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Anticoagulation Monitoring in Left Ventricular Assist Device Patients

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Abstract

The use of left ventricular assist devices (LVAD) provides a treatment strategy for advanced heart failure patients to prolong life and serve as a mediator (bridge to transplant) until an organ becomes available in patients considered suitable candidates for heart transplantation. The use of LVAD therapy is complicated by the constant risk of bleeding and thrombotic events. We reviewed and analyzed the effectiveness of our current heparin protocol with respect to overall anticoagulation and time in therapeutic range (TTR). Our analysis demonstrated that patients did not achieve therapeutic anticoagulation for at least 24 hours following initiation of heparin and that only 40% of the time patients were considered therapeutic. Even after patients achieved a therapeutic activated plasma thromboplastin time (aPTT) TTR was only approximately 50% with less than 50% of tests resulting within range. Individual centers should perform ongoing assessment of effectiveness of individual heparin protocol for LVAD patients to ensure anticoagulation is optimized in these highly complex patients.

Keywords: anticoagulation, heparin, ventricular assist devices, time in therapeutic range

Introduction

Left ventricular assist devices have become an essential component in heart failure management.[1-5] While heart transplant remains the only definitive therapy for patients with advanced heart failure (AHF), left ventricular assist device (LVAD) therapy provides a viable option for patients deemed candidates for transplant or as destination therapy in ineligible candidates.[1-5] Unfortunately, despite significant advancements in LVAD therapy, its use continues to be complicated by bleeding risks and pump thrombosis.[6-10] The use of anticoagulation therapy following LVAD implantation remains non-standardized, varying significantly amongst various centers and continues to evolve with emerging data.[10] In 2014, a report demonstrated an unexpected significant increase in the rate of pump thrombosis and strokes in patients implanted with the Heartmate II, a continuous-flow LVAD at three major LVAD programs.[11] Unfortunately, the exact etiology for pump thrombosis was not established but potential causes could relate to changes in anticoagulation practices, surgical technique, and change in pump design or manufacturing.

The manufacturers for the Heartware and HeartMate II devices provide recommendations regarding anticoagulation and antiplatelet therapy but do not provide strategies to achieve and maintain these parameters.[12-13] During the study period, we utilized the atrial fibrillation (AF)/stroke prophylaxis heparin protocol following LVAD placement with a therapeutic aPTT range defined as 60-80 seconds. The use of this protocol has not been formally reviewed in this patient population and the potential risks/benefits remain unclear. With continued concern surrounding the risk of pump thrombosis and strokes within LVAD patients, our center wanted to evaluate current systemic intravenous anticoagulation practices to assess overall management in an effort to reduce the risk for pump thrombosis and strokes.

Methods

This was a single-center, retrospective descriptive analysis conducted at an academic medical center. Patients >18 years of age who were implanted or readmitted with a Heartmate II or Heartware LVAD between January 2013 and June 2015 were considered for inclusion. Patients were excluded from the analysis if they were not initiated on the AF/stroke prophylaxis heparin protocol or if they achieved therapeutic anticoagulation on fixed dose heparin. Additionally, patients requiring an LVAD exchange were excluded from analyses following pump exchange but were considered for inclusion at any point prior to the exchange. The therapeutic range of the AF/stroke prophylaxis protocol was defined as 60-80 seconds. Adjustments to goal range were considered deviations from standard therapy and excluded from analysis. Patients initiated on heparin protocol post-LVAD implantation were analyzed separately than patients readmitted and started on heparin protocol. In an effort to standardize heparin management, our institution utilizes adjust body weight

Heparin initiation time was defined as end anesthesia time until initiation of heparin, while heparin protocol initiation was end anesthesia time until initiation of AF/stroke prophylaxis protocol. When patients were transitioned from fixed dose heparin to AF/stroke prophylaxis protocol, both heparin rate immediately preceding transitioning to protocol and heparin rate (units/kg/hr) were recorded. In addition to time in therapeutic range (TTR), we also assessed time subtherapeutic and supratherapeutic defined as aPTT ranges of 0 to 59.9 and 80.1 to 200.1, respectively. We also recorded percentage of aPTT tests within range, time from protocol initiation to first therapeutic aPTT value and heparin rate at the time of first therapeutic value. Percentage of time subtherapeutic, therapeutic, and supratherapeutic were evaluated utilizing a modified version of the Rosendaal method which assesses percentage of aPTT values in range.[14]

