide therapy was considered when GI bleeding was refractory to these modifications. Patients received an intramuscular injection of 20 mg of octreotide LR every four weeks for secondary prevention of GI bleeding after insurance approval. Medical costs were covered by insurance and all octreotide therapy was administered in the outpatient clinic. During octreotide therapy, antiplatelet and anticoagulation therapies were managed similar to the pre-octreotide period, with individual variation based on patient risk.

Variables evaluated

All variables including baseline characteristics were obtained from the electronic medical record. The main endpoint of this study was the number of GI bleeding events encountered during the study period. Also, we recorded the type and number of infused blood products and the number of GI procedures during the overall observational period, including both hospitalizations and the ambulatory setting.

The percent of days on LVAD support with any aspirin administration and the percent of days with INR >2.0 were calculated during the pre- and post-octreotide periods in each

patient. The aspirin dose, LVAD speed, and hemoglobin levels were averaged during the pre- and post-octreotide periods in each patient.

Statistical analyses

Statistical analysis was performed using SPSS Statistics 22 (SPSS Inc, Chicago, IL, USA). Two-tailed p-value under 0.05 was considered as statistical significant. Data were expressed as mean ± SD unless otherwise indicated. Continuous parameters obtained before and during octreotide therapy were compared by using the Wilcoxon signed-rank test. Categorical parameters obtrained before and during octreotide therapy were compared by using McNemar's test. Comparisons of background characteristics stratified by the occurrence of GI bleeding were performed by using an unpaired t-test or Mann–Whitney U test for continuous variables and chi-square test or Fisher's exact test for categorical variables. Prognostic impact of octreotide was assessed by Kaplan-Meier analysis and compared by Mantel-Cox test.

RESULTS

Baseline Characteristics

Thirty LVAD patients (20 HeartMate II, 9 HVAD, and 1 HeartAssist 5) were enrolled (Table 1). Patients were 66.4 ± 8.8 years old and 16 (53%) were male. The majority of patients were implanted as destination therapy (83%) and 14 (47%) had an ischemic etiology of their cardiomyopathy. Patients were followed for 1243.8 ± 787.6 days following LVAD implantation. The duration between the time of LVAD implantation and octreotide initiation was 745.0 ± 728.9 (42–2613) days. Patients continued octreotide therapy for 498.8 ± 356.0 days without any complications associated with its use. There was no discontinuation of octreotide during the study period.

Changes in medications and LVAD speed between the pre- and post-octreotide therapy periods are summarized in Table 2. The percent of days with INR >2.0 was significantly increased after octreotide initiation (p = 0.003). Mean aspirin dose and percent of days with any aspirin administration were comparable. Mean LVAD speeds remained unchanged.

GI bleeding events

Prior to octreotide initiation, patients had an average of 3.0 ± 2.4 GI bleeding events, for a total of 91 GI bleeding events (3.4 ± 3.1 events/year; median 2.3 event/year). Mean time from device implantation to the first event was 419.9 ± 544.8 days (median 163; IQR, 44– 694).

Following octreotide initiation, only 13 patients (43%) experienced GI bleeding events (for a total of 23 events). Time from octreotide initiation to the first GI bleeding event was 257.9 ± 305.9 days (median 114; IQR 31–400 days). Seventeen patients (57%) were free from GI bleeding for an average follow-up time of 466.6 ± 367.5 days (median 334 days; IQR, 169– 757 days).

The frequency of GI bleeding decreased significantly during octreotide therapy to 0.7 ± 1.3 events/year (p <0.001; Figure 1), leading to a higher 1-year event-free rate during octreotide therapy compared to the pre-octreotide period (Figure 2; 71% vs. 37%, p = 0.019).

Among 25 patients who continued octreotide therapy for over 6 months, 18 patients (72%) were free from GI bleeding during 6-month octreotide therapy. There was no significant difference in background characteristics between those with and those without GI bleeding during octreotide therapy, including age, co-morbidities, frequency of prior GI bleeding, and concomitant therapy at the time of octreotide initiation (Supplementary Table 1).

Clinical outcomes associating with GI bleeding

There was a significant reduction in blood product utilization following octreotide initiation (Table 3; p <0.05 for all). There was also a significant reduction in the use of GI procedures following octreotide initiation (p <0.05). The mean hemoglobin level increased significantly in the post-octreotide period compared with the pre-octreotide period (9.82 ± 0.83 vs. 9.24 ± 0.84 g/dL, p = 0.006).

