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Review Article

Perioperative Use of Coagulation Factor Concentrates in Patients Undergoing Cardiac Surgery

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Coagulopathy and bleeding are common in patients undergoing cardiac surgery, with a perioperative transfusion rate in excess of 50%. The mechanism of coagulopathy associated with cardiac surgery using cardiopulmonary bypass is multifactorial. Historically, coagulation factor–mediated bleeding in such instances has been treated with allogeneic plasma transfusion. Coagulation factor concentrate use for treatment of hemophilia, congenital factor deficiencies and, more recently, emergency warfarin reversal is common. Formulations of factor concentrates include single and multifactor concentrates and both human and recombinant-derived products. Off-label use of factor concentrates for coagulopathy and bleeding associated with cardiac surgery has been described for decades; however, sound clinical research with regard to this practice is limited. This review highlights the literature discussing the use of factor concentrates in patients undergoing cardiac surgery and provides an overview of reasonable uses or lack thereof for factor concentrates in clinical practice.

Key Words: coagulation factor concentrates; prothrombin complex concentrates; cardiac surgery; cardiopulmonary bypass; coagulopathy; bleeding; transfusion

COAGULOPATHY AND BLEEDING are appreciated complications directly associated with increased risk for morbidity and mortality in patients undergoing cardiac surgery. The historic mainstay of treatment in such instances has been with allogeneic transfusion products. Coagulation factor concentrates have been available for decades and have been used in the treatment of hemophilia and other congenital factor deficiencies. With recent Food and Drug Administration (FDA) approval of 4-factor inactive prothrombin complex concentrate (PCC) for emergency warfarin reversal, there has been a seemingly increased interest in the off-label use of factor concentrates for treatment of the factor-mediated coagulopathy and bleeding associated with cardiac surgery and cardiopulmonary bypass (CPB). The purpose of this review was to highlight the historic and current literature discussing the use of factor concentrates in patients undergoing cardiac surgery.

Bleeding and Cardiac Surgery

Patients undergoing cardiovascular surgery represent a complex cohort, with increased risk for bleeding and allogeneic blood transfusion. The overall perioperative transfusion rate for patients undergoing cardiovascular surgeries has

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exceeded 50% in some studies.[1] The transfusion rate for allogeneic hemostatic transfusion products (eg, plasma, platelets, cryoprecipitate) after cardiac surgery has been reported at nearly 11% in several studies.[2,3] It is well appreciated that cardiac surgery patients needing perioperative transfusion are at increased risk for morbidity and mortality.[4,5] A 70% increase in 5-year mortality has been reported in patients who received perioperative transfusion for cardiac surgeries.[6] The coagulopathy associated with cardiac surgery using CPB is multifactorial. A quantitative reduction of coagulation factors from hemodilution and consumption, hyperfibrinolysis, and quantitative/qualitative platelet abnormalities occurs, among other processes.[7] In the post-CPB period, there are a significant reductions in thrombin generation and both procoagulant and anticoagulant factors, aside from tissue factor pathway inhibitor, which increases.[8] The historic mainstay of treatment of nonsurgical bleeding after CPB secondary to coagulopathy from factor deficiencies has been with fresh frozen plasma (FFP). In recent decades the use of factor concentrates has gained popularity in this setting, yet sound prospective clinical research detailing this practice is lacking.

Overview of Factor Concentrates

Factor concentrate(s) broadly describes several products that can be further categorized by (1) whether they contain active or inactive coagulant factor(s) and (2) whether they contain a single coagulation factor (eg, recombinant activated factor VII [rFVIIa]) or multiple coagulation factors (eg, PCCs). Table 1 summarizes available factor concentrates; factor(s) contained within each product; the nature of contained factors (human-derived vs. recombinant); additives such as heparin; FDA-approved indications and dosing; and absolute contraindications to use. Human-derived factor concentrates are produced from donor plasma, which typically has undergone cryoprecipitate removal (cryo-poor plasma) and various processing and virucidal procedures.[9] Single and multifactor human concentrates originally surfaced in the 1970s and 1980s for the treatment of hemophilia.[9] In the 1980s, use of recombinant technology led to the development of several additional single-factor concentrates.[9] Recombinant technology entails transfection of human genes into other species (eg, hamsters), resulting in the expression of human proteins such as coagulation factors. Off-label use of factor concentrates for rescue therapy in bleeding cardiac surgical patients has been described for nearly 2 decades. More recently, strategic point-of-care, laboratory-based protocols using factor concentrates to treat bleeding have been detailed, and the use of such drugs in cardiac surgery is growing increasingly common. Factor concentrates offer several advantages over allogeneic transfusion products, such as ambient storage with ability for rapid reconstitution and a lower infusion volume, theoretically reducing the risk of volume overload and transfusion-associated circulatory overload. In addition, a reduced risk for infectious complications, transfusion-associated acute lung injury, and universal blood type compatibility make factor concentrates desirable.[10] These procoagulant therapies, however, are not without risk of thromboembolic (TE) complications, highlighting the importance of cautious use, given the paucity of sound clinical evidence.

Prothrombin Complex Concentrates

Inactive Prothrombin Complex Concentrates

Initially developed for the treatment of hemophilia B, inactive PCCs have gained widespread popularity after FDA approval for treatment of bleeding and/or emergency reversal in patients taking warfarin. Inactive PCCs exist as both 3-factor (II, IX, X, minimal VII) and 4-factor (II, VII, IX, X), with the latter containing higher levels of factor VII (FVII) in addition to antithrombin III, proteins C and S, and heparin (Table 1).

A recent meta-analysis comparing PCC with FFP for reversal of warfarin in 2,114 mixed medical and surgical patients reported that PCC use was associated with reduced all-cause mortality, quicker time to international normalized ratio (INR) correction, higher rate of INR normalization, and a lower risk of post-transfusion volume overload without a significant difference in TE complications.[10] Most major medical and surgical societies now recommend use of PCC for treatment of bleeding or need for emergency reversal in patients taking warfarin.[11]

The off-label use of inactive PCCs in cardiac surgeries is limited to mostly retrospective studies and small population specific prospective observational studies. In a 2006 retrospective study of 60 cardiac surgery patients, Fraser et al reported that patients receiving PCC for persistent bleeding after administration of allogeneic transfusion products had a reduction in clinically significant bleeding and improved laboratory parameters without report of any TE complications.[12] Bruce et al found that in 24 consecutive patients receiving PCC after cardiac surgery to reverse effects of warfarin not treated effectively with allogeneic transfusions, patients receiving PCC demonstrated improvement in transfusion requirements and bleeding without TE complications.[13] In a prospective study of 40 patients on warfarin anticoagulation with an INR >2.1 presenting for urgent cardiac surgery randomly assigned to receive PCC or FFP, Demeyere et al found that the PCC arm had a significantly reduced time to INR correction ($p = 0.007$), required significantly less additional dosing ($p < 0.001$), and required less red blood cell (RBC) transfusion, with a similar adverse event (AE) rate compared with the FFP arm.[14] In a retrospective review, Arnekian et al reported on 77 patients who had received PCC, FFP, or PCC plus FFP after CV surgery.[2] The PCC group required less RBC transfusion ($p < 0.0007$) and required fewer mediastinal reexplorations ($p = 0.002$) without, in AE or TE complications.[2] In a large retrospective study of 108 treated pulmonary endarterectomy patients, those who received PCC had significantly less postoperative blood loss than those who received FFP, without differences in RBC transfusion, morbidity/mortality, and TE complications.[15] Cappabianca et al reported retrospectively on the use of PCC versus FFP as a first-line therapy after CPB and found