Survival, thrombosis and bleeding outcomes were also evaluated. Bleeding events were assessed during heparin therapy and up to 48 hours after its discontinuation with an event being defined as an episode of internal or external bleeding leading to death, reoperation, permanent injury, or necessitating transfusion of more than 2 units of blood within a consecutive 24 hour periods. To be classified as a bleeding event, patients were required to be actively on the specified heparin protocol. Thrombosis endpoints were assessed from initiation of heparin therapy until the end of the study analysis. Thrombosis endpoints included thrombus formation within the device or systemic events including cardioembolic stroke, thrombotic stroke/transient ischemic attack, myocardial infarction, deep vein thrombosis (DVT) or pulmonary embolism (PE). All events were assessed through review of medical records, including progress, surgical, and radiographic reports.

Results

During the study time frame a total of 135 patients underwent LVAD implantation with 62 patients meeting the implanting group inclusion criteria. Patients were excluded for the following reasons: achieved therapeutic aPTT on fixed dose heparin (n=26), utilized bivalirudin for anticoagulation (n=14), only received fixed dose heparin (n=9), did not receive anticoagulation (n=8) were not initiated on standard protocol (n=8), received less than24 hours of heparin (n=1). Of the eight patients excluded from the analysis due to LVAD pump exchange four of the exchanges were the result of LVAD thrombosis. Further evaluation identified that only one of the four device thrombosis were previously on the AF/stroke prophylaxis heparin protocol. A total of 52 patients who were readmitted and initiated on heparin protocol and included in the readmission cohort.

Baseline demographics are reported for patients included within both cohorts. (Table 1) Patients were predominately male (initial: 84% and re-implant: 94.2%) who were more likely to be implanted with HeartMate II (initial: 80.6% and re-implant: 80.8%) as compared to Heartware (initial: 19.4% and re-implant: 19.2%). Large discrepancies were noted between actual body weight and adjusted body weight within both cohorts.

Table 1. Baseline Demographics

Baseline Demographics	Initial Implant (n=62)	Readmission (n=52)
Age	54.2 years (27-73.8)	53.9 years (28.2-71.3)
Gender (male)	54 (87%)	49 (94.2%)
Race		
Caucasian	24 (38.7%)	24 (46.2%)
African American	25 (40%)	14 (26.9%)
Other	13 (20.1%)	14 (26.9%)
Weight	96.3 kg (53.8-180)	101.7 kg (67.5-179.6)
Heparin dosing weight	83.5 kg (56-133.5)	82.5 kg (58.0-123)
Indication for LVAD		
Ischemic Cardiomyopathy	37 (59.7%)	
Non-Ischemic Cardiomyopathy	25 (40.3%)	
Type of LVAD		
Heartmate II	50 (80.6%)	42 (80.8%)
HVAD	12 (19.4%)	10 (19.2%)
Comorbidities		
Diabetes mellitus	21 (36%)	
Atrial Fibrillation	20 (32.3%)	
Respiratory Failure	9 (14.5%)	
Renal Failure	21 (36%)	
Liver failure	5 (8.1%)	
Other	32 (51.6%)	

Kg = kilogram; LVAD = left ventricular assist device;

Within the initial implantation cohort, 93.5% (n=58) of patients were discharged from the hospital while 4% required pump exchange or died. (Table 2) A total of 8 patients (12.9%) developed thrombus formation which was confirmed by radiologic studies at a subsequent point following LVAD implantation. Bleeding events were demonstrated in 17.7% (n=11) of patients while receiving heparin.