There were 63 endoscopic procedures before octreotide therapy, and 18 endoscopic procedures following octreotide initiation. The endoscopic results before and after octreotide therapy are summarized in Table 4. AVMs were identified during endoscopy 44% of the time prior to octreotide therapy, and 28% of the time following octreotide therapy. The bleeding source was less frequently identified following octreotide therapy (p = 0.03), and fewer invasive therapies were performed during endoscopy following octreotide therapy (p = 0.047).

The overall survival rate following octreotide therapy was 78% at 1 year and 73% at 2 years. Eleven patients (35%) died during the study period. The leading cause of death was heart failure (seven patients) followed by device thrombosis (three patients) and one patient due to sepsis.

DISCUSSION

In this prospective study, we investigated the impact of octreotide therapy for the secondary prevention of GI bleeding in patients with continuous-flow LVADs. Our main findings are: 1) Tthere was a significant reduction in the frequency of GI bleeding during octreotide therapy without any associated complications despite unchanged antiplatelet therapy and increase in the levels of anticoagulation therapy, 2) There was a significant reduction in blood product utilization during octreotide therapy, and an increase in the hemoglobin level following octreotide initiation, 3) There was a significant reduction in GI procedures as well as invasive therapies during octreotide therapy.

Management of recurrent GI bleeding

Although several agents have been purported to reduce the frequency of GI bleeding in patients with recurrent GI bleeding episodes, there are no definitive studies to guide their use. Medical therapies that may act directly or indirectly to inhibit angiogenesis and

generation of immature vascular networks in the GI tract, including hormone therapy and thalidomide, have been investigated.[18, 19]

Some investigators have suggested that a reduction of LVAD speed to promote aortic valve opening and enhance arterial pulsatility may be effective to reduce GI bleeding.[17] However, a recent study of a partial ventricular support device, in which pulse pressure was fully preserved, reported a relatively high rate of non-surgical GI bleeding and epistaxis.[20] This observation raises questions about the association of diminished pulsatility with the generation of AVMs and increased bleeding risk.

Long-term reduction of anticoagulation and antiplatelet therapy has also been suggested as a means to prevent recurrent bleeding. However, results of the US-TRACE study showed that despite discontinuation of anticoagulation therapy, antiplatelet therapy or both, patients continued to bleed.[21] We observed a similar finding in this study prior to octreotide initiation and it has been shown that reduced anticoagulation is associated with an increased risk of thromboembolic events.[9] Thus, to date, no strategy has been proven to reduce the rate of GI bleeding in LVAD patients.

Efficacy and safety of the octreotide therapy

In the present study, octreotide therapy reduced the frequency of GI bleeding. The total number of units of RBCs and FFP infused, and number of days in the hospital decreased for the overall cohort during octreotide therapy. Furthermore, the mean hemoglobin level increased after octreotide therapy, probably related to the reduction in the frequency and magnitude of GI bleeding. The magnitude of each GI bleeding event, as assessed by blood product usage during each event, also decreased during octreotide therapy. Furthermore, the necessity for GI procedures as well as invasive therapies also decreased during octreotide therapy. The percent of days with INR >2.0 was increased following octreotide initiation, which can be explained by a reduction in the frequency of events necessitating warfarin discontinuation. Accordingly, prevention of recurrent GI bleeding by octreotide therapy has the potential to improve patient quality of life and improve cost-effectiveness of LVAD therapy.

The mechanism by which octreotide reduces GI bleeding in LVAD patients has not been investigated. Contributing mechanisms are hypothesized to include decreases of portal vein pressure due to splanchnic vasodilatation, enhancement of platelet aggregation, inhibition of GI angiogenesis as well as suppression of digestive enzymes.[11]

We did not observe any octreotide-associated adverse events such as bradycardia or digestive symptoms. A prior phase I study also reported no adverse events including GI bleeding following 16-weeks of octreotide therapy among 8 LVAD patients. This study had no comparison group and octreotide was administered for primary prevention of GI bleeding. Therefore, the risk for GI bleeding among patients in that study may not be as high as our patients.[15] In our cohort, three patients experienced pump thrombosis during octreotide therapy, possibly related to inability to maintain therapeutic anticoagulation levels due to recurrent GI bleeding.

