Protocol Adherence When Managing Massive Bleeding Following Complex Cardiac Surgery: A Study Design Pilot

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Objective: **High-quality prospective trials of hemostatic "rescue" therapy to control massive bleeding in cardiac surgery are lacking. Wide variability in the care of patients with severe bleeding following cardiopulmonary bypass has precluded accurate comparison of treatment groups in previous studies. This study identified the use of a management protocol for early identification and uniform treatment of patients with massive bleeding for application in future trials of hemostatic rescue agents.**

Design: **A prospective, nonblinded, interventional feasibility study.**

Setting: **A university teaching hospital.**

Participants: **Forty-three adult patients undergoing complex cardiac surgery.**

Interventions: **Study participants undergoing high-risk cardiac surgery received standardized treatment in accordance with a bleeding management protocol.**

Measurements and Main Results: **Twenty-seven patients (63%) had severe bleeding following heparin reversal and received conventional hemostatic resuscitation per protocol. Six patients had massive refractory bleeding. Compliance with protocol tasks was $\geq$90% in 4 of 5 categories (anticoagulation, hemostasis scoring, recording blood loss, protocol transfusion) with the exception being submission of laboratory samples (76%). Measured bleeding rates (mL/h) following heparin reversal were clearly differentiated in those with hemostasis scores $\geq$3 compared to those with scores $\leq$2 (1,420 $\pm$ 957 *v* 147 $\pm$ 96; p $<$ 0.001).**

Conclusions: **Adherence to a management protocol for massive bleeding is feasible and allows for homogenous treatment of patients before study arm randomization in future "rescue" therapy trials. The authors' protocol allowed for prompt and accurate identification of patients with severe bleeding refractory to conventional therapy. This review resolved several key barriers in the design of severe bleeding management trials.**

KEY WORDS: cardiac surgery, coagulation, hemorrhage, cardiopulmonary bypass, transfusion

SEVERE BLEEDING OCCURS IN 10% to 15% of patients undergoing cardiac surgical procedures.[1–3] Although such patients represent a small subset of the cardiac surgical population, they account for 80% of all blood products transfused during cardiac surgery.[4,5] Many go on to require massive transfusion and/or re-exploration, both of which are associated with marked increases in morbidity and mortality.[2,6,7] The use of hemostatic rescue agents, such as recombinant activated factor VIIa (rFVIIa; Novo Nordisk, Bagsvaerd, Denmark), has been recommended for achieving hemostasis when conventional therapy has failed. However, high-quality evidence for establishing a clear benefit-risk profile for the use of agents such as rFVIIa is lacking, as highlighted in a recent systematic review.[8] Underpowered trials, lack of standardized care *before* rescue therapy, and the evolving efficacy of conventional therapy all have been cited as factors undermining the utility of earlier studies of hemostatic rescue agents.[9–11] Although rFVIIa remains the most widely studied rescue intervention for refractory nonsurgical bleeding after cardiopulmonary bypass, a growing number of factor concentrates such as prothrombin complex and fibrinogen, are being studied for *off*-label use for severe bleeding following cardiac surgery.[12]

Ensuring homogenous treatment for all study arms, other than the investigational therapy itself, is essential when conducting a high-quality randomized trial.[13] Standardizing care of patients with severe bleeding in terms of hemostatic management before allocation to a rescue intervention is an integral prerequisite to generating reliable results and reproducible outcomes.[9] Although some heterogeneity is unavoidable in the setting of massive bleeding, attempting a uniform management strategy adds validity to the ensuing randomization process. Management protocols for intractable bleeding after cardiopulmonary bypass (CPB) must address several key barriers. These include adherence to an algorithm during a volatile clinical period, quantification of bleeding severity, and systematic provision of conventional treatment before reaching the rescue intervention phase.

The primary aim of this feasibility study was, thus, to assess adherence to a bleeding management protocol for the treatment of patients with massive refractory bleeding after cardiopulmonary bypass. The secondary aim of the study was to evaluate the use of a hemostasis scoring system to allow for rapid

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quantification of bleeding severity and identification of patients with refractory nonsurgical bleeding who potentially would benefit from rescue therapy in future clinical trials.

METHODS

The authors conducted a prospective, single-center, controlled trial at a quaternary medical center between March 2008 and April 2009. The study protocol was approved by the local Human Research Ethics Committee and written informed consent was obtained from all participants. Eligible patients included adults aged 18 to 85 years of age who were at increased risk of excessive bleeding because of the complexity of the planned surgical procedure.[3,14,15] Patients undergoing either first-time isolated coronary artery bypass grafting (CABG) or valve procedures, or having nonelective surgery, were ineligible for participation. Patients were excluded if they had known or suspected coagulopathy, a history of a significant thromboembolic event within 6 months, active infection, received clopidogrel or other $P2Y_{12}$ inhibitors within 5 days of surgery, refused transfusion of donor blood products, were pregnant, or weighed $\geq$ 150 kg or $\leq$ 40 kg at the time of surgery.

