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Tissue plasminogen activator in left ventricular assist device-related intravascular hemolysis after failed augmented anticoagulation

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Abstract

Objectives: We sought to examine the efficacy and safety of adding fibrinogen-guided low-dose multi-day Alteplase™ tissue plasminogen activator (tPA) in the management of intravascular hemolysis (IVH) in patients with the HeartMate II (HM-II) continuous flow (CF) left ventricular assist device (LVAD) who failed to achieve IVH resolution with conventional augmented anticoagulation (AAC).

Background: IVH in patients with LVAD is often treated with AAC, failing which pump exchange is considered. We hypothesized that a trial of low-dose tPA after failed AAC therapy could resolve IVH and prevent pump exchange in some patients.

Methods: We performed a retrospective study of 31 HM-II CF LVAD patients admitted to our center from January 2015 to January 2020 for IVH management who received tPA following failed AAC. Primary 6-month outcomes included successful IVH resolution, unsuccessful IVH resolution requiring pump exchange, gastrointestinal bleeding, ischemic and hemorrhagic cerebrovascular accident (CVA), and death.

Results: Thirty-one patients with IVH were treated with tPA following failed AAC. Successful resolution of IVH occurred in 22/31 (71%) patients. Pump exchange occurred in 9/31 (29%) patients. Gastrointestinal bleeding occurred in 7/31 (22.6%) patients. Ischemic CVA occurred in 6/31 (19.4%) patients.

Conclusions: Management of IVH with administration of low-dose tPA after failed AAC is feasible and may prevent pump exchange in some patients.

Keywords

Augmented anticoagulation, tPA, tissue plasminogen activator, LVAD, left ventricular assist device, IVH, intravascular hemolysis

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Background

Pump thrombosis is a life-threatening complication of continuous flow (CF) left ventricular assist device (LVAD). Elevated lactate dehydrogenase (LDH) an indicator of intravascular hemolysis (IVH) and predicts development of pump thrombosis. While pump exchange is standard treatment of IVH per current guidelines, most centers have

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treatment protocols which include augmented anticoagulation (AAC) with intravenous unfractionated heparin (UFH) and agents such as glycoprotein IIB/IIA antagonists or direct thrombin inhibitors, the failure of which leads to pump exchange.[1–3] AAC is more likely to result in sustained medical resolution of IVH in patients with LDH levels of 2.5–3.2 versus >3.2 upper limit of normal (ULN) (ULN = 230 U/L).[4] Patients who do not achieve resolution of IVH are more likely to undergo pump exchange. Unfortunately, pump exchange is associated with significantly increased risk of mortality.[4–6]

Full-dose systemic and catheter-directed thrombolytics have been used for IVH with variable success but with high rate of intracranial bleeding.[7,8] Low-dose Alteplase™ tissue plasminogen activator (tPA) (24–50 mg infusion) has been used in the management of pulmonary embolism successfully with only 10% risk of major bleeding and no intracranial or fatal bleeding.[9] We hypothesized that a trial of low-dose tPA after failed AAC therapy could resolve IVH and prevent pump exchange in some patients (Figure 1).

We designed and implemented a tPA protocol which adds fibrinogen-guided low-dose multi-day tPA administration as an intermediate step between failed AAC and pump exchange for the management of IVH. Low-dose tPA was defined as 18 mg over 6 h/day (3 mg/h rate of infusion). We examined the safety and efficacy of the tPA protocol. To the best of our knowledge, no study to date has evaluated the use of low-dose systemic tPA with multi-day administration in the management of IVH in patients with the HeartMate II (HM-II) CF-LVAD (Abbott Laboratories, Abbott Park, IL, USA).

Methods

Study design, protocol definitions, and participants

We performed a retrospective chart review of HM-II CF LVAD patients admitted to the Houston Methodist Hospital from January 2015 to January 2020 for IVH management. We included all patients who continued to exhibit IVH following failed AAC. IVH was defined as two consecutive readings of LDH ⩾600 U/L, that is, 2.6 times the ULN (ULN = 230 U/L). We excluded patients with contraindications to tPA therapy (Table 1).