Table 2. Outcomes following initial implantation

Outcomes – Initial Implantation	(n=62)
Survival	
Discharge from hospital	58 (93.5%)
Pump exchange	2 (3.2%)
Death	2 (3.2%)
Thrombus	8 (12.9%)
Bleeding	11 (17.7%)
Blood product utilization, median (Range)	
Red Blood Cell	6 (0-23)
Fresh Frozen Plasma	3 (0-12)
Platelet	2 (0-8)
Cryoprecipitate	0 (0-4)
Factor administration, n (%)	1 (2%)

During initial LVAD implantation, heparin was initiated an average of 32.6 hours following completion of end anesthesia time. (Table 3) Patients were initiated on protocol heparin nearly 64 hours later with average conversion of heparin rate from 667.2 units/hr (100-1800) to 12.8 units/kg/hr (6-22). An additional 32 hours was required from initiation of heparin protocol for patients to achieve their 1st therapeutic aPTT with an average heparin rate of 17 units/kg/hr. Overall, patients were within therapeutic range 40% of the time during the initial implantation cohort. (Table 3) When patients weren't therapeutic they were more frequently noted to be subtherapeutic (37.9%) as compared to supratherapeutic (16.7%).

With respect to the readmission cohort, numerically, there was a similar protocol initiation rate (13.6 units/kg/hr) and heparin rate at 1st therapeutic aPTT value (16.7 units/kg/hr) but patients achieved therapeutic aPTT nearly 3 hours earlier. Despite this TTR was essentially unchanged at 44.2%. (Table 3) Overall, patients were considered supratherapeutic only 13.2% of the time.

Table 3. Anticoagulation outcomes

Anticoagulation	Initial Implantation (n=62)	Readmission (n=52)
Heparin initiation – post implant hours	32.6 (7.4-140.5)*	N/A
Heparin protocol initiation – post implant hours	96.2 (14.6-267.3)	N/A
Heparin rate prior to protocol conversion units/hour	667.2 (100-1800)+	N/A
Protocol initiation rate units/kg/hour	12.8 (6-22)	13.6 (7 – 16)
Hours to 1st therapeutic aPTT (from protocol initiation)	32.3 (2.9-86)¥	29.0 (5.3 – 93.7)¥
Heparin rate at 1st therapeutic aPTT units/kg/hour	17 (6-26)	16.7 (11 - 24)
Hours in range (% of time) Subtherapeutic (0 - < 60) Therapeutic (60 – 80) Supratherapeutic (>80 – 200)	 37.9 (0 – 100) 40.4 (0 – 85.2) 16.7 (0 – 37.9)	 41.8 (6.7 – 84.2) 44.2 (0 – 100) 13.2 (0 – 37.1)
aPTT tests in range (% of time) Subtherapeutic (0 - < 60) Therapeutic (60 – 80) Supratherapeutic (>80 – 200)	 41.9 (0 – 100) 34.7 (0 – 75) 19.8 (0 – 40)	 46.4 (16.7 – 87.5) 39.9 (0 – 100) 14.3 (0 – 30.8)

aPTT = activated partial thromboplastin time;
* 4 patients were not initiated on fixed dose heparin
+ 4 patients not initiated on fixed dose heparin; unable to equate fixed rate prior to protocol initiation
¥ 2 patients (initial) and 1 patient (readmission) did not achieve therapeutic aPTT prior to heparin discontinuation

Regarding maintenance of therapeutic anticoagulation following achieving a therapeutic aPTT value the cohorts were nearly identical with 48.8% in the initial implantation and 52.3% in the readmission cohorts, respectively. (Table 4)

Table 4. Time in therapeutic range once patient reaches first therapeutic aPTT

	Initial Implantation (n=50)[+]	Readmission (n=52)[*]
% hours within range	48.8 (0-96.9)	53.9 (14.4 – 100)
% of tests in range	42.7 (0-75)	50.2 (0 – 100)

[+] 2 patient did not achieve therapeutic aPTT and time in therapeutic range was not calculated

[*] 1 patient did not achieve therapeutic aPTT and time in therapeutic range was not calculated

