American Journal of Case Reports

ISSN 1941-5923
© Am J Case Rep, 2017; 18: 294-298
DOI: 10.12659/AJCR.902320

Received: 2016.11.10
Accepted: 2017.01.17
Published: 2017.03.23

An Anti-Coagulation Conundrum: Implantation of Total Artificial Heart in a Patient with Heparin-Induced Thrombocytopenia Type II

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 44
Final Diagnosis: Heparin-induced thrombocytopenia Type II
Symptoms: Congestive heart failure • short of breath
Medication: —
Clinical Procedure: LVAD explantation • TAH insertion
Specialty: Anesthesiology

Objective: Rare co-existance of disease or pathology

Background: Heparin-induced thrombocytopenia (HIT) is a rare but life-threatening complication of heparin administration. It can present a major clinical dilemma for physicians caring for patients requiring life-saving urgent or emergent cardiac surgery. Studies have been published examining the use of alternative anticoagulants for patients undergoing cardiopulmonary bypass (CPB), however, evidence does not clearly support any particular approach. Presently, there are no large-scale, prospective randomized studies examining the impact of alternative anticoagulants on clinical outcomes for HIT-positive patients requiring cardiac surgery.

Case Report: We present the case of a patient who underwent SynCardia Total Artificial Heart (TAH) implantation following a recent left ventricular assist device (LVAD) placement. The patient was receiving argatroban for type II HIT with anuric renal failure, and developed a thrombus which occluded the inflow cannula of the LVAD. Based on a published study and after establishing consensus with the surgical, anesthesiology, perfusion, and hematology teams, we decided to use tirofiban as an antiplatelet agent to inhibit the platelet aggregation induced by heparin, and ultimately used heparin as the anticoagulant for cardiopulmonary bypass.

Conclusions: When selecting anticoagulation for a HIT-positive patient requiring CPB, so that benefits outweigh risks, it is of paramount importance that the decision be based on a multitude of factors. The team caring for the patient should have a shared mental model and be familiar with the pharmacology, devices used, and local practices. These three elements should be integrated with patient-specific comorbidities along with local monitoring capabilities to ensure safe, efficient patient care.

MeSH Keywords: Acute Kidney Injury • Anticoagulants • Cardiopulmonary Bypass • Heart, Artificial • Heparin

Full-text PDF: http://www.amjcaserep.com/abstract/index/idArt/902320

Background

Our case report describes an alternative to heparin for the implantation of a total artificial heart (TAH). Cardiopulmonary bypass (CPB) in patients with heparin-induced thrombocytopenia (HIT) is challenging, particularly in patients with renal impairment requiring dialysis. Other anticoagulants have been used as a substitute for heparin in similarly difficult cases [1–4]. R-hirudin and danaparoid sodium are associated with hemorrhage; and severe hypotension can be related to another alternative technique, the administration of unfractionated heparins combined with the platelet inhibitor tirofiban, a gpIIb/III antagonist. Although cases also have been successfully managed with bivalirudin [1], this can be challenging in the setting of renal failure. Our report adds to the literature of alternative, successful techniques that can be used safely for complex adult cardiac cases.

Case Report

We present a case of a 44-year-old male with recently diagnosed non-ischemic dilated cardiomyopathy with an ejection fraction of 10–15% and an automatic implantable cardioverter defibrillator (AICD) for primary prevention. The patient had no other significant past medical or surgical history, except previous uneventful orthopedic procedures. The patient was admitted with a congestive heart failure (CHF) exacerbation unresponsive to medical management and underwent insertion of a HeartWare left ventricular assist device (LVAD). The postoperative course was complicated by fever, right ventricular (RV) failure, ischemic hepatitis, renal failure requiring continuous renal replacement therapy (CRRT), ventricular and atrial tachycardia, platelet serotonin-release assay positive HIT, and thrombus in the left ventricle (LV) around the inflow cannula and in the mitral valve (Figure 1). The surgical team's only viable option was the implantation of a SynCardia TAH. One of the primary concerns was the management of anticoagulation for CPB in the setting of HIT combined with anuric renal failure. After an interdisciplinary discussion involving the surgeon, anesthesiologist, hematology service and the perfusion team, a consensus about the management was reached.

The argatroban infusion was discontinued upon arrival of the patient to the operating room. General anesthesia was induced uneventfully using ketamine, fentanyl, midazolam, and cisatracurium. Endotracheal intubation was accomplished in a standard fashion. Prior to induction, a double lumen introducer with single lumen infusion catheter was placed in the right internal jugular vein using ultrasound-guidance. In coordination with the surgeon, approximately ten minutes prior to aortic cannulation, a bolus of 10 mcg/kg of tirofiban was administered and an infusion of 0.15 mcg/kg/minute was initiated. Eight minutes later, a full dose (400 IU/kg) of unfractionated heparin was administered; the endpoint of our heparin administration was to maintain activated clotting times (ACT) greater than 480 seconds for the duration of CPB.