Low-dose tPA protocol

After patients were diagnosed with IVH, AAC regimen was initiated in the inpatient setting with intravenous UFH as anticoagulant with a goal partial thromboplastin time (PTT) of 60–80 s, and dual antiplatelet drugs (aspirin 325 mg daily and dipyridamole 75 mg 3–4 times a day). If PTT remained therapeutic for 72–96 h and LDH remained elevated, and/or the patient had worsening heart failure or end organ dysfunction, this was considered failure of AAC regimen. Patients then underwent fibrinogen-guided low-dose multi-day tPA administration as an intermediate step between AAC and pump exchange.

The decision was made to administer tPA on a day-by-day basis depending on the patient's eligibility for tPA. Patients were eligible for tPA if they had persistent LDH ⩾ 600 U/L and fibrinogen ⩾200 mg/dL (Figure 2). On each day of tPA administration, intravenous UFH was held and tPA was administered when PTT ⩽ 50 and INR ⩽ 1.9. Seven patients received a bolus of 3 mg of tPA on the first day of tPA administration. The tPA protocol was subsequently modified to include no initial bolus. tPA was given as a continuous infusion of 3 mg/h for 6 h for a total daily dose of 18 mg. UFH was restarted 2 h post-completion of tPA infusion (goal PTT 60–80 s). Serum LDH and fibrinogen were rechecked the following morning and low-dose tPA infusion was repeated daily for a maximum of 7 days to achieve a goal of LDH <600 U/L. If IVH was not resolved after completion of the tPA protocol and/or the patient had worsening heart failure or end organ dysfunction, treatment was considered a failure and we proceeded with pump exchange. Complications of tPA therapy were monitored closely through frequent neurological exams and assessment of vital signs: every 15 min for the first hour of infusion; every 30 min for the second hour of infusion; and every 1 h until the end of the infusion. Patients were also monitored for signs and symptoms of bleeding, including epistaxis, gastrointestinal hemorrhage, hematoma, hematuria, bloody nasogastric aspirate, or a drop in hemoglobin. The prescriber was contacted for any neurological changes; systolic blood pressure less than 90 mmHg; or heart rate <60 or >120 beats per minute. Patients underwent emergency computed tomography if intracranial bleed was suspected.

Study design

HM-II CF LVAD patients admitted on and after January 2015 for IVH who failed AAC were managed per the tPA protocol. As patients with recurrent IVH represent a sicker cohort with higher risk for morbidity and mortality, our primary analysis included patients with a first event of IVH. Primary 6-month outcomes included successful IVH resolution, unsuccessful IVH resolution requiring pump exchange, gastrointestinal bleeding, ischemic and hemorrhagic cerebrovascular accident (CVA), and death. Bleeding events were counted from tPA administration up to 48 h after the last dose of tPA. Outcomes were analyzed at 6-month follow up.

We further performed a subgroup analysis in patients with LDH greater than 3.2 ULN on admission to assess efficacy and safety of tPA administration. We also performed a secondary analysis on patients with recurrent IVH who previously had successful IVH resolution with tPA administration.