Standard anesthetic and surgical management and blood conservation techniques were followed; These are summarized in the Supplemental Materials' Methods section.

Bleeding Management Protocol

The design of the authors' bleeding management protocol (BMP) (Fig 1) was based on available evidence and the expert opinions of a multidisciplinary group of cardiac anesthesiologists, cardiac surgeons, critical care specialists, transfusion medicine specialists, and hematologists to specifically address rapid or massive blood loss.[1,4,15–19] Consensus was achieved following a series of moderated conferences and protocol reviews. The BMP outlined a uniform approach for the following: Anticoagulation, blood conservation techniques, measurement of blood loss, visual scoring of bleeding severity, and administration of blood products in both the operating room (OR) and intensive care unit (ICU). Routine laboratory coagulation tests were obtained in all subjects at prespecified time points, including platelet count, fibrinogen levels, activated partial thromboplastin time (aPTT), and prothrombin time (PT). Results were used to guide therapy when available, but were not required to execute the treatment algorithm. Although thromboelastography (TEG) is used routinely at the authors' institution during cardiac surgical

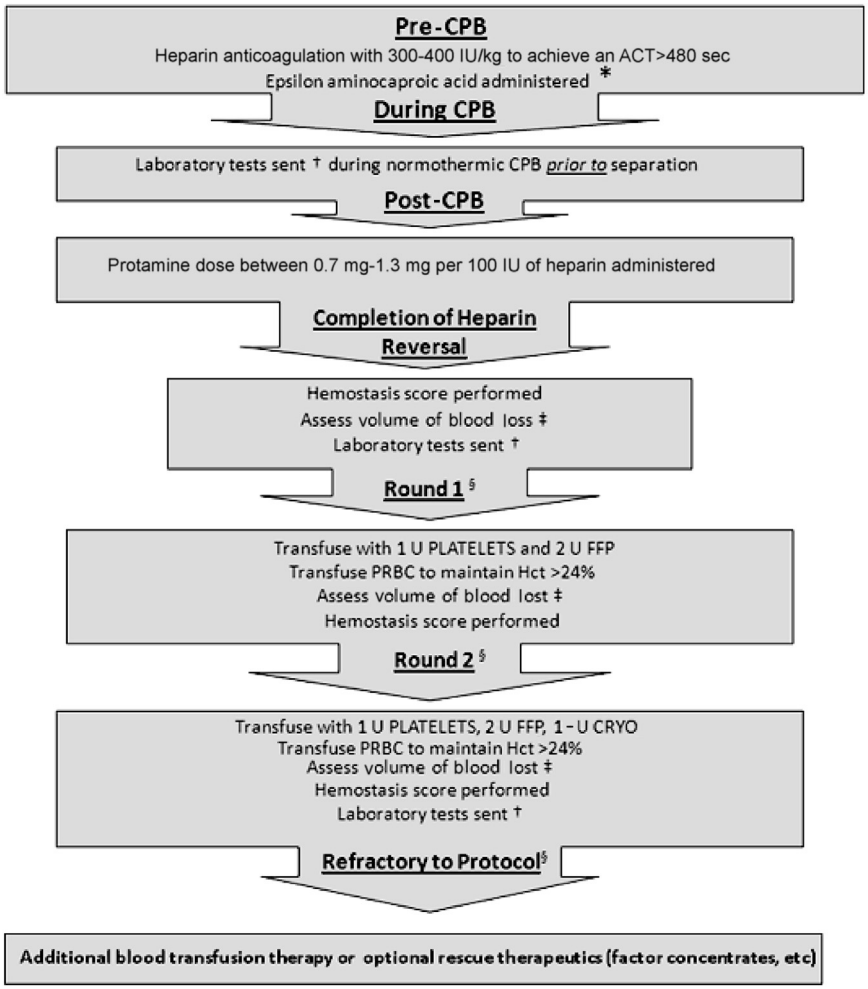

Fig 1. Bleeding Management Protocol (applied to 43 participants). Compliance monitored for up to 16 required tasks (maximum # of potential tasks related to extent of progression through the BMP). *Loading dose, pump prime and infusion; †Hemoglobin/platelet count/fibrinogen level/PT/aPTT; ‡Volume in cell saver/wall suction/mediastinal drains recorded; §Administer if hemostasis Score $\geq$ 3; ¶Laboratory results used to guide administration of component therapy, if available, but not required for decision branch-points in the BMP; ‖Performed when transfusion therapy was complete.