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Original Article

Intraoperative Administration of 4-Factor Prothrombin Complex Concentrate Reduces Blood Requirements in Cardiac Transplantation

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Objective: Assessing the efficacy of intraoperative 4-factor prothrombin complex concentrate (4F-PCC) use in blood product utilization, time to chest closure, intensive care unit (ICU) and hospital length of stay (LOS), thromboembolic complications, renal injury and mortality in left ventricular assist device (LVAD) patients on home anticoagulation therapy with warfarin, undergoing orthotopic heart transplantation (OHT).
Design: Retrospective analysis of OHT patients at Tufts Medical Center from May 2013 to October 2016.
Setting: Single-institution, university hospital setting.
Participants: Patients with preexisting LVADs who received orthotopic heart transplants (n = 74; 32 patients 4F-PCC, 42 patients no 4F-PCC).
Interventions: Warfarin reversal using 4F-PCC in patients with LVADs undergoing orthotopic heart transplantation with the 4F-PCC dosing partitioned such that one-third was given pre-CPB and two-thirds were given post-CPB.
Measurements and Main Results: The 4F-PCC group required less plasma (6 [IQR 4] *v* 1.31 [IQR 2] U, $p < 0.001$), cryoprecipitate (10 [IQR 10] *v* 7.50 [IQR 5] U, $p < 0.001$), and packed red blood cells (5 [IQR 4] *v* 2 [IQR 1.5] U, $p < 0.001$) and had a shorter time to chest closure (618.8 ± 111.4 *v* 547.9 ± 110.1 minutes, $p = 0.008$). There was no difference in platelet transfusion (2 [IQR 1] *v* 2 [IQR 1] U, $p = 0.16$), ICU or hospital LOS, acute kidney injury, or mortality. No thrombotic complications occurred.
Conclusions: Replacing plasma with 4F-PCC to reverse preoperative warfarin anticoagulation during OHT was associated with a shorter time to chest closure and less blood product utilization, without an increase in acute kidney injury, thromboembolic complications, or death.

Key Words: Orthotopic Heart Transplantation; Four Factor Prothrombin; Complex Concentrate; 4F-PCC; Coagulopathy; Transfusion

PATIENTS PRESENTING FOR orthotopic heart transplantation (OHT) are frequently supported with left ventricular assist devices (LVAD).[1] The most common anticoagulation regimen for LVAD patients utilizes oral warfarin with a target international normalized ratio (INR) of 2 to 3 to prevent thromboembolic events. Due to the unpredictability of organ

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availability, rapid reversal of warfarin-induced coagulopathy is needed to prevent perioperative coagulopathy. Although vitamin K and fresh frozen plasma (FFP) are commonly utilized to antagonize the effects of warfarin, both agents have limitations. Vitamin K requires a significant amount of time to antagonize the effects of warfarin as its mechanism of action relies on counteracting warfarin's inhibition of the C1 subunit of the enzyme vitamin K epoxide reductase, which is necessary for the activation of the vitamin K-dependent coagulation factors. Limitations of FFP include the time needed to thaw the product, risk of transfusion-associated circulatory overload, and the possibility of transfusion-related acute lung injury. Transfusion of blood products in the transplant population also increases the risk of allosensitization with the introduction of antibodies leading to possible organ rejection.[2] A recently approved alternative for warfarin reversal is prothrombin complex concentrate. The non-activated 4-factor prothrombin complex concentrate (4F-PCC) Kcentra® (CSL Behring, King of Prussia, PA) contains high concentrations of the vitamin K-dependent clotting factors depleted by warfarin (factors II, VII, IX, X, protein C, and protein S), and minimal antithrombin III and heparin.[3] A few institutions have reported reversal strategies for patients undergoing OHT that include preoperative administration of PCCs.[4–7] Additionally, the efficacy of split dosing of 4F-PCCs with half the dose given pre-bypass and half the dose given post-bypass has been established through randomized comparison against FFP.[8] In the authors' protocol for warfarin reversal in LVAD patients undergoing OHT, a fraction of the PCC dose was given post-bypass. All patients received 10 mg intravenously (IV) vitamin K preoperatively, then 4F-PCC was dosed intraoperatively according to patient weight and preoperative INR based on the package insert dosing guidelines.[3] Of note, one-third of the dose was given pre-bypass and two-thirds of the dose was given post-bypass. In this analysis, the authors evaluated their protocol by comparing blood product utilization, time to chest closure, ICU length of stay (LOS), overall length of hospital stay, thrombotic complications and incidence of acute kidney injury, and 30-day mortality with an immediately recent, historical control group. The authors hypothesized that intraoperative administration of 4F-PCC would primarily decrease blood product utilization and secondarily decrease time to chest closure and reduce ICU and overall hospital LOS, without increasing acute kidney injury, thromboembolic events, or mortality.