Cardiopulmonary bypass (CPB) was conducted using a centrifugal pump and mild hypothermia. Heparin (5,000 IU) was added to the CPB prime volume in addition to a cardiotomy reservoir. Citrate phosphate double dextrose (CP2D) was used as the anticoagulant for cell salvage per institutional standards. Coagulation status was followed hourly by obtaining a thromboelastogram (TEG) (Figure 2) and serial ACT measurements every 15 minutes. The initial ACT was 253 seconds and CPB time was 187 minutes. The left ventricular device was explanted with circumferential thrombus (Figure 3). The tirofiban infusion was stopped approximately one hour prior to weaning and separation from CPB. Two doses of tranexamic acid were given, one of 9 mg/kg (850 mg) during CPB and one of 7 mg/kg (700 mg) after CPB.

After CPB, heparin was reversed with 350 mg of protamine. The surgeon observed blood in the field without any surgical source of bleeding. TEG demonstrated a prolonged R-time, therefore fresh frozen plasma (FFP) transfusion was initiated. Repeat TEG continued to show R-time prolongation and so cryoprecipitate was infused in addition to FFP. Three-factor prothrombin complex concentrate (PCC) was administered for a total dose of 4,000 IU as well as recombinant factor IX, 1,000 IU of AlphaNine. Platelets were administered for a reduced maximum amplitude on the TEG. The patient developed pulmonary edema resulting in severe oxygenation impairment requiring veno-venous extracorporeal membrane oxygenation (VV ECMO). Three hours after weaning from CPB, clots were observed, concurrent with a clinical improvement in coagulopathy. In total, the patient received 20 U of red blood cells (PRBC), 19 U FFP, 30 U cryoprecipitate, and 5 doses of platelets, in addition to tranexamic acid.

The patient was transferred to the intensive care unit (ICU) on high-dose vasopressors and with an open chest, as the surgeon was unable to re-approximate the sternum secondary to significantly decreased biventricular TAH output which was concomitant with a decline in bilateral cerebral oximetry.

Four hours after arrival to the ICU, the patient required chest re-exploration for a drop in TAH output that was unresponsive to volume administration. No obvious sources of bleeding were found.

The patient remained sedated for several days and exhibited complete neurological function after the sedation was discontinued. He was eventually weaned off of vasoactive support but required tracheostomy and ongoing hemodialysis.

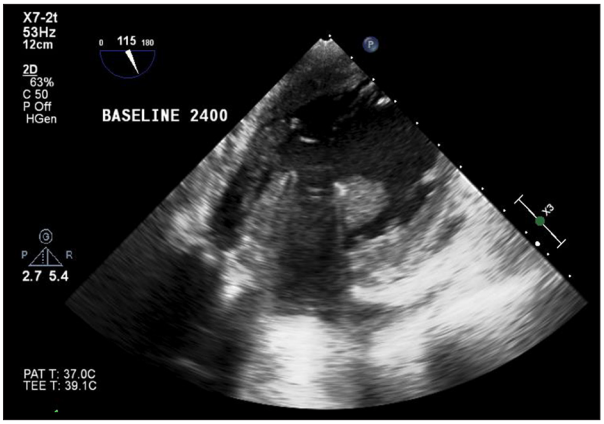

Figure 1. Transesophageal echocardiography demonstrating thrombus around the left ventricular assist device cannula.

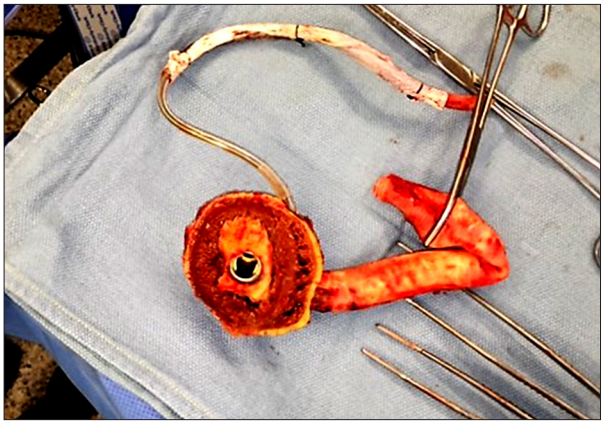

Figure 3. Explanted left ventricular assist device cannula demonstrating circumferential thrombus.

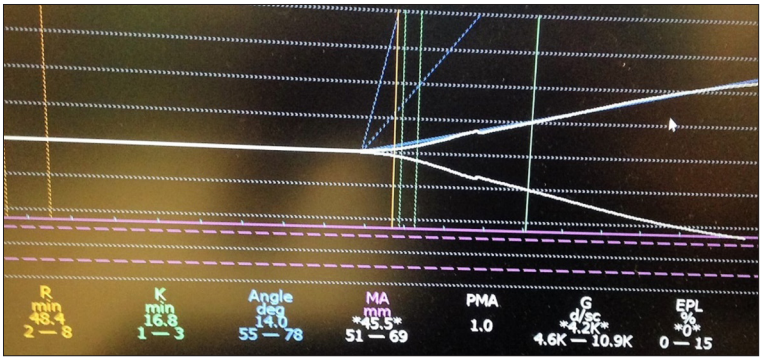

Figure 2. Initial thromboelastography demonstrating prolonged R-time and decreased alpha angle and maximum amplitude.

