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Evaluation of Outpatient Anticoagulation Bridging After Left Ventricular Assist Device Implantation

Rebecca A. Rainess,[1]* Laren Alderman,[1] Teresa Cicci,[1] Monty Yoder,[1] Barbara Pisani,[1] Thomas O'Neill,[1] and Diego Malaver[1]

[1]Wake Forest Baptist Health, Winston-Salem, NC

*Corresponding author: rebeccarainess2@gmail.com

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Abstract

Objective: The aim of this study is to evaluate the safety of outpatient anticoagulation bridging following left ventricular assist device (LVAD) implantation.
Methods: This study is a retrospective, single-center cohort of adult patients who underwent LVAD implantation (HeartMate II™ or HeartMate 3™) and received warfarin and at least one dose of therapeutic enoxaparin or fondaparinux for outpatient anticoagulation bridging. The primary endpoint was the incidence of bleeding complications within one week of completing the bridging episode. Secondary endpoints included the incidence of new hemolysis or thrombosis within 30 days, INR at the time of bridge initiation, duration of anticoagulation bridge, and management of bleeding events associated with the bridging episode.
Results: Data from 155 bridging episodes in 44 patients were analyzed. The primary endpoint occurred 30 times during 26 encounters. Of these events, 14 systemic bleeding episodes (9.03%) occurred. Localized bleeding complications consisted of injection site adverse reactions, including bruising (7.74%), bleeding (1.94%), and hematomas (0.65%). The majority of bleeding episodes were successfully self-managed by the patient and required monitoring only (83.33%). Only one new hemolysis event occurred (0.65%) and no new thrombotic events occurred within 30 days of any bridging episode.
Conclusion: Results of this study suggest that pharmacist-managed outpatient anticoagulation bridging may be safely initiated in the LVAD patient population, given patients have close follow-up monitoring.

Introduction

The left ventricular assist device (LVAD) is a mechanical circulatory support pump that augments systemic blood flow by assisting the left ventricle in ejecting blood to the aorta.[1] These devices are generally reserved for patients with end-stage heart failure who are refractory to standard medical therapies. Both the HeartMate II™ and HeartMate 3™ LVADs (Abbott) are FDA-approved to provide intermediate-to-chronic hemodynamic support to both patients awaiting heart transplant (i.e., bridge to transplant) and patients who are ineligible for transplant (i.e., destination therapy).[1]

Although LVAD implantation has been associated with prolonged survival and improved quality of life, these devices carry an intrinsic risk of bleeding, and thromboembolic (e.g. pump thrombosis, stroke) complications.[2] To reduce the risk of thrombotic complications, systemic anticoagulation is recommended post-implantation.[3] Current standards of care post-LVAD implantation include an antiplatelet agent (aspirin, generally) and warfarin titrated to an international normalized ratio (INR) of 2.0-3.0.[4,5] Although associated with a decreased incidence of thrombotic events, anticoagulation therapy further enhances the bleeding potential. Therefore, careful monitoring and management of anticoagulant therapy is required to mitigate the competing risks of bleeding and thrombosis. Previous studies have demonstrated that LVAD patients whose warfarin therapy is managed by pharmacists have higher time in therapeutic range versus usual care, without significant difference in bleeding or thrombosis.[6,7]

Despite appropriate dosing and monitoring, there is a potential for significant variations in anticoagulation status in patients receiving warfarin. Minimal data exist regarding the safety and efficacy of outpatient anticoagulation bridging with rapid-acting parenteral anticoagulants (e.g. enoxaparin, fondaparinux) in this patient population. Limited data suggest that there may be up to a four-fold increase in major bleeding events during the low molecular weight heparin (LMWH) bridging period.[8] Trials assessing the need for periprocedural bridging in patients with non-valvular atrial fibrillation have shown that the risk of bleeding often outweighs the potential benefit, since the short-term risk of thrombotic complications (i.e. stroke) is less than one percent, however this study was not conducted on LVAD patients.[9] The objective of this study was to evaluate the safety of outpatient anticoagulation bridging with treatment-dose enoxaparin or fondaparinux in patients who have undergone LVAD implantation.

