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Thrombolytics in VAD management — A single-center experience

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ABSTRACT

Background: With continued increase in the use of mechanical circulatory support, the incidence of device thrombus remains a challenge. This study is a retrospective analysis of data at a single center to assess the safety and efficacy of thrombolytic use in durable mechanical assist devices.
Methods: Data was analyzed retrospectively from 154 patients who underwent left ventricular assist device (LVAD) implantation from 1/1/2005 to 6/30/2014. The HMII device was implanted in 131 patients while 23 received the HVAD. LVAD thrombus was diagnosed when lactate dehydrogenase levels exceeded 1000 units/l accompanied by clinical signs of hemolysis and heart failure, echocardiographic data and surges in pump power. TPA (tissue plasminogen activator) protocol consisted of a 5 mg intravenous bolus followed by 3 mg/h infusion in normal saline for 10 h. If symptoms persisted another cycle of TPA at 1 mg/h was continued up to 48 h.
Results: The TPA group had a 70% success rate. Success was defined as complete resolution of hemolysis and clinical symptoms with no requirement for LVAD exchange at 30 days. 95% survival was noted at 30 days and 90% were free of a hemorrhagic stroke in the TPA group. The rates of hemorrhagic strokes in the TPA group and the control group were not different (OR = 0.92).
Conclusion: The TPA protocol described here was successful consistently. Though this study is limited by its size and retrospective nature it leads the way for larger studies to generate more robust comparisons between different types of mechanical assist devices as well as the tailored use of thrombolytics in this patient population.

1. Background

Left ventricular assist devices (LVADs) have rapidly evolved as a standard therapy for end stage heart failure either as bridge to transplant (BTT) or as destination therapy (DT). The continuous-flow LVADS are smaller, less audible and more durable than the older pulsatile pumps. The smaller size allows placement in patients with a smaller body habitus [1]. With the extension of life and the more frequent use of these devices, complications have also evolved in this population of patients. Of these, bleeding and thrombosis have been the two major challenges.

The HeartWare HVAD (centrifugal pump) and the HeartMate II (axial-flow) provide unloading of the left ventricle throughout the cardiac cycle. This property leads to low pulse pressures and predisposition to arteriovenous malformations in the gastrointestinal tract contributing to bleeding. Bleeding is one of the most common adverse events in the first month after implantation [2]. Additionally the shear forces generated by these pumps accentuate the bleeding risk due to acquired von Willebrand disease which is known to resolve after device explant [2]. Passive hepatic congestion secondary to biventricular failure can also predispose these individuals to increased bleeding complications.

Thrombus formation is the other complication that affects the mechanical circulatory support population. Mechanical causes of thrombosis include post-surgical ventricular debris, emboli secondary to clots in the left atrial appendage and endocardial surface of the LV as well as inflow cannula malposition [3]. Inadequate anti-coagulation or anti-platelet therapy can contribute to thrombus formation. Interaction of prosthetic material with blood, leads to significant prolongation of hematologic, inflammatory, or immunologic responses. Prolonged activation of endothelial and coagulation systems after continuous flow-VAD implantation also seem to contribute to observed thrombosis. Intercellular adhesion molecules, E-selectin, tissue factor and D-dimer have all been shown to be up regulated status post-implantation [4,5].

Both HeartWare (HVAD) and HeartMate II (HMII) patients are susceptible to thrombosis. Increasing incidence of pump thrombosis has been well documented in literature [6–8]. Pump thrombosis can cause life-threatening device malfunction and embolic strokes. Patients with end-stage heart failure also tend to be in a pro-inflammatory state which can promote thrombosis. Multiple mechanisms appear to contribute to pump thrombosis [3–8].

Pump thrombosis is typically diagnosed by combination of increasing lactate dehydrogenase (LDH)/plasma free hemoglobin, low

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haptoglobin, hematuria, low flow, cardiogenic shock, inability to unload the left ventricle, pump power surges and sustained power elevations [3]. Imaging modalities, such as CT and echocardiogram, are often used to help identify thrombosis [9,10]. The efficiency of these modalities to visualize the interior aspect of the pump is limited hence the entire clinical picture needs to be used to arrive at the diagnosis. There is limited data on the best therapy for pump thrombosis at present. Recommendations for management vary widely ranging from medical management to catheter-directed thrombolysis and/or pump exchange as the first option [7–20].

The incidence of device thrombosis has been estimated as 2–13% in adult continuous-flow devices [3,6,8,21,22]. Prevention of thrombosis would be the most ideal strategy, which seems far away in the present day. The optimal doses of antiplatelet and anticoagulation treatments are still undefined due to lack of well-designed/controlled clinical trials. Despite a fairly rigid regimen of anticoagulation and antiplatelet measures, pump thrombosis still occurs and has devastating consequences [23–27]. In addition to the existing routinely used regimens, other anticoagulants/antiplatelet agents reported in the literature include dipyridamole, pentoxifylline, dextran, and fluindione [28–31].

Several etiologies for pump thrombosis, and the dilemma faced with treatment options, make this an important area of ongoing research [6,8,22,32]. Though much knowledge has been gained in the field of anticoagulation, it is still difficult to pinpoint the few factors that predispose the patient to a device thrombus. Hence, the definition of a universal robust anticoagulation protocol still remains ambiguous.