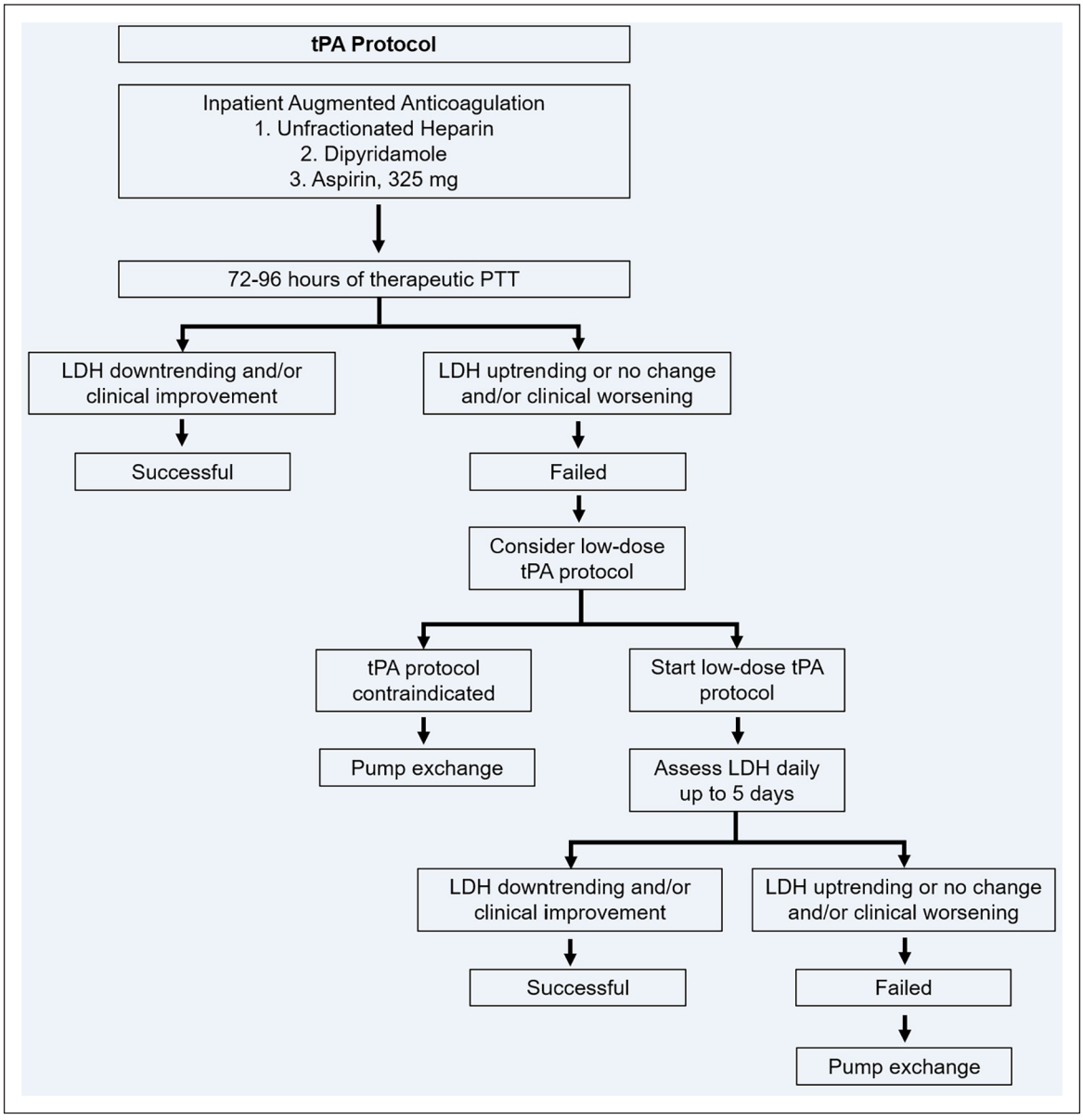

Figure 1. tPA Protocol.
LDH: lactate dehydrogenase; PTT: partial thromboplastin time; tPA: Alteplase™ tissue plasminogen activator.

Table 1. Contraindications for tissue plasminogen activator (tPA) administration.

Contraindications for tPA administration
Acute internal bleeding
History of intracranial hemorrhage
Severe uncontrolled hypertension (mean arterial pressure >90 mmHg)
Serious head trauma
Stroke within the past 3 months
Presence of intracranial conditions that may predispose to bleeding • *Arteriovenous malformation* • *Aneurysm* • *Certain neoplasms*
International normalized ratio >2.0
Platelet level <100,000

Major bleeding was defined according to the International Society on Thrombosis and Hemostasis criteria.[10] These criteria include fatal, that is, suspected or confirmed bleeding as the cause of death; symptomatic bleeding in a critical area (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial, or intramuscular with compartment syndrome confirmed on computed tomography); and clinically overt, that is, associated with a drop in hemoglobin of 2 g/dL or more within a 24-h time frame or requiring transfusion of two or more packed red blood cell (PRBC) units.[10] Hemostasis was defined as the absence of PRBC transfusions.

Our study was conducted with approval from the Houston Methodist Hospital institutional review board. Charts were reviewed for relevant clinical and laboratory data.