Methods

Study Design, Setting, and Patient Population

This study was a single-center retrospective cohort study. Patients included were adults 18 years of age and older who had undergone implantation of either HeartMate II or HeartMate 3 LVAD at our institution. All subjects were outpatients receiving concurrent warfarin therapy and at least one dose of enoxaparin or

fondaparinux as a bridge to therapeutic INR between September 1, 2015 and June 30, 2018. Warfarin and bridging therapy was managed by clinical pharmacists using an established protocol, operating under collaborative practice agreements within the Advanced Heart Failure (AHF) service. The protocol allows pharmacists to independently initiate bridging when the INR is less than 1.[8] For most patients, dosing for enoxaparin is 1 mg/kg every 12 hours, rounded to the nearest 10 mg or nearest syringe size, with a typical maximum dose of 120 mg. Dosing for fondaparinux is 5 mg daily for patients weighing less than 50 kg, 7.5 mg daily for patients weighing 50 to 100 kg, and 10 mg daily for patients weighing more than 100 kg. Both enoxaparin and fondaparinux are dosed based on the patient's total body weight. For complex patient cases (e.g. borderline therapeutic INR, creatinine clearance (CrCl) <30 mL/min, prior major bleeding event, or actual body weight greater than 120 kg) the pharmacist and AHF clinic attending physician collaborate to determine the optimal anticoagulation regimen.

Criteria for study exclusion included transfer of care outside our health system, any hospitalization before completion of outpatient bridging episode, patient reported non-adherence to the prescribed anticoagulation regimen, and incomplete medical record documentation. The decision to exclude patients who were hospitalized before completion of an outpatient bridging episode was based on the potential for the hospitalization to act as a confounding variable. Upon hospitalization, bridging may be discontinued for a variety of reasons and if continued, would be administered by a healthcare professional, rather than self-administered by the patient. Additionally, anticoagulation therapy is often held or adjusted during hospitalizations due to the need for invasive procedures. Pregnant women and prisoners were also excluded from this analysis. The study protocol was approved by the local institutional review board.

Data Collection

Clinical data was collected retrospectively through review of the electronic medical record, including progress notes documented by both clinical pharmacists and physicians. Data collection included demographic information, pre-specified laboratory results, pertinent concomitant medications, number and dose of enoxaparin or fondaparinux injections, and adverse outcomes (e.g. bleeding events, hemolysis/thrombotic events).

Endpoints

The primary endpoint was the incidence of patient-reported or provider-diagnosed (via complete blood count results) localized or systemic bleeding complications within 7 days of completing an anticoagulation bridging episode. Secondary endpoints included the incidence of new hemolysis or thrombotic events within 30 days. Additional variables collected for primary endpoint analysis included the time from device implantation to first bridging episode in patients who underwent device implantation between August 1, 2015 and June 30, 2018, pre- and post-bridge lactate dehydrogenase (LDH), INR at the time of bridge initiation, etiology of subtherapeutic INRs, duration of bridging episodes, management of bleeding events, post-bridge platelet count, time to localized bleeding, and time to systemic

bleeding. Hemolysis was defined as elevated LDH greater than or equal to 600 IU/L (2.5 times the upper limit of normal), in accordance with current practice guidelines.[3,10]

Analysis

The results were downloaded and reviewed. Questions with “yes,” “no,” and “sometimes” answer choices were assigned values of 1 (yes), 0 (no), and 0.5 (sometimes). Answers from programs with multiple respondents were consolidated to a single response. Questions of fact were assigned the majority response, while questions of perspective were averaged based on the assigned value of each answer. Average answers of >0.5 were considered “yes,” and average answers of <0.5 were considered “no” for questions without a sometimes option. Questions involving ranking were consolidated by averaging the rank of each response and re-ordering based on the averages. If the average answer for a question was indeterminate, the program was excluded for the question.