Methods

Population

Upon approval by Tufts Medical Center Institutional Review Board, the authors performed a retrospective analysis of 96 consecutive patients undergoing OHT from May 2013 to October 2016 at Tufts Medical Center. All data were acquired from the electronic medical record, which became available in May 2013; therefore, patient data were analyzed retrospectively up until the first available cases in 2013. Patients with preexisting LVADs that were anticoagulated with warfarin were selected for analysis, excluding those with simultaneous, additional organ transplants. The following baseline characteristics were recorded: age, sex, body mass index (BMI), heart failure etiology (ischemic versus non-ischemic), preoperative ejection fraction, preoperative international normalized ratio (INR), preoperative hematocrit, preoperative platelet count, preoperative creatinine, cardiopulmonary bypass (CPB) duration, 4F-PCC dosage, and last temperature in the operating room (OR).

Patient Management

Aspirin and warfarin dosing for LVAD anticoagulation was discontinued once patients were positively matched for OHT. After drawing baseline INR, hemoglobin, hematocrit, platelet count, electrolytes, blood urea nitrogen, and serum creatinine levels, patients received Vitamin K 10 mg IV. All patients received a loading dose of 5,000 mg of aminocaproic acid followed by an infusion at 1g/h. Upon initiation of CPB, a second 5,000 mg bolus dose of aminocaproic acid was given to account for the increase in volume of distribution with the bypass circuit. Heparin anticoagulation was initiated with a 400 U/kg IV bolus and monitored with activated clotting time (ACT) by the Hemochron Signature Elite (ITC, Edison, NJ) using ACT Plus cartridges. The minimum ACT for CPB was 430 seconds; measurements were performed 3 minutes after each heparin dose and additional heparin was given as needed during the procedure. Protamine sulfate was administered at a dose of 1:1 to the heparin loading dose.

In the 4F-PCC group, non-activated, 4F-PCC (4F-PCC, Kcentra®, CSL Behring, King of Prussia, PA) was dosed in U/kg based on the patient's preoperative INR. Specifically, if the INR was between 2 and 4, patients received 25 units 4F-PCC/kg actual body weight rounding up to the nearest vial. If INR was between 4 and <6, patients received 35 U/kg actual body weight rounding up to the nearest vial and if INR was >6, patients received 50 U/kg actual body weight rounding up to the nearest vial. No partitioned fractions of vials of 4F-PCC were given to the patients. One-third of the dose was given pre-CPB and two-thirds of the dose was given post-CPB after protamine administration. 4F-PCC was administered centrally over 30 minutes using a syringe pump. Recombinant factor VIIa was not used on any patient. Blood product administration was at the discretion of the surgeon, anesthesiologist, and critical care team and was guided by conventional laboratory coagulation monitoring (PT, PTT, fibrinogen, and platelet count), visualization of clot in the surgical field, and blood loss from thoracostomy tubes.

Comparisons and Definitions

Patients who received 4F-PCC in the post-CPB period ("4F-PCC") were compared with patients who did not receive 4F-PCC ("No 4F-PCC"). Primary outcome measures included intraoperative blood product utilization (cryoprecipitate, FFP, platelets, and packed red blood cells [PRBC]), time to chest closure, ICU LOS, and total postoperative LOS in the hospital. All blood products were standardized in units. Another point