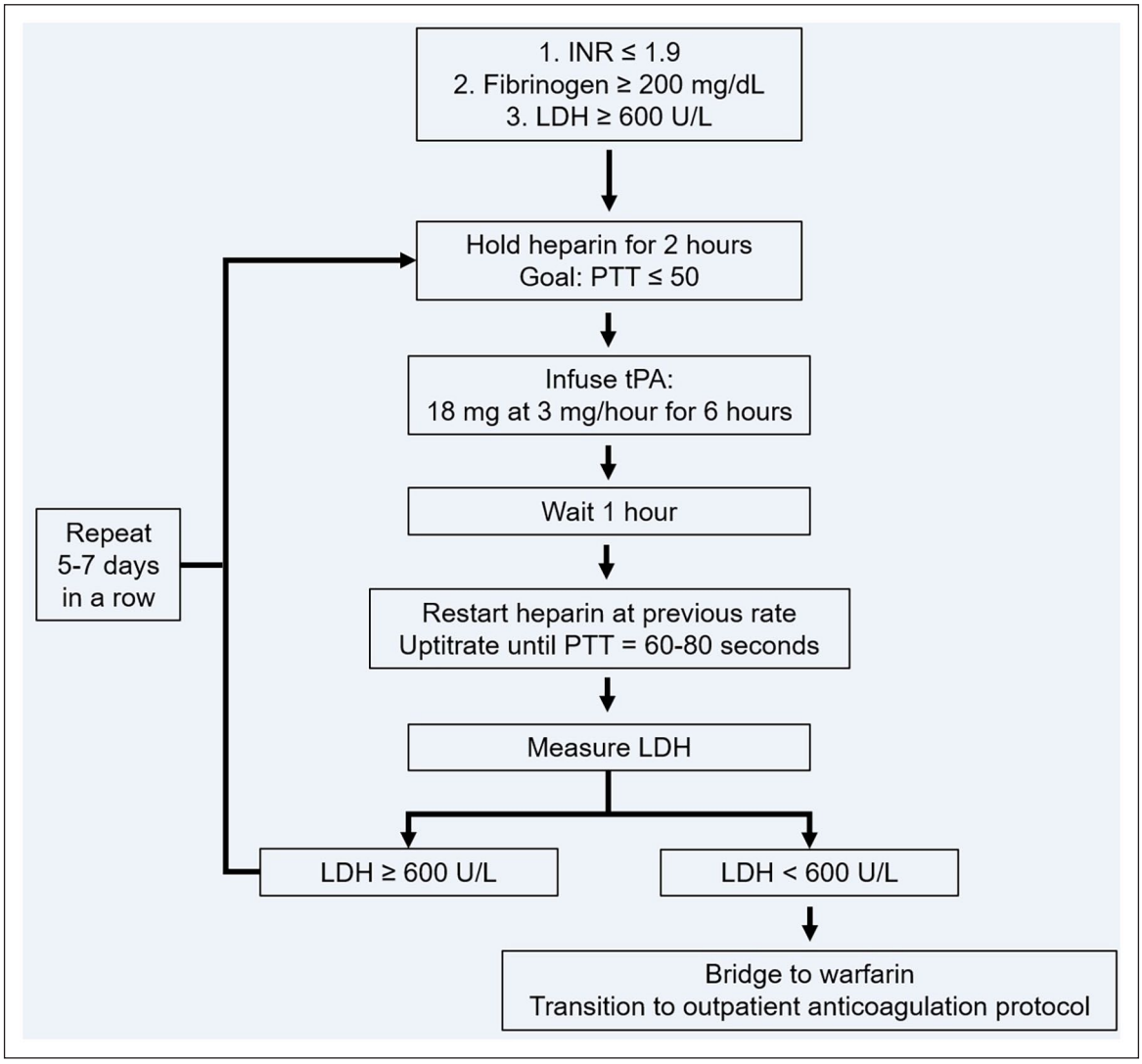

Figure 2. tPA Eligibility and administration.
INR: international normalized ratio; LDH: lactate dehydrogenase; PTT: partial thromboplastin time; tPA: Alteplase™ tissue plasminogen activator.

Statistical analysis

Demographic and clinical data were reported as median and interquartile range (IQR) for continuous variables, and as frequencies and proportions for categorical variables.