Results

Characteristics of the Study Population

A total of 54 patients were screened for enrollment, of which 44 qualified for study inclusion. Ten patients were excluded from the study as a result of not having any bridging episodes during the study time frame (n=9) or having their care transferred to another health care system (n=1). Additionally, fifteen bridging episodes in 12 patients were excluded due to patient hospitalization before completion of the bridging episode or lack of follow-up. No patients were hospitalized due to bleeding prior to completion of the bridging episode. In total, 155 bridging episodes were included in the analysis.

Recent dietary modification was the single most common factor that contributed to the need for bridging and was reported in 24 encounters (15.48%). Other common etiologies of subtherapeutic INRs included missed or incorrect warfarin doses (12.90%), recent warfarin dose changes (9.68%), and clinically significant drug interaction(s) (6.45%). Twenty-one bridging episodes (13.55%) resulted from a combination of more than one contributing factor. Investigators were unable to definitively identify the cause of subtherapeutic INRs in more than one-third of all encounters (36.77%).

The mean age across encounters was 55 years (Table 1). The majority of included patients were male (n=36). The HeartMate II LVAD was the primary device implanted in most patients (93.18%). At the time of their bridging event, 43.18% of patients had a history of LVAD-related hemolysis or thrombosis and 18.18% of patients had a history of LVAD-related bleeding. Enoxaparin was the predominant bridging anticoagulant and was prescribed in all but two encounters (98.71%). The mean enoxaparin dose used was 0.95 mg/kg actual body weight, and almost all patients were prescribed enoxaparin at a frequency of every 12 hours (96.08%).

Bridging was initiated at a mean INR of 1.62, and episodes lasted an average of 4.7 days. Concomitant octreotide therapy was prescribed in 2 patients (4.55%) in the study.

Table 1. Patient Demographics

	n = 44 patients
Age (yr) – mean age across bridging encounters (SD)	55.07 (± 11.52)
Male gender – no. (%)	36 (81.82%)
Race – no. (%) White Black Other	 25 (56.82%) 17 (38.64%) 2 (4.54%)
Weight (kg) – mean (SD)	96.13 (± 17.37)
Creatinine clearance (mL/min) – mean (SD)	83.12 (± 28.39)
Baseline platelet count (10^9/L)– mean (SD)	231.38 (± 61.87)
Type of LVAD – no. (%) HeartMate II™ HeartMate 3™	 41 (93.18%) 3 (6.82%)
History of LVAD-related bleeding at the time of the bridge – no. (%)	8 (18.18%)
History of LVAD-related hemolysis/ thrombosis at time of bridge – no. (%)	19 (43.18%)
Bridging anticoagulant used – no. (%) Enoxaparin Fondaparinux	 43 (97.73%) 1 (2.27%)
Antiplatelet therapy – no. (%)† Aspirin 81 mg Aspirin 325 mg None	 39 (88.64%) 1 (2.27%) 4 (9.09%)
†Five patients switched antiplatelet regimens during the study time frame	

Study Outcomes

Primary and secondary outcomes are described in Table 2 and Table 3. Localized bleeding complications occurred within 7 days of bridge discontinuation in 16 encounters in 13 patients (10.32%). The majority of these events were attributed to either bruising or bleeding at the injection site (n=15; 93.75%). Systemic bleeding complications were reported in 14 encounters in 8 patients (9.03%). Of these, epistaxis (n=6), hematuria (n=2), and gastrointestinal bleeding (n=2) were the most frequently reported adverse reactions. The majority of bleeding events were self-managed (83.3%), though 5 encounters (16.67%) required provider follow up. Provider management of the bleeding events were as follows: no change in therapy (n=2), held one dose of warfarin (n=1), enoxaparin discontinued (n=1), CBC ordered and enoxaparin continued (n=1). No bleeding events resulted in a hospitalization or required a blood transfusion, and all were effectively managed in the outpatient setting. One patient (2.27%) developed new hemolysis within 30 days of a bridging episode, despite adherence to anticoagulation as advised. Of the 155 bridging encounters, 7.09% were associated with a subtherapeutic INR less than 2.0 at the time of bridge discontinuation, versus 16.77% with a supratherapeutic INR greater than 3 at bridge discontinuation. Only three bridging episodes (1.9%) were discontinued when the INR was less than 1.8.

