# Impact of Prothrombin Complex Concentrate on Blood Use, Cost, and Outcomes in Heart Transplantation

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*Background.* **Left ventricular assist device (LVAD) recipients undergoing heart transplantation have increased bleeding risk. We compared conventional warfarin reversal with fresh frozen plasma vs 4-factor prothrombin complex concentrate (PCC) and the effect on transfusion requirements, blood bank costs, and clinical outcomes.**

*Methods.* **A retrospective review identified 60 consecutive LVAD recipients undergoing heart transplantation divided into two groups: 30 (no PCC) received fresh frozen plasma and 30 (PCC) received PCC. Patient characteristics, intraoperative and postoperative transfusion requirements, short-term clinical outcomes, and blood bank costs were compared. PCC association with transfusion requirements was assessed by multivariate linear regression.**

*Results.* **Patients who received PCC were younger (50 ± 11 vs 57 ± 13 years, $p = 0.02$), fewer had ischemic cardiomyopathy (23% vs 60%, $p = 0.01$), had more than one prior sternotomy (7% vs 30%, $p = 0.04$), and had higher preoperative hemoglobin (11.8 ± 1.8 vs 10.4 ± 1.8 g/dL, $p = 0.01$). The PCC group had a significantly shorter bypass time (185 vs 217 minutes, $p = 0.01$), received less fresh frozen plasma (2 vs 5 units, $p = 0.03$), cryoprecipitate (0 vs 2 units, $p = 0.05$), and total blood products (9 vs 13.5 units, $p = 0.03$) intraoperatively, and was less likely to require delayed sternal closure (3% vs 23%, $p = 0.05$). On multivariate linear regression, PCC was significantly associated with decreased intraoperative transfusion ($\beta = -6.09$, $p = 0.02$). There was no difference in thromboembolic events or in-hospital death. Total blood bank costs were $4,949 for PCC and $3,677 for no PCC ($p = 0.01$).**

*Conclusions.* **Although more costly, PCC reduced transfusion requirements and delayed sternal closure in heart transplant recipients bridged with LVAD, justifying its use over traditional warfarin reversal.**

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Heart transplant recipients bridged with left ventricular assist devices (LVADs) have an increased risk of perioperative bleeding due to prior sternotomy, presence of acquired von Willebrand disease, and anticoagulation with vitamin K antagonists [1–3]. Before transplantation, the therapeutically increased international normalized ratios (INRs) of these patients were traditionally lowered with fresh frozen plasma (FFP) and vitamin K. Limitations of this approach include need for ABO compatibility, thawing time, increased volume and time of infusion, longer time to effect, and risk of infection and transfusion-related lung injury [4, 5]. Blood product transfusion may also increase the risk of sensitization and allograft rejection in heart transplant recipients.

An alternative to FFP are prothrombin complex concentrates (PCCs), which contain vitamin K–dependent coagulation factors. PCCs are more costly but have the advantage of not requiring ABO compatibility, thawing, and are infused at a lower volume, which is particularly important in the heart failure population [5, 6]. A prospective randomized trial demonstrated that 4-factor PCC reversed the INR more quickly and was superior in achieving effective hemostasis in patients undergoing urgent or emergency operations or invasive procedures compared with plasma [5]. Others have found that PCCs were effective in controlling coagulopathic bleeding refractory to conventional transfusion therapy in patients undergoing cardiac operations [7]. In addition, a single-center study demonstrated decreased FFP use in heart transplant recipients reversed with 3-factor PCC compared with historical controls reversed with plasma [8]. Importantly, no differences in thromboembolic complications were found with the use of PCCs.

The use of newer 4-factor PCCs to reverse vitamin K antagonists in heart transplant recipients bridged with LVADs is understudied and limited to a single case series

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**Abbreviations and Acronyms**

CI = confidence interval
FFP = fresh frozen plasma
INR = international normalized ratio
IQR = interquartile range
LVAD = left ventricular assist device
PCC = prothrombin complex concentrate
PRA = panel reactive antibody
PRBC = packed red blood cells

[9]. The purpose of this study was to determine the effect of 4-factor PCC on blood usage, blood costs, and clinical outcomes in heart transplant recipients bridged with LVADs.

## Patients and Methods

This study was approved by the Montefiore Medical Center Institutional Review Board. On October 1, 2014, our institution began using KCentra (CSL Behring, King of Prussia, PA), a 4-factor PCC, in all LVAD patients undergoing heart transplantation and who were anticoagulated with warfarin with a goal INR of 2.5 to 3.5. We identified through retrospective review 30 consecutive patients treated with this strategy (PCC group, up to October 2015), and the prior 30 consecutive patients treated with traditional FFP reversal to serve as historical controls (no-PCC group, back to February 2011).

