Use of human fibrinogen concentrate during proximal aortic reconstruction with deep hypothermic circulatory arrest

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ABSTRACT

Objective: Human fibrinogen concentrate (HFC) is approved by the Food and Drug Administration for use at 70 mg/kg to treat congenital afibrinogenemia. We sought to determine whether this dose of HFC increases fibrinogen levels in the setting of high-risk bleeding associated with aortic reconstruction and deep hypothermic circulatory arrest (DHCA).

Methods: This was a prospective, pilot, off-label study in which 22 patients undergoing elective proximal aortic reconstruction with DHCA were administered 70 mg/kg HFC upon separation from cardiopulmonary bypass (CPB). Fibrinogen levels were measured at baseline, just before, and 10 minutes after HFC administration, on skin closure, and the day after surgery. The primary study outcome was the difference in fibrinogen level immediately after separation from CPB, when HFC was administered, and the fibrinogen level 10 minutes following HFC administration. Additionally, postoperative thromboembolic events were assessed as a safety analysis.

Results: The mean baseline fibrinogen level was 317 ± 49 mg/dL and fell to 235 ± 39 mg/dL just before separation from CPB. After HFC administration, the fibrinogen level rose to 331 ± 41 mg/dL ($P < .001$) and averaged 372 ± 45 mg/dL the next day. No postoperative thromboembolic complications occurred.

Conclusions: Administration of 70 mg/kg HFC upon separation from CPB raises fibrinogen levels by approximately 100 mg/dL without an apparent increase in thrombotic complications during proximal aortic reconstruction with DHCA. Further prospective study in a larger cohort of patients will be needed to definitively determine the safety and evaluate the efficacy of HFC as a hemostatic adjunct during these procedures. (J Thorac Cardiovasc Surg 2016;151:376-82)

Study Cohort
Administered 70 mg/kg of Human Fibringogen Concentrate at separation from CPB during Aortic Reconstruction with Deep Hypothermic Circulatory Arrest

Use of fibrinogen concentrate as a hemostatic adjunct in aortic surgery.

Central Message

Fibrinogen concentrate may be a useful hemostatic adjunct during aortic reconstruction with hypothermic circulatory arrest.

Perspective

In this prospective, pilot study it is shown that fibrinogen concentrate administered at the FDA-approved dose (70 mg/kg) increased serum fibrinogen by approximately 100 mg/dL without an apparent increase in thrombotic complications during proximal aortic reconstruction with DHCA, suggesting fibrinogen concentrate may be a useful adjunct for coagulopathy management during these procedures.

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Surgery of the aortic arch with deep hypothermic circulatory arrest (DHCA) is often associated with coagulopathic bleeding as a result of coagulation factor consumption during prolonged periods of cardiopulmonary bypass (CPB) and hypothermia-related platelet dysfunction.[1] Fibrinogen consumption is particularly exaggerated during these procedures, and the ability to replete fibrinogen represents an important element for the correction of this coagulopathy.[1] Fibrinogen is traditionally replaced by transfusion with plasma or cryoprecipitate.[2,3] However, in addition to the increased morbidity and mortality risk that results from large volume blood product transfusion,[3-5] the use of plasma or cryoprecipitate for fibrinogen replacement has several specific disadvantages.[6] First, the amount of fibrinogen given with plasma or cryoprecipitate transfusion is unknown, prohibiting the ability to replete fibrinogen in a

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Abbreviations and Acronyms
CPB = cardiopulmonary bypass
DHCA = deep hypothermic circulatory arrest
FDA = Food and Drug Administration
HFC = human fibrinogen concentrate
PRBC = packed red blood cells

targeted manner. Second, cryoprecipitate and plasma delivery requires product thawing, which can result in critical delays in the setting of acute operative bleeding. Third, there is no virus inactivation or elimination process for cryoprecipitate, imparting the risk of virus transmission upon transfusion. Lastly, plasma and cryoprecipitate contain alloantigens, which can result in anaphylaxis or less severe hypersensitivity reactions.[6]

For these reasons, human fibrinogen concentrate (HFC) (RiaSTAP; CSL Behring, Marburg, Germany) represents an attractive alternative for the correction of acquired fibrinogen deficiency compared with plasma or cryoprecipitate. HFC is a highly purified, lyophilized, virus-inactivated fibrinogen powder manufactured from human plasma. Current evidence suggests that fibrinogen concentrates are well tolerated and can quickly restore hemostasis in patients with fibrinogen deficiencies.[7,8] Several European reports on the use of HFC for trauma-related massive hemorrhage and acquired perioperative fibrinogen deficiency, including in the setting of cardiothoracic surgery, have also been published previously.[9-16] However, in the United States, HFC is reserved for replacement therapy in congenital fibrinogen deficiency and reports in the United States testing the efficacy of HFC in correcting acquired fibrinogen deficiency in aortic surgery are lacking. As such, the primary aim of this study was to test the hypothesis that use of HFC at the approved US Food and Drug Administration (FDA) dose of 70 mg/kg increases fibrinogen levels in the high-risk setting of coagulopathic bleeding of proximal aortic reconstruction with hemiarch replacement after DHCA.