Table 2. Primary Outcomes

	n = 155 Encounters
Localized bleeding within 1 week of completing bridging episode	16 (10.32%)
Injection site bruising	12 (7.74%)
Injection site bleeding	3 (1.94%)
Injection site hematoma	1 (0.65%)
Systemic bleeding within 1 week of completing bridging episode	14 (9.03%)
Bright red blood per rectum	2 (1.29%)
Gingival bleeding	1 (0.65%)
Post-operative bleeding	2 (1.29%)
Epistaxis	6 (3.87%)
Hematuria	2 (1.29%)
Menorrhagia	1 (0.65%)

Overall bleeding was not associated with any of the following variables: creatinine clearance (p=0.87), pre-bridge INR (p=0.78), post-bridge INR (p=0.38), enoxaparin dose (p=0.59), or pre- versus post-bridge LDH (p=0.99) according to the Wilcoxon rank test. Patients who experienced any bleeding event tended to have a lower mean post-bridge INR compared to those who did not develop bleeding complications (INR 2.50 versus 2.61, respectively); however, this was not statistically significant. The mean age of patients who had any bleeding event was

higher compared to patients who did not experience bleeding events (58.96 ± 8.23 versus 48.44 ± 13.44; p=0.0075).

Table 3. Secondary Outcomes

	n = 155 Encounters
New hemolysis within 30 days	1 (0.65%)
New thrombosis within 30 days	0 (0.00%)
Management of bleeding events Provider follow-up No change in therapy One dose of warfarin held Enoxaparin discontinued CBC ordered and enoxaparin continued Self-managed/observation only	30 5 (16.67%) 2 1 1 1 25 (83.33%)
INR at bridge – mean (SD)	1.63 (± 0.19)
INR after bridge – mean (SD)	2.58 (± 0.48)
Post-bridge platelet count (10^9/L) – mean (SD)	218.76 (± 55.25)
Duration of anticoagulant bridging (days) – mean (SD)	4.69 (± 2.39)
Time to localized bleeding event (days) - mean (SD)	5.58 (± 2.77)
Time to systemic bleeding event (days) – mean (SD)	3.47 (± 2.96)

Discussion

The results of our study appear to be similar to previous trials and suggest a potential antithrombotic benefit of bridging with enoxaparin in the outpatient setting for patients with LVADs who have subtherapeutic INRs while on warfarin. These results suggest that outpatient bridging was associated with a moderate risk of overall patient-reported bleeding events. However, the majority of bleeding events were injection-site reactions commonly associated with subcutaneous medication administration.

More than 80% of systemic bleeding events observed in this study were nuisance bleeding events, primarily epistaxis, which self-resolved without provider follow-up. Only one patient with a prior history of bleeding experienced a systemic bleeding event during a bridging episode, which could suggest that history of bleeding is not correlated with bleeding during a bridging episode. The overall incidence of

bleeding in this study was more closely correlated with increasing patient age rather than impaired renal function, which is likely attributed to appropriate renal dose adjustments by the clinical team. However, our study included a limited number of patients with advanced renal disease requiring clinically significant enoxaparin or fondaparinux dose adjustments.

No substantial risk of hemolysis or thrombosis was identified within 30 days of a bridging episode, and the single episode of hemolysis did not result in a subsequent thrombotic event or admission. Although patients in this study did experience hemolysis and/or thrombotic events during the study timeframe, the occurrence of these events did not coincide with bridging episodes. This observation further supports the hypothesis that LMWH is effective when used for outpatient anticoagulation bridging in the setting of subtherapeutic INRs. Additionally, given the risk of thromboembolic complications associated with the HeartMate II device, it is expected that outpatient bridging practices would be associated with a lower cost of care by avoiding hospitalizations for inpatient bridging

It is well-established that LVAD patients are at an increased risk of post-implantation complications, including thromboembolism and bleeding.[11] The occurrence of these adverse events complicates anticoagulation management given their associated healthcare costs and the impact on patient morbidity and mortality. Prior to initiating and prescribing anticoagulant therapy in the LVAD population, patient-specific factors related to anticoagulation, such as renal function, concomitant medications, past INR trends, risk of thrombosis versus bleeding complications, and patient compliance should be considered. This allows for individualized treatment modifications, which aim to reduce the risks of thrombotic or bleeding complications.