Discussion

Our analysis demonstrated that patients were supratherapeutic following LVAD implantation only 16.7% of the time, likely owing to ongoing bleeding concern following implantation. Despite overall totality of therapeutic heparin being 40%, after achieving a therapeutic aPTT the ongoing TTR only increased to 48.8%. Even with a relatively low TTR, the subsequent risk of thrombus (12.9%) was similar, albeit on the higher side, to what has been demonstrated in published literature.[15,16] Patients were separated into two distinct groups as they represent vastly different management strategies. Patients who are immediately post-operative are at much higher bleeding risk, and careful consideration of anticoagulation must be taken. Patients being readmitted on the other hand, are potentially at a higher risk of thrombus formation and might require more aggressive anticoagulation management. Of the eight patients excluded from the analysis due to LVAD exchange, four were the result of device thrombosis but only one of the thrombosed devices previously received the evaluated protocol. As this was a descriptive, retrospective study assessing effectiveness of the heparin protocol to achieve and maintain therapeutic anticoagulation establishing a causal relationship to development of thrombosis was not possible.

The use of LVAD therapy has significantly improved the life span of advanced heart failure patients serving as destination therapy or as bridge to transplant, it is not without complications.[1-5; 17] The optimal LVAD will provide cardiac support to heart failure patients while eliminating the need for a driveline, and reducing or eliminating the risk for thrombotic and bleeding events. Vast strides have been made to further advance the pump design and with improved technology these complications may become obsolete.[17] As pump technology continues to evolve optimization of anticoagulation and antiplatelet therapy has been shown to reduce the rate of pump thrombosis up to 50%.[18] To capitalize on these findings the *PREVEN*tion of HeartMate II Pump *T*hrombosis Through Clinical Management (PREVENT) study was designed to establish whether a standardize approach for surgical implant technique, anticoagulation, and pump speeds following HMII implantation would reduce the risk of pump thrombosis. Full adherence to implant techniques, anticoagulation and pump speeds significantly reduced the risk of pump thrombosis (1.9% vs. 8.9%; $p < 0.01$) and the composite outcome (suspected thrombosis, hemolysis, and ischemic stroke) at 6 months (5.6% vs 17.7%; $p<0.01$).[19] Despite, the significant benefit noted with full adherence to key recommendations overall, the recommendations were inconsistently followed with 78% adherence to surgical recommendations, 95% to heparin bridging, and 79% to pump speeds >=9,000 RPMs.[19]

It is difficult to determine whether a specific recommendation from the PREVENT study had an impact on reduction in pump thrombosis as the study was not powered to assess individual components effect on pump thrombosis. It could be argued that the anticoagulation and antiplatelet recommendations within PREVENT be strictly followed. The median INR within the analysis was 2.1 (IQR 1.9-2.3) but median time spent at a target range (2.0-2.5) was only 31% (IQR 19%-44%).[19] Unfortunately, a protocol for achieving and maintaining specific aPTT values was not discussed by the study investigators and the results regarding time within therapeutic range of heparin were not reported.

Raschke et al. produced a landmark study demonstrating that heparin dosing based on patients' body weight resulted in more rapid anticoagulation as well as fewer recurrent thrombotic events when compared to "standard care" nomogram.[20] In an effort to advance heparin anticoagulation, Schlicht et al. compared the Raschke nomogram with an institution-specific modified nomogam to achieve therapeutic aPTTs. The authors were able to demonstrate a reduction in time to achieve therapeutic aPTT's while simultaneously reducing the risk of over anticoagulation (as evaluated based on aPTT values >90 secs).[21] It should be noted that the Raschke nomogram was built on the premise of rapidly achieving aPTTs of 1.5-2.5 times the control which may not be appropriate for all heparin indications and modification of institutional protocols based on indications may help optimize anticoagulation.

Despite protocol development through titration to specific anticoagulant markers, little data exists on how effective protocols are at maintaining therapeutic anticoagulation. Kim et al. tried to demonstrated the effectiveness of unfractionated heparin through assessment of achieving and maintain therapeutic

aPTT as well as adequacy of the hospital nomogram.[22] Their results demonstrated a high percentage of patients achieving a therapeutic range at 24 hours (69.5%; n=91) and 48 hours (90.1%; n=18) with a therapeutic aPTT proportion of only 39.2%.