Future octreotide therapy for GI bleeding in LVAD patients

Age, history of GI bleeding, and implantation as destination therapy are strong risk factors for GI bleeding during LVAD therapy.[6, 13] We did not find an association of age, frequency of GI bleeding, or LVAD support duration with refractoriness to octreotide therapy, which was assessed by freedom from an event during 6-months of octreotide therapy. Hemodynamic, echocardiographic, or endoscopic parameters may be helpful to more fully uncover the global effects of octreotide therapy.[22, 23] Measurement of GI bleeding-associated factors such as vascular endothelial growth factor and portal vein pressure before and during octreotide therapy may also be useful for optimal patient selection.[15]

Interestingly, all six patients with HVAD were free from GI bleeding during octreotide therapy. The relationship between device types and GI bleeding remains controversial,[24] but this should be analyzed in larger-scale studies, particularly including the most recently introduced HeartMate 3.[2]

Other therapies such as danazol and thalidomide may have a potential hemostatic role in LVAD patients.[18, 19] They lack sufficient evidence for routine clinical use, but can be administered orally and may be cheaper than octreotide. However, the adverse event profile for both agents is significant. Strict patient selection and careful monitoring are required for thalidomide therapy due to pancytopenia and neuropathy. Patients may not tolerate long-term danazol therapy because of its androgenic effects. The relative efficacy, safety, and cost-effectiveness of octreotide and these other agents should be studied.

Finally, the doses and dosing schedules of octreotide we used were based on previous case reports.[14, 15] However, optimization of dosing specifically for LVAD patients is warranted. These factors, in addition to varied indications for the use of octreotide among institutions, may underlie discordant reports with some case reports showing positive effects and others showing no effect on bleeding.[12–16]

Study Limitations

This is a prospective study with a moderate cohort size from a single center. Furthermore, the study was nonrandomized, and pre-treatment data from the same patients were used to assess the prospective effects of octreotide. A randomized control study would be best method to evaluate the use of octreotide in this patient population, but may not be practical given the severe consequences of refractory GI bleeding on patient quality-of-life.

The timing of initiation of octreotide therapy (both in terms of time from LVAD implant and in terms of number of prior GI bleeds) varied widely among patients. These time biases may have affected the outcomes. Most of the enrolled patients were treated with HeartMate II or HVAD. Our results may not simply be adopted in patients with other devices such as HeartMate 3.[2]

Conclusions

Octreotide therapy may be useful to prevent recurrent GI bleeding refractory to conventional therapies in patients with continuous-flow LVADs.

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Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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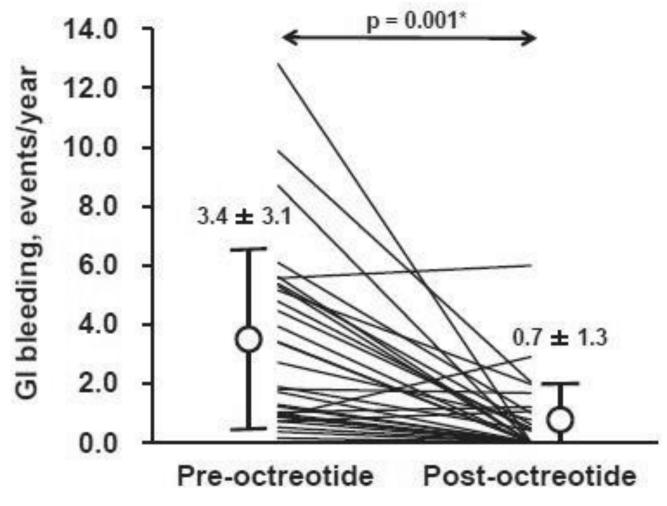
Figure 1.
Comparison of frequency of GI bleeding between pre- and post-octreotide therapy.
GI, gastrointestinal. *p <0.05 by Wilcoxon signed-rank test.

GI bleeding-free proportions surviving

1.0
0.8
0.6
0.4
0.2
0.0

1st year post-octreotide

71%

37%

1st year post-LVAD implant (off-octreotide)

$p = 0.019^*$ by Mantel-Cox test

0   100   200   300   400

Duration, days

Patient number

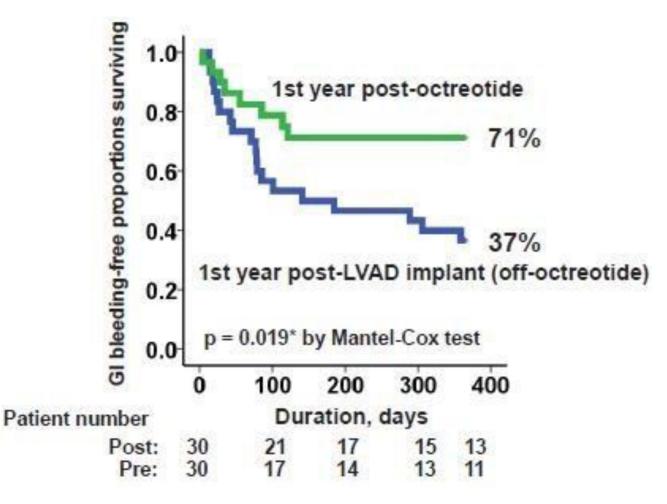|					
Post:	30	21	17	15	13
Pre:	30	17	14	13	11

Figure 2.
Comparison of GI bleeding-free proportions surviving between post-LVAD implantation off-octreotide period and post-octreotide therapy period.
*p <0.05 by Mantel-Cox test.