Results

Study population

Between January 2015 and January 2020, a total of 31 patients were admitted with IVH and received tPA therapy after failed conventional AAC (Table 2). The median age of the cohort was 62 years (IQR 52–68) with 27/31 (87.1%) males and 4/31 (12.9%) females. Median time on chronic LVAD support was 453 days (IQR 144.0–1022.4). Median total bilirubin on admission was 1.0 mg/dL (IQR 0.7–1.5). Median AST on admission was 62.0 U/L (IQR 45.5–99.25). Median LDH following failed AAC was 1342 U/L (IQR 978.0–1697.0).

Six-month primary outcomes

Successful resolution of IVH occurred in 22/31 (71%) patients (Figure 3). Among the remaining nine patients who failed the tPA protocol, all 9/31 (29%) underwent pump exchange. Gastrointestinal bleeding occurred in 7/31 (22.6%) patients. Ischemic CVA occurred in 6/31 (19.4%) patients, though none had major neurological deficits. Of the nine patients who underwent pump exchange, 1/9 patients (11.1%) died within 6 months. There were no hemorrhagic CVA events.

Median tPA duration was 3 days (IQR 2–5). Median tPA dose received was 72 mg (IQR 36–90). Median time between the last dose of tPA and pump exchange was

Table 2. Baseline characteristics for 31 patients who underwent tissue plasminogen activator (tPA) protocol.

Baseline characteristics	
Patient demographics	
Median age	62 (IQR 52–68)
Male	27 (87.1%)
Median time on chronic LVAD support	453 days (IQR 144.0–1022.4)
Pertinent laboratory data	
Median LDH following failed AAC	1342 U/L (IQR 978.0–1697.0)
Median total bilirubin on admission	1.0 mg/dL (IQR 0.7–1.5)
Median AST on admission	62.0 U/L (IQR 45.5–99.25)

AAC: augmented anticoagulation; AST: aspartate aminotransferase; LDH: lactate dehydrogenase; LVAD: left ventricular assist device.

5 days (IQR 3–30). Median pre-tPA LDH was 1197 U/L (IQR 951.3–1542) in tPA responders and 1802 U/L (IQR 1333–2350) in non-responders who underwent pump exchange.

Subgroup analysis in patients with LDH > 3.2x ULN on admission

In a post-hoc analysis from the PREVENT study, patients with IVH and LDH > 3.2 ULN did not respond well to AAC. Hence, we studied this subpopulation to assess if tPA would be a viable option for these patients. 29/31 (93.5%) patients presented with LDH > 3.2 ULN following AAC and prior to receiving tPA. Among these 29 patients, 20/29 (69.0%) had successful resolution of IVH, and 9/29 (31.0%) underwent pump exchange.

Secondary analysis on patients with recurrent IVH

Of the 22 patients who underwent successful IVH resolution under the tPA protocol, 7/22 (31.8%) had a recurrence event within 6 months. In 3/7 (42.9%) patients, IVH recurrence was treated by medical management, followed by a second IVH recurrence that was successfully resolved with repeat tPA administration. 1/7 (14.3%) patients had two recurrence events; IVH in both recurrences was successfully resolved with repeat tPA administration. 1/7 (14.3%) patients who had IVH recurrence underwent pump exchange, had a second IVH recurrence and underwent unsuccessful tPA administration followed by orthotopic heart transplant. 2/7 (28.6%) patients with IVH recurrence underwent pump exchange.

Discussion

In this analysis of management of IVH in patients with the HM-II CF-LVAD at a single center, we found: (1) a protocol incorporating low-dose multi-day administration of tPA following failed conventional AAC is effective in decreasing the frequency of pump exchange; (2) this protocol, when feasible, is a safe strategy without increased risk of major bleeding or neurological events; (3) this strategy can also be implemented in patients with IVH and LDH > 3.2 ULN, in whom an AAC alone is not successful; and (4) repeat administration of tPA in patients with recurrent IVH who previously had successful IVH resolution with tPA administration may further delay pump exchange.