PATIENTS AND METHODS

Study Design and Patient Population

This was a single-center, prospective, pilot, off-label study designed to determine whether HFC increases fibrinogen levels when administered as a 1-time 70 mg/kg dose upon separation from CPB during nonemergent proximal aorta/hemiarch reconstruction with DHCA. The study protocol was approved by the Duke University Medical Center Institutional Review Board, and informed consent was obtained from each patient who was enrolled. Patients aged ≥18 years undergoing nonemergent proximal thoracic aortic reconstruction (ascending aorta with or without aortic valve or root) with hemiarch replacement and DHCA from December 2010 to April 2012 were eligible for the study. Exclusion criteria were concomitant coronary artery bypass grafting, coronary artery stenting within the past 3 years, refusal of blood transfusion, myocardial infarction within the past 3 months, pregnancy, an international normalized ratio >1.5, thienopyridines within 5 days of surgery, aspirin (325 mg) within 48 hours of surgery (81 mg aspirin was acceptable), platelet count < 100,000/mm^3, inability to obtain written informed consent, and known coagulopathy.

Conduct of Surgery

Surgical techniques and the conduct of operation used for proximal aortic repair and hemiarch replacement were as described previously.[17] Porcine heparin was administered as a 300 U/kg bolus and then supplemented to maintain an activated clotting time longer than 480 seconds during CPB. Additionally, a 5000-unit bolus of heparin was given before circulatory arrest. Before the portion of the aortic reconstruction requiring DHCA, the patient was cooled on CPB until electrocerebral inactivity was detected by electroencephalography as described.[18,19]

Transfusion and Coagulopathy Management

An institutional transfusion algorithm has been developed for the management of bleeding and coagulopathy when separating from CPB in cases of aortic reconstruction with DHCA (Figure 1). This algorithm is based on our previously published experience on transfusion requirements during these procedures[1] as well as societal perioperative transfusion guidelines.[2,3] In brief, antifibrinolytic therapy with epsilon-aminocaproic acid is administered as a 5-g bolus followed by a 1-g/h infusion continued in the intensive care unit. Before separation from CPB, upon rewarming and reperfusion, the bypass pump is primed with 4 units plasma. This quantity was selected based on the fact that it represented the 25th percentile plasma requirement after aortic reconstruction with DHCA in our prealgorithm experience.[1] Also before separation from CPB, hemofiltration is performed to ameliorate coagulation factor dilution, and a set of laboratory test results are obtained to help guide management. Protamine sulfate is then administered until activated clotting time is normalized. At the time of separation from CPB, an additional 5-g bolus of epsilon-aminocaproic acid is given, and a 0.3 μg/kg dose of desmopressin acetate is administered to help correct platelet dysfunction and increase factor VIII and von Willebrand factor levels. If hemostasis is not immediately achieved, 1 unit platelets is transfused followed by a second if bleeding persists. At this point, laboratory results are rechecked, and if bleeding persists an additional unit of platelets and 2 units plasma are administered. Based on laboratory results, cryoprecipitate (if fibrinogen level <200 mg/dL), platelets (if <100,000/mm^3 more than the pre-CPB separation platelet value), and/or 2 plasma units are then transfused. If bleeding continues, recombinant activated factor VII (1-2 mg) is administered.[20] If hemostasis is still not obtained, packed red blood cells (PRBCs) and plasma are administered at 1:1 with additional cryoprecipate, platelets, and hemostatic adjuncts administered at clinician discretion, with guidance from laboratory and functional tests. With regard to red blood cell transfusion, serial hematocrit samples are drawn before and after separation from CPB. The return of washed, shed red blood cells (BRAT II blood cell salvage machine; Cobe Cardiovascular Inc, Arvada, Colo) to the patient is used in all cases and additional PRBC transfusion is generally avoided if hematocrit is >0.20.

In total, although this algorithmic approach for the management of bleeding and coagulopathy after CPB with DHCA is mostly empirical, it was developed to allow the reliable and timely management of the severe coagulopathic bleeding that often occurs in aortic reconstruction with DHCA. Although intraoperative laboratory testing, including thromboelastography and platelet agglutination, are employed when available, our approach is not ultimately reliant on such tests. Although these intraoperative tests can be useful in directing intraoperative transfusion when coming off CPB,[21-23] they often do not provide information rapidly enough to guide therapy with acute intraoperative bleeding. Therefore, the supplemental information provided by intraoperative laboratory testing is used in conjunction with clinical judgment to modify the protocol when