Table 1

Background characteristics

	N = 30
Age, years	66.4 ± 8.8
Race (Caucasian)	17 (57%)
Body Mass Index	30.9 ± 8.0
Gender (Male)	16 (53%)
Destination Therapy	25 (83%)
Ischemic Etiology	14 (47%)
Devices	
HeartMate II	20 (67%)
HVAD	9 (30%)
HeartAssist 5	1 (3%)
Hypertension	20 (67%)
Diabetes Mellitus	14 (47%)
Atrial Fibrillation	11 (37%)
History of Ventricular Tachyarrhythmia	7 (23%)

Table 2

Changes in patient management parameters before and after octreotide initiation

	Pre-octreotide period	Post-octreotide period	P value
%days with INR >2.0, %	22.7 ± 22.9	45.4 ± 37.0	0.006[*]
Mean aspirin dose, mg/day	72.7 ± 111.7	57.6 ± 54.7	0.77
%days with any aspirin administration, %	37.5 ± 42.2	48.7 ± 39.2	0.34
Mean LVAD speed, rpm			
HeartMate II (N = 20)	9171.5 ± 426.7	9127.0 ± 374.2	0.68
HVAD (N = 9)	2588.9 ± 130.5	2654.4 ± 164.3	0.43
HeartAssist 5 (N = 1)	8698.4 ± 98.4	9089.5 ± 99.7	-

[*]
p <0.05 by Wilcoxon signed-rank test

Table 3

Changes in therapeutic parameters associating with GI bleeding

	Pre-octreotide period	Post-octreotide period	P value
Mean hemoglobin level, g/dL	9.24 ± 0.84	9.82 ± 0.83	0.003[*]
Per year amount			
RBC, unit/year	20.2 ± 24.6	7.1 ± 10.3	0.002[*]
FFP, unit/year	13.1 ± 19.1	3.6 ± 5.0	0.002[*]
LOS, day/year	35.4 ± 47.3	8.7 ± 28.3	<0.001[*]
GI procedure, time/year	2.9 ± 3.1	0.4 ± 0.7	<0.001[*]
Per event amount			
RBC, unit/event	2.5 ± 2.7	1.0 ± 1.7	0.004[*]
FFP, unit/event	1.3 ± 2.1	0.1 ± 0.4	0.001[*]
LOS, day/event	9.1 ± 6.3	4.5 ± 7.9	0.015[*]
GI procedure, time/event	0.8 ± 0.2	0.3 ± 0.5	<0.001[*]

RBC, red blood cell; FFP, fresh frozen plasma; LOS, length of stay.

[*] p <0.05 by Wilcoxon signed-rank test

Table 4

Results of endoscopic procedures

	Pre-octreotide (N = 63)	Post-octreotide (N = 18)	P value
Lesions identified as source of GI bleeding			
Arteriovenous malformation	28 (44%)	5 (28%)	0.18
Erosion, gastritis or colitis	8 (13%)	1 (6%)	0.48
Dieulafoy lesion	2 (3%)	0 (0%)	0.42
Diverticulum	1 (2%)	0 (0%)	0.75
No active site identified	24 (38%)	12 (67%)	0.028[*]
Localization of GI bleeding			
Esophagus	2 (3%)	0 (0%)	0.42
Stomach/duodenum	17 (27%)	5 (28%)	0.94
Small intestine	12 (19%)	0 (0%)	0.042[*]
Large intestine	8 (13%)	1 (6%)	0.52
Unknown origin	24 (38%)	12 (67%)	0.028[*]
Performed therapy			
Clipping	5 (8%)	0 (0%)	0.24
Argon plasma coagulation	19 (30%)	3 (17%)	0.28
Infrared radiation embolization	2 (3%)	0 (0%)	0.42
No invasive therapies	37 (59%)	15 (83%)	0.044[*]

[*] p <0.05 by McNemar's test