Low-dose thrombolysis as a strategy for treatment in IVH

In this paper, we present a tPA protocol which includes the addition of low-dose thrombolytics following conventional AAC that will allow for maximization of IVH resolution while maintaining a safe clinical profile. Our protocol starts with intensification of antiplatelet therapy by using full-dose aspirin and the addition of dipyridamole, along with maintenance of therapeutic anticoagulation level (goal PTT 60–80 s) by using intravenous UFH. This is followed by tPA if the level of LDH does not normalize after 72–96 h of AAC.

Thrombolytic use through both systemic and catheter-directed routes have been reported by other centers in both centrifugal and axial CF pumps. The thrombolytic dose in studies with systemic administration ranged from 0.5 to 1.0 mg/kg administered as a fast infusion within 30–60 min.

The tPA dose in our protocol was calculated using a 70 kg patient at 0.25 mg/kg/day, which calculates to 18 mg/day. Compared to existing studies, our protocol uses a lower maintenance dose of 3 mg/h for a shorter period per day as well as intermittent therapy, which allows reassessment of hemolytic markers on daily basis.

Efficacy of low-dose tPA in the management of IVH

Medical management with AAC for pump thrombosis is known to have modest efficacy. Intravenous UFH remains the most commonly used agent in this context; however, its efficacy is reported as low as 23%.[11] This resulted in the need for pump exchange or heart transplantation in 48% of patients.[11] Using intravenous UFH in conjunction with

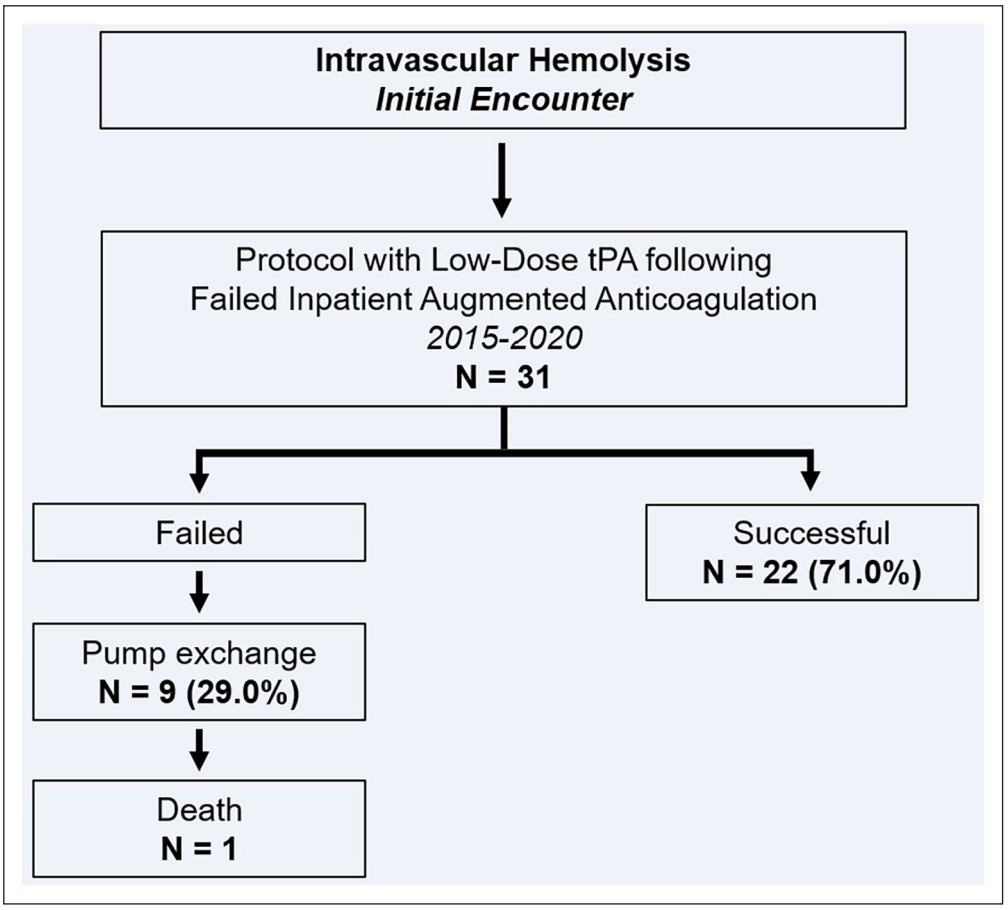

Figure 3. Six-month primary outcomes.
tPA: Alteplase™ tissue plasminogen activator.