Aarab et al. evaluated UFH in critically ill patients requiring anticoagulation for a variety of indications.[23] Time to therapeutic range was 24 hours in 56% of the 101 patients admitted to the ICU and medium care unit. The results within the current analysis demonstrated that irrespective of the cohort the overall time within therapeutic range was less than 50%. Additionally, following the first therapeutic aPTT value, irrespective of the group, the time in therapeutic range was only approximately 50%. Several centers have reported heparin protocol development for use in various MCS devices but to our knowledge there hasn't been a study discussing effectiveness of individual protocols within the LVAD population.[24-26]

One of the difficulties with utilizing aPTT values to assess for heparin effectiveness relates to the broadness of the aPTT test. There are a variety of disease states and factors that can influence the aPTT value, many of which are seen within the advanced heart failure and LVAD population.[27] In fact, the aPTT test provides a better representation of overall coagulopathy as opposed to heparin concentration. Our study showed that patients were within therapeutic range only 40.4% of the time with only 34.7% of aPTT values being therapeutic. Somewhat surprisingly, there was not a noticeable difference in time within therapeutic range 44.2% with only 39.9% of tests within range in the readmission cohort. Upon achieving a therapeutic aPTT maintenance of therapeutic anticoagulation was only demonstrated 50% of the time, irrespective of cohort analyzed. These data suggest that while significant improvements can be made with heparin monitoring and dosing, they are consistent to previously reported heparin protocols.[22,,23] The use of anti-factor Xa levels for monitoring systemic heparin anticoagulation has been discussed as a better marker for heparin effect on anticoagulation.[28] Several studies, outside the MCS population, have demonstrated less dose titrations and more consistent anticoagulation with the anti-factor Xa test.[29-31] Additionally, with mechanical circulatory devices patients, it has been reported that there exists a significant discordance between the two monitoring tests which raises the question of which should be utilized to adjust and monitor heparin.[32] In a patient population with potential ongoing coagulopathy, the use of a sole marker to monitor anticoagulation may negatively impact patient care and predispose patients to bleeding or thrombotic events. Further research is required to elucidate the best monitoring strategy in a very dynamic patient population.

There are several limitations of this study that merit mentioning including the retrospective nature of the design. First, while the authors tried to develop a study protocol that objectively assessed patient management through defining heparin protocol procedures, the analyses are limited by the retrospective nature of the study and the reliance of documentation by the medical team. Additionally, patient management strategies could evolve based on physician experience (presenting a historical bias) or could change based on clinical scenario. These factors provide a potential confounder if included, as changes in protocol could be the result of increased bleeding or thrombosis risk leading the clinician to modify therapeutic targets. The authors felt that the retrospective nature of the study and reliance on

documentation prevented a clear association between protocol changes and rationale behind changes. Therefore, in an effort to eliminate this limitation, the authors chose to exclude patients who had protocol modifications. It is important to note that individual patients may require different degrees of heparin if they are at higher or lower risk for bleeding and a single protocol may not be suitable for all LVAD patients. The fact that 73 patients were excluded for various reasons speaks to the overall heterogeneity within this patient population, especially with respect to INTERMACS score at time of implantation and risk for post-operative complications.

Secondly, the authors did not include the average pump speed or range of pump speed, which has been associated with outcomes. The authors felt that without a prospective protocol in place the association between pump speeds and heparin anticoagulation would be difficult to address. Further, due to a potential change in management practice as a result of patient inclusion into the PREVENT study, we did not feel this information would be beneficial.

Finally, as the primary emphasis of this study was to evaluate the effectiveness of the AF/stroke prophylaxis heparin protocol on achieving and maintaining therapeutic anticoagulation, assessment of differing protocols on clinical outcomes was not possible. Given the small sample size of this analysis, a direct comparison would unlikely be powered to distinguish any differences in outcomes. However, this analysis should be utilized as a starting point for subsequent analyses addressing the question of how differences in heparin protocols may influence clinical outcomes.

Conclusion

Patients initiated on heparin atrial fibrillation and stroke prevention protocol only achieved therapeutic anticoagulation approximately 40% of the time. Even after patients achieved a therapeutic aPTT, time in therapeutic range was only 48.7%; however, despite these seemingly low values the demonstrated risk of thrombosis was similar to published literature. Individual centers should perform ongoing assessment of effectiveness of individual heparin protocol for LVAD to ensure anticoagulation is optimized in these highly complex patients.

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