PCC dosing was based on IUs of factor IX by weight and given in the admitting unit as part of preoperative preparation or by the anesthesiology team in the operating room before incision. Patients with an INR of less than 4 received 25 IU/kg up to 2,500 IU. Patients with INR of 4 to 6 received 35 IU/kg up to 3,500 IU. Patients with INR exceeding 6 received 50 IU/kg up to 5,000 IU. Patients in the no-PCC group received FFP, and patients in both groups received intravenous or subcutaneous vitamin K preoperatively at the discretion and clinical judgement of the operating surgeon. INR was not rechecked after administration of FFP or PCC, so the effectiveness of the reversal was not measured before the transplant operation. All operations were conducted by one of 2 surgeons (D.G. and David D'alessandro).

### *Study Outcomes*

Baseline demographic and laboratory values were compared. The primary outcome was blood product use intraoperatively, including packed red blood cells (PRBC), single-donor platelets, frozen plasma, cryoprecipitate, and total blood product use. Intraoperative transfusion was determined by estimated blood loss and administered at the discretion of the operating surgeon. Secondary outcomes included 24-hour postoperative blood product transfusion, cardiopulmonary bypass time, and 24-hour chest tube output, and short-term clinical outcomes, including incidence of reoperation for bleeding, coagulopathy requiring open chest, time to extubation, intensive care unit length of stay, 30-day in-hospital thromboembolic events (defined as strokes, deep vein thrombosis, and pulmonary embolus), and 30-day in-hospital death. Costs of anticoagulation reversal along with intraoperative and 24-hour postoperative blood product usage were calculated based on $1.32 per IU PCC, $232 per unit of PRBCs, $44 per unit of FFP, $532 per unit of single-donor platelets, and $500 per 5 pooled units of cryoprecipitate.

### *Statistical Analysis*

Continuous variables are expressed as mean ± SD and were compared with the *t* test for normally distributed data as assessed by visual inspection of histograms. Nonnormally distributed data are expressed as median (interquartile range [IQR]) and were compared with the Wilcoxon rank sum test. Categoric variables are expressed as number (%) and were compared with the $\chi^2$ test and the Fisher exact test if more than 25% of expected values were less than 5.

Multivariate linear regression was performed with two outcomes: (1) total intraoperative transfusion requirement and (2) combined total intraoperative and 24-hour postoperative transfusion to assess for independent factors associated with transfusion requirements. Covariates for the multivariate linear regression were selected based on preoperative factors deemed clinically associated with transfusion requirements or those found statistically significantly different between the PCC and no-PCC groups. These variables included PCC use, age, sex, ischemic cardiomyopathy, greater than one prior sternotomy, preoperative hemoglobin, and device type.

All data analysis was conducted with Stata 13.1 software (StataCorp, College Station, TX). Two-sided $p$ values of less than 0.05 were considered significant.

## Results

### *Study Population*

Demographics and laboratory values of patients in the PCC and no-PCC group are reported in Table 1. Patients receiving PCC were younger (50 ± 11 vs 57 ± 13 years, $p = 0.02$), had a lower proportion with ischemic cardiomyopathy (23% vs 60%, $p = 0.01$), had more than one prior sternotomy (7% vs 30%, $p = 0.04$), and had higher preoperative hemoglobin (11.8 ± 1.8 vs 10.4 ± 1.8 g/dL, $p = 0.01$). They were not significantly different in other preoperative characteristics, including INR (2.3 ± 0.5 vs 2.4 ± 1.1, $p = 0.81$). The PCC group received a median 2,087 units (IQR, 1,725 to 2,350 units) of concentrate, and the no-PCC cohort received 2.5 units (IQR, 2 to 4 units) of FFP preoperatively. The proportion of patients receiving vitamin K preoperatively was not significantly different (77% no PCC vs 90% PCC, $p = 0.30$).

### *Intraoperative Outcomes and Blood Product Use*

Cardiopulmonary bypass time was significantly shorter in patients reversed with PCC (185 [IQR, 154 to 210] vs 217 [IQR, 189 to 249] minutes, $p = 0.01$), but ischemic times were not significantly different (237 [IQR, 190 to 245] vs 234 [IQR, 184 to 260] minutes, $p = 0.50$). Patients in the