other agents such as glycoprotein IIb/IIIa inhibitors and/or a direct thrombin inhibitor, results in only a slight increase in the rate of complete resolution (49%).[11] In a group of patients supported with the HeartWare Ventricular Assist Device (Medtronic, Dublin, Ireland), medical management resulted in resolution of pump thrombosis in 50% of cases.[12] In patients with the HM-II CF LVAD, our data indicate an even lower percentage of IVH resolution using conventional medical therapy. In a pre-tPA historical control group of 27 patients admitted to our institution between 2008 and 2019, resolution of IVH failed to occur in 55.5% of AAC patients as compared to only 29% of patients undergoing tPA therapy. In addition, 40.7% of patients on the AAC protocol required pump exchange as compared to only 29% of patients in the low-dose tPA protocol. Thus, there is a need for therapy prior to proceeding with pump exchange, which is well-associated with significant mortality and morbidity. Our data indicate that tPA is an effective treatment in patients with pump thrombosis with resolution of IVH in 77.8% of patients on admission. This is generally in agreement with earlier data which show resolution of pump thrombosis between 60% and 63% in patients supported with the HM-II CF LVAD.[13,14]

Safety of low-dose tPA in the management of IVH

Bleeding continues to be a major adverse event in the management of patients supported with LVAD, with gastrointestinal bleeds being the most common.[15] As bleeding is the most common complication of tPA, use of tPA in LVAD patients can increase this risk. An appreciation of bleeding adverse events becomes particularly important in the treatment of pump thrombosis, as its incidence increases up to 49% based on the medical regimen used.[11] Of the nine patients who underwent pump exchange in our study, only one patient died 5 months after the initial IVH episode; however, this is unlikely to be related to tPA use due to its short half-life. In addition, none of our patients developed intracranial hemorrhagic complications or other major bleeding due to tPA. Any bleeding events that occurred were minor, and no patients required PRBC transfusion.

In a meta-analysis of prior case reports and small cohorts of pump thrombosis, the pooled major bleeding risk in the various thrombolytic regimens was 29% compared to 12% in patients treated without thrombolytics.[11] This is likely related to the different protocols used in the literature.

Recently, a more defined tPA protocol was reported to carry a lower risk of bleeding; however, hemorrhagic CVA was still seen in 10% of patients.[14] Although this might be due to the administration of tPA bolus, its elimination did not improve the rate of intracranial bleeding in a different study.[16] We elected to modify our tPA protocol to no bolus after one patient developed an ischemic stroke. Compared to prior studies, we used a lower tPA dose over a shorter period per day. Furthermore, we included only patients with fibrinogen level $\geq$200 mg/dL based on prior data that showed that patients receiving tPA for acute lower extremity intravascular thrombosis had a 28% increased risk of major bleeding when fibrinogen was $\leq$150 mg/dL.[17] These changes decreased the incidence of major bleeding with none of our patients developing fatal or intracranial bleeding or requiring PRBC transfusion. Of patients who received tPA, 19.4% developed ischemic CVAs, though none had major neurological deficits. However, this cannot be attributed to tPA due to its short half-life.

Selection of patients

Our center's initial experience of tPA therapy came out of a necessity of treating patients with IVH who were considered high-risk for surgery or who were reluctant to undergo another surgery. While this strategy is now instituted in all patients with IVH at our center, we believe it should be considered in those patients who are at high surgical risk; listed for heart transplantation; and/or reluctant to undergo another surgery. As demonstrated in our study, in patients who present with LDH $>$ 3.2 ULN, low-dose tPA following failed AAC remains an effective strategy.

Conclusions

Administration of low-dose tPA following failed AAC is an effective and safe strategy in the management of IVH in selected HM-II CF-LVAD patients.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Bhimaraj has consulting agreements with Abbott, Abiomed, Care Dx, and Maquet. All other authors report no disclosures.

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Consent

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate.

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Tweet

We explored the use of low-dose tPA in the management of intravascular hemolysis in HeartMate II patients. Check out our results here! #HeartFailure

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