Efficacy of immunomodulation in the treatment of profound thrombocytopenia after adult cardiac surgery

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Objective: Causes of profound thrombocytopenia (platelet count <60 K) developing days after cardiac surgery include heparin platelet factor 4 antibodies, thrombotic thrombocytopenic purpura–like antibodies, and endotoxin generated by pulmonary infections. Modulation of immune-mediated profound thrombocytopenia with intravenous immunoglobulin could be efficacious for any of these conditions.

Methods: From 2002 to 2010, profound thrombocytopenia developed in 20 consecutive patients within days after cardiac surgery; 19 patients underwent valve or aortic operations, and 1 patient underwent coronary bypass. Risk profiles were high preoperatively: Patients' mean age was 73 years, 50% underwent nonelective procedures, 100% had comorbidities, and 25% underwent reoperations. When decreasing platelet counts approached 60 K, intravenous immunoglobulin was started at 1.5 g/kg intravenously over 5 days. Anticoagulation and platelet transfusions were avoided. In 1 patient, profound thrombocytopenia failed to reverse promptly, and daily plasmapheresis was introduced. Platelet counts before and after interventions were assessed with linear regression analyses over time, including a spline function and statistical knot coincident with starting intravenous immunoglobulin.

Results: In 19 of 20 patients, profound thrombocytopenia stabilized and rebounded within 2 to 4 days after initiating intravenous immunoglobulin. In the remaining slow-responding patient, addition of plasmapheresis was associated with rapid recovery. In every patient, coincident multiorgan failure reversed, and 19 of 20 patients recovered uneventfully and survived hospitalization with no limb ischemia or tissue loss. No complications of intravenous immunoglobulin therapy or plasmapheresis were observed.

Conclusions: Although mechanisms of profound thrombocytopenia after cardiac surgery are poorly understood, they likely relate to inappropriate autoimmune moieties causing peripheral platelet aggregation and multiorgan failure. A protocol involving immunomodulation with intravenous immunoglobulin supplemented by plasmapheresis appeared safe and efficacious. Direct immunologic interventions for profound thrombocytopenia could improve postoperative outcomes. (J Thorac Cardiovasc Surg 2014;147:808-15)

Profound thrombocytopenia (pT) occurring early postoperatively is observed in approximately 1% to 3% of patients after adult cardiac surgery.[1] The disorder can be associated with diffuse intravascular platelet deposition, strokes, multiorgan failure, venous thrombi, pulmonary embolism, limb loss, and death.[2] Although this syndrome is commonly called heparin-induced thrombocytopenia (HIT) in current practice, it is likely that true heparin-associated platelet factor 4 (PF4) antibodies are etiologic in only a minority of patients.[1] Other likely causes for postoperative platelet aggregation include thrombotic thrombocytopenic purpura (TTP)-like antibodies,[3] infectious superantigens,[4,5] and gram-negative endotoxin.[6,7] Whatever the cause, most agree that surgical pT is mediated by immune activation/dysfunction producing inappropriate autoantibodies and peripheral platelet aggregation. The current therapeutic standard probably is anticoagulation with direct thrombin inhibitors,[8] although plasmapheresis for removal of autoantibodies recently has shown promise.[9]

Many types of immune-mediated thrombocytopenia exist in general medical practice.[6] In recent years, another direct immune intervention, immune modulation using intravenous immunoglobulin (IVIG), has become a primary therapy for many of these disorders.[10] IVIG contains active normal human antibodies from more than 10,000 donors and is highly effective in modulating immune dysfunction and "normalizing" pathologic immunologic moieties. In fact, treatment of "acute immune-mediated thrombocytopenia" currently is an on-label indication for IVIG.[11] Because postoperative pT seems to be primarily immune mediated, IVIG also could be useful in the postsurgical setting. This article reports the results of treating pT with immune modulation using IVIG. Many of these concepts have been published,[12] and the purpose of this

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Abbreviations and Acronyms
HIT = heparin-induced thrombocytopenia
Ig = immunoglobulin
IVIG = intravenous immunoglobulin
PF4 = platelet factor 4
pT = profound thrombocytopenia
TTP = thrombotic thrombocytopenic purpura

communication is to present specific pT data and associated discussion.

MATERIALS AND METHODS

Ethical Considerations

This clinical effort to use IVIG for the purpose of treating pT after adult cardiac surgery was initiated within a standard cardiac surgical practice in the setting of a worsening high-risk problem with less than satisfactory solutions. One could reason that immune modulation for pT was a Food and Drug Administration on-label indication for IVIG,[11] and the concept was based on existing literature support in similar clinical situations.[13-16] Before IVIG was started, possible therapeutic benefits and risks were discussed with the patients and families, and all agreed to proceed. The chart review and de-identified data analysis were performed at a later date under a waiver of informed consent by the Western Institutional Review Board.