The cost of pump replacement in cases of thrombosis is often deemed the most expensive complication associated with LVADs. A review of data from 2009-2010 determined that the mean cost of initial pump implantation for Medicare beneficiaries was $175,420, while the cost of pump replacement was $90,147.12 Anticoagulation therapy is used to reduce the risk of thrombotic complications but is associated with an increased risk of bleeding.[3]

A previous trial by Bhatia et al. estimated an event rate of 0.53 major bleeding events per patient-year in patients bridged with enoxaparin for subtherapeutic INR, making bleeding complications the most common complication associated with anticoagulation in patients with LVADs.[8] The high bleeding rates observed in that trial as compared to our study could possibly be due to the long mean duration of bridge (18 days), as well as the inclusion of in-patient periprocedural and post-hospitalization bridging, which were excluded in our study.

Strengths of this study include the diversity of the patient population in terms of gender, race, and baseline history of LVAD related complications, robust documentation of anticoagulation management outcomes, and a relatively large sample of bridging encounters. Patients included in this study had close follow-up monitoring by clinical pharmacists during each bridging episode, with INRs being

evaluated at least twice weekly during periods of sub- or supratherapeutic anticoagulation.

Limitations

Limitations of this study include its retrospective, single-center study design, relatively small patient sample size, and minimal inclusion of fondaparinux and HeartMate 3 devices. Additionally, the descriptive study design of this assessment limits our ability to assess the comparative risk of bleeding and thrombosis in patients who did not receive anticoagulation bridging in response to subtherapeutic INRs. Given that the HeartMate 3 device has a lower intrinsic risk of thromboembolic complications compared to other durable LVADs, the risk of bleeding associated with anticoagulation bridging may outweigh the slight risk of thrombosis.[5] Because adverse events and compliance were self-reported by patients, investigators may not have been able to fully capture all outcomes. Additionally, the impact of unmeasured confounding factors (e.g. procedures) may have influenced outcomes. Future studies are warranted to further define optimal anticoagulation practices in this population, including the INR threshold for initiating bridging and the duration of bridging episodes, as well as to determine the most effective strategies for preventing and managing complications.

Surveys of this nature have several limitations that impact the ability to include a totality of responses. Selection bias was likely present as known SWs were contacted to complete the survey, in addition to posting on the sites described above. Additionally, our limited sample size may or may not accurately reflect the larger consensus of the field. With respect to the team member survey, it must be considered that respondents may not have a full understanding of the role that the VAD SW fills at their program. As a result, answers may not encompass the entire scope of the SWs activity in some cases. In addition, physicians were underrepresented among VAD team member respondents. As the leaders of the VAD care team, it is perhaps most important to understand the physician perspectives of the VAD SW.

Conclusion

The results of this study demonstrate that outpatient anticoagulation bridging with enoxaparin in patients with LVADs was associated with a moderate risk of localized minor bleeding complications at the injection site. The overall incidence of bleeding seen was about 20%, however the incidence of systemic bleeding requiring provider follow-up seen in this study was minimal, with nearly half of all systemic bleeding consisting of epistaxis. New hemolysis and thrombotic events were generally not associated with bridging episodes. Overall, these results suggest that enoxaparin may be considered in the outpatient setting as a short-term bridge in LVAD patients with subtherapeutic INRs. Given the incidence of bleeding observed in this study, it is important that clinicians weigh the risk of bleeding versus thrombotic events on a case-by-case basis when considering enoxaparin as a bridging strategy. If a bridging strategy is implemented, close

patient follow-up may help minimize the risk of bleeding by ensuring prompt cessation of enoxaparin therapy once a therapeutic INR is achieved. Conclusions regarding the utility of outpatient bridging with fondaparinux or within the HeartMate 3 population are unable to be made due to minimal inclusion during this retrospective review.

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