Unfortunately, he developed a sternal wound infection requiring multiple irrigation and debridement procedures and was unable to ever sleep restfully. The patient's wishes to withdraw care were honored approximately six months after TAH implantation.

Discussion

HIT type 2 is an immune-mediated disorder triggered by the production of antibodies, mostly IgG, against platelet factor-4: heparin complexes. The macro-molecular complex triggers platelet activation and destruction and release of prothrombin micro-particles, creating a prothrombotic state. In the setting of a patient undergoing cardiac surgery requiring CPB, currently available literature does not clearly support a particular management strategy. To be considered an appropriate alternative to heparin for cardiac surgery, a potential agent should be readily available. There should be a clinically timely point of care measurement of the drug effect. The agent's metabolism should be minimally affected by patient comorbidities, or at least in such a way as to have predictable pharmacokinetics. Finally, the agent in question should be readily familiar to the team caring for the patient. In the United States, bivalirudin, argatroban, and lepirudin are approved for the treatment of HIT. Alternative anticoagulation choices for cardiac surgery are danaparoid, lepirudin, bivalirudin, and the use of an antiplatelet agent with heparin. Low molecular weight heparins, ancrod, and argatroban are not ideal agents for the management of CPB [5].

Argatroban is a direct thrombin inhibitor with a relatively short elimination half time (39–51 minutes), but elimination decreases with moderate hepatic impairment with minimal renal clearance. Case reports describe the use of argatroban, for on- and off-pump [6,7] procedures, with acceptable clinical outcomes in some patients; however, intraventricular thrombus, as well as thrombus within the CPB circuit, has also been described. Argatroban does not have a practical point of care method of monitoring. Danaparoid is a low molecular weight glycosaminoglycan that inhibits factor X (half time 25 hours); it is eliminated renally and is not reversed by protamine. With renal impairment, its use has been associated with uncontrolled hemorrhage [8].

Lepirudin, a recombinant hirudin, is a direct irreversible thrombin inhibitor which acts by binding to free and bound thrombin. It has been used in patients for CPB, but excessive bleeding

has been reported. The average plasma half time of 80 minutes can be increased to greater than 120 hours in the presence of renal failure, even though hemofiltration and forced diuresis can be performed at the termination of CPB. There are no approved reversal agents for lepirudin.

Bivalirudin is a reversible thrombin inhibitor with a short half time (~25 minutes) and is cleared primarily by enzymatic breakdown by plasma proteases. These properties make it an attractive alternative for anticoagulation for CPB. However, clearance is decreased by 80% in patients with kidney failure. Though the elimination might be enhanced by hemofiltration, the kinetics and the appropriate point-of-care monitoring strategies are both unknown. Thrombus may be found in areas of stagnant blood, such as the chest cavity or the venous reservoir. After separation from CPB, additional bivalirudin should be added to the CPB circuit since it can rapidly clot due to the metabolism of bivalirudin by proteolytic enzymes [5,9].

Another alternative anticoagulation method for HIT-positive patients requiring cardiac surgery involves administering a potent platelet inhibitor immediately before the administration of heparin. Reports of cases where iloprost, a prostacyclin analog, was administered before heparin showed successful clinical outcomes, but noted profound hypotension as a side effect [5,10].

Unlike the aforementioned agents, tirofiban has unique properties that make it a suitable adjunct to routine anticoagulation management. It binds competitively to the glycoprotein gpIIb/IIIa receptor to cause shorter inhibition of platelet function than the other agents previously discussed. The half-time of tirofiban is approximately two hours and elimination is predominantly (>70%) biliary; its platelet-bound half-life is short, on the order of seconds. Upon discontinuation of tirofiban, platelet function returns to normal in 4–8 hours [4,11]. However, newer studies such as the TENACITY trial recommend decreasing the dose of continuous infusion if the patient has renal impairment [12].

In patients undergoing implantation of the SynCardia TAH, there is a precarious balance between minimizing the risk of excessive bleeding and avoiding thrombosis of the device. Multiple variables are involved which are difficult to completely predict and control, particularly in the setting of multi-organ dysfunction. We previously described the successful use of a glycoprotein gpIIb/IIIa inhibitor in combination with heparin [13], but there have been many possible approaches described previously; none of them are risk free or adjusted to patients with other end-organ dysfunctions. Similarly, at the present time there are no large, randomized clinical trials comparing anticoagulation alternatives to heparin for cardiac surgery in patients with HIT. Given the fact that individual physicians only occasionally manage such patients, all the data is based on low-quality observational studies and case reports. However, since our experience in June 2015, the FDA has approved an alternative called cangrelor, an intravenous P2Y12 inhibitor which has an immediate onset of antiplatelet effect with a half-life of three to five minutes and can be quickly reversed.

Conclusions

In conclusion, when selecting anticoagulation for a HIT patient, so that benefits outweigh risks, it is of paramount importance that the decision be based on a multitude of factors. The team caring for the patient should have a shared mental model and be familiar with the pharmacology, devices, and local practices. These three elements should be integrated with patient-specific comorbidities along with local monitoring capabilities to ensure safe, efficient patient care.

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