Population

Twenty consecutive patients experiencing pT after adult cardiac surgery from 2002 to the middle of 2010 were assessed. The first 14 patients were part of a previous report on general immune dysfunction from 2002 to the end of 2009,[12] and the final 6 patients were from the subsequent half-year. Nineteen patients underwent valve or aortic operations, and 1 patient underwent coronary bypass. Detailed characteristics of the overall immune dysfunction population have been described,[12] and for the patients experiencing pT in this analysis, specific data are provided in Table 1. Risk profiles were high: Patients' average age was 73.0 ± 15.6 years (mean ± standard deviation), 50% underwent nonelective procedures, 100% had comorbidities, 25% underwent reoperations, and more than half were female. Criteria for diagnosis of pT included a dramatically decreasing platelet count days after adult cardiac surgery, averaging a 20 K decrease the day before starting IVIG (Figure 1), with no other cause evident, and with the platelet count approaching 60 K. Most patients had pulmonary infiltrates associated with pulmonary dysfunction, leukocytosis, and some degree of multiorgan failure at the time of pT development, and the few who did not eventually developed pulmonary infiltrates within days. Postoperative immunoglobulin (Ig)G levels were low in most (Table 1),[12] but were only available later in the series. Heparin PF4 antibody tests were not available early in the series, but when obtained in later patients, all results were negative.

General Management Protocol

Most patients with pT had evidence of pulmonary infection with worsening pulmonary infiltrates, signs of sepsis, leukocytosis, deterioration of pulmonary mechanics, and impairment of pulmonary gas exchange.[12] Multiple-drug intravenous antibiotics (consisting of combinations of piperacillin/tazobactam, cefepime, tobramycin, and meropenem [vancomycin was used only for specific indications]) were started in all patients, according to the University of Kentucky antibiotic protocol for management of hospital-acquired pneumonia.[17,18] Platelet transfusions and anticoagulation with thrombin inhibitors were avoided. All patients were maintained under full intensive care unit care and had documentation of good cardiac status with a Swan–Ganz catheter and a transthoracic echocardiogram at the outset. Pulmonary cultures were obtained in all patients, including bronchial washings or protected brush cultures in patients undergoing therapeutic fiberoptic bronchoscopy. Significant renal dysfunction also developed in 45% of patients, manifested by oliguria or aneuria with increasing creatinine, despite intravenous dopamine and diuretic support.[12]

Intravenous Immunoglobulin Therapy

When the rapidly decreasing platelet count approached 60 K (Figure 1) and after family agreement, IVIG therapy (Carimune; ZLB Behring Inc, King of Prussia, Pa) was begun at a dose of 18 or 24 g/d (depending on the size of the patient, ~0.3 g/kg/d) intravenously for 5 days to a total dose of 1.5 g/kg. In the subsequent spline function analysis, the first day of IVIG infusion was considered IVIG day 0 for placement of a statistical knot. More detailed clinical management principles have been outlined by Rankin and colleagues,[12] including the importance of early enteral nutritional support. However, with IVIG therapy, most patients rapidly regained their appetites and promptly resumed good oral nutrition.

Analysis Protocol

In all patients, platelet counts were obtained almost daily as part of routine postoperative care. At a later time, retrospective chart review was performed, and platelet values were documented for 3 days before (day −3) beginning IVIG therapy (on day 0) and for 5 days afterward (day +5). For a variety of reasons in the clinical setting, 18 of the total 180 platelet count data points (9 data points × 20 patients) were missing, and these were interpolated by using the arithmetic average of adjacent data points. In the 20 patients, full IVIG therapy was initiated between the second and fifth postoperative days. When IVIG was started on postoperative day 2, the preoperative platelet count was used as the day −3 data point. By using each patient as his or her own control, the therapeutic effect of IVIG was assessed with linear regression analysis of platelet counts over time using a spline function and a statistical knot at day 0, coincident with beginning IVIG.

RESULTS

Most patients had signs of pulmonary infection coincident with pT. Three patients presented initially with isolated pT, but pulmonary infiltrates eventually developed. Thus, postoperative nosocomial infection was the probable cause in most patients, if not all. No patients had other complications or evidence of alternative sources of infection, and no other patients during this period had pT treated differently or any evidence of limb ischemia. At the time of IVIG initiation, most patients' conditions were deteriorating, with rapidly decreasing platelet counts (Figure 1), worsening ventilator status, and developing multiorgan failure.[12] In the linear regression analysis over the 3 days before IVIG, the platelet counts were decreasing rapidly, and when the decision for IVIG was made (day 0), general morbidity often was high. Postoperative IgG levels were usually low in this population (Table 1), although quantitative IgG levels were available only in later years. After beginning IVIG on day 0, improvement in clinical course and reversal of thrombocytopenia were observed uniformly over the subsequent 5 days. In the spline function analysis, and using each patient as his or her own control,

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