As the standard of care in most centers is LVAD exchange which is a procedure associated with a high mortality and morbidity, a trial of TPA thrombolysis may be appropriate prior to such a major surgical undertaking in the absence of any contraindications. This retrospective study therefore seeks to examine results of thrombolytic treatment administered peripherally for LVAD thrombosis in both HVAD and HMII patients at a single center. The specific aims are 1) to determine if device thrombosis can be successfully treated with tissue plasminogen activator (TPA) protocol used in this center 2) to assess complications associated with TPA treatment.

2. Methods

This retrospective study was approved by Institutional Review Board Spokane (IRB#1942) in Spokane, Washington. A retrospective chart review was performed on patients who had either received a HeartMate II LVAD [Thoratec Corp., Pleasanton, CA] or a HeartWare HVAD LVAD [HeartWare Inc., Framingham, MA] for BTT or DT during the time period of January 1st, 2005 to June 30th, 2014. Patients who did not survive implant or received biventricular assist devices were excluded from the analyses. The sample included both men and women, who were 18 years or older. Patients included in this analysis were hemodynamically stable and underwent VAD exchange if they failed TPA treatment. The anticoagulation protocol consisted of aspirin and coumadin as per manufacturer's recommendations (target INR of 1.8 to 2.5 for HMII and 2.0 to 3.0 for HVAD). On admission PT/INR, PTT, CBC, complete metabolic panel, fibrinogen and a thromboelastogram with platelet mapping were obtained. A 2-D echocardiogram was also performed on admission.

2.1. Patient population and characteristics

Patient demographics collected included gender, age at LVAD implant, Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profile, indication for LVAD (BTT or DT), type of LVAD and history of comorbidities such as ischemic cardiomyopathy, hypertension, diabetes mellitus, peripheral vascular disease, tobacco use, anemia or hypercoagulable syndrome.

Analyses of factors that predispose to LVAD thrombus included length of VAD support, type of LVAD, history of peripheral vascular disease (PVD), tobacco use, hypercoagulable state, anemia, hypertension and diabetes. Additional outcome variables were evaluated for patients who met the criteria for suspected LVAD thrombus, including time to thrombus event, time to the second thrombus event (if applicable), use of TPA, and LVAD exchange. Any differences in time to occurrence of suspected thrombus between the two LVAD types were also evaluated. Adverse events such as renal failure, hemorrhagic CVA, and right ventricular failure were evaluated in conjunction with TPA administration. Success with TPA administration was defined as resolution of hemolysis and no indication for LVAD exchange for 30 days.

3. Study design

Retrospective analyses were performed on patient charts after IRB approval. The study population comprised of 154 patients who underwent left ventricular assist device (LVAD) implantation (131-HeartMate II and 23-HVAD) from 1/1/2005 to 6/30/2014. They were divided into four groups — HM II with device thrombosis, HVAD with device thrombosis, HM II with no device thrombosis, and HVAD with no device thrombosis (Fig. 1A). A total of 24 patients were diagnosed with LVAD thrombus. Of these, 20 patients received TPA infusions, 3 underwent LVAD exchange and 1 patient was placed on heparin and Plavix (Fig. 1B). Patients who were hemodynamically unstable underwent LVAD exchange.

3.1. Diagnosis of thrombosis

Occurrence of LVAD thrombus was suspected with elevated LDH, hematuria, elevated quantitative plasma free hemoglobin. Diagnosis of LVAD thrombus was made when lactate dehydrogenase levels exceeded 1000 units/l in addition to clinical signs of hemolysis and heart failure and echocardiographic findings listed above. The plasma free hemoglobin was monitored concomitantly but absolute cut off values were not used to make a diagnosis due to high variability in the assay values at this center. A cannula flow velocity of >2 m/s by echocardiography with more frequent opening of the aortic valve than at baseline in the context of increasing left ventricular internal dimension in diastole (LVIDd) without any manual speed changes was considered suggestive of a thrombus.

3.2. TPA protocol

TPA protocol typically consisted of a 5 mg intravenous bolus followed by 3 mg/h infusion in normal saline for 10 h. In cases where thrombus persisted as defined by laboratory data and clinical signs another cycle of TPA at 1 mg/h was continued up to 48 h. The total TPA dose never exceeded a maximum limit of 100 mg. All TPA infusions were performed via a peripherally inserted central intravenous line in the cardiac intensive care unit.

3.3. Statistical analysis

Descriptive statistics (mean, median, and standard deviation) were used to characterize the patient population, including baseline characteristics, thrombosis rates between devices, and results of TPA treatment and associated events. Success rates for TPA treatment were computed. Inferential statistics were used to test for independence between groups. A t-test was used to compare means for age and time to LVAD thrombosis, with confidence intervals denoted. The Chi-square test or Fischer's exact test (for small sample size) was used to test for independence between categorical variables. The Cramer's V test was utilized to calculate correlation. Odds ratios (OR) were calculated for categorical data. Statistical tests were performed using SPSS and Excel. Results were considered significant if $p < 0.05$.