Physicians have long sought alternatives to transfusion of allogeneic blood products for managing patients with or at risk of excessive blood loss. The complications of allogeneic blood, including transfusion reactions, transmission of infectious agents, and acute lung injury, are well known; however, the repletion of the cellular and soluble components of blood becomes necessary when the losses (and attendant volume resuscitation) themselves contribute to ineffective hemostasis. The appropriate trigger for the administration of platelets and plasma coagulation factors is controversial, as is the proper sequence for their administration and methodology for preparing factor replacement products. In this issue of *Anesthesiology*, Rahe-Meyer et al. report data from a randomized controlled trial (RCT) demonstrating potential of fibrinogen concentrate as a first-line therapy to reduce transfusion in patients undergoing high-risk surgical procedures.

Fibrinogen (factor I) is a large glycoprotein (340 kDa) that circulates as a soluble plasma component. Its plasma concentration (approximately 150–400 mg/dl) is exceeded only by albumin and immunoglobulins, and as an acute phase protein, its concentration increases after surgery and trauma, often exceeding 600 mg/dl. Fibrinogen plays two critical roles in hemostasis. First, in its soluble form, it serves as the ligand for activated GPIIb-IIIa receptors on platelets, constituting the cross bridges among platelets required for aggregation and primary hemostatic plug formation. Second, when cleaved by thrombin (factor IIa), fibrinogen is converted into fibrin, which polymerizes into an insoluble form that stabilizes the hemostatic plug and provides a firm meshwork for clot propagation.

The appropriate plasma concentration for fibrinogen in the bleeding patient is not known; however, both recent laboratory and clinical studies suggest that higher is better. Indeed, before 2008, transfusion guidelines from American and European societies recommended a plasma fibrinogen target of approximately 100 mg/dl, whereas more recent European guidelines target levels of 150–200 mg/dl. Recommendations are based primarily on expert opinion and laboratory studies with few RCTs to guide treatment. The saturation of platelet fibrinogen receptors and normal clot initiation in vitro, as assessed by prothrombin and activated partial thromboplastin times, are known to occur at fibrinogen concentrations at or below the 100 mg/dl threshold. However, clot formation in vivo is far more complex than these few in vitro tests might suggest. Recent laboratory studies demonstrate a direct relationship between fibrinogen concentration and viscoelastic measures of clot strength that extends through the entire physiologic range for fibrinogen up to 1,000 mg/dl. These in vitro studies are corroborated by multiple observational studies and nonrandomized trials, which suggest improved hemostasis when fibrinogen concentrations exceed 200 mg/dl.
In the prospective double-blinded RCT reported here, Rahe-Meyer et al.\textsuperscript{1} tested the hypothesis that the administration of fibrinogen concentrate, as first-line therapy for intraoperative bleeding, would reduce allogeneic blood transfusions in patients undergoing thoracic aortic aneurysm surgery with cardiopulmonary bypass. Subjects who developed intraoperative bleeding after separation from cardiopulmonary bypass were randomized to receive intravenous injection of fibrinogen concentrate or matched placebo. Clinically relevant bleeding was defined as a 5-minute bleeding mass of 60–250 g, as measured by weight of surgical sponges, after protamine administration and appropriate surgical hemostasis. The dose of fibrinogen administered was targeted to achieve a thromboelastometry test result (fib-tem test on ROTEM device, Munich, Germany) of 22 mm for the maximum clot firmness test, which corresponds roughly to a fibrinogen concentration of 360 mg/dl. The median dose of fibrinogen administered was 8 g, and the mean values of maximum clot firmness and fibrinogen concentrations actually achieved were 16.2 (SD 2.8) mm and 260 (SD 48) mg/dl, respectively, which were both significantly higher than in the placebo group. Perioperative management in both groups was otherwise similar and protocolized, including a laboratory-based algorithm for transfusion of red cells, platelets, and fresh frozen plasma until a bleeding mass of less than 60 g was achieved intraoperatively and chest tube drainage was less than 400 mL/h in the intensive care unit. The primary endpoint was the total number of allogeneic units (red cells, platelets, and fresh frozen plasma) transfused in the 24 h after the administration of study drug.

Twenty-nine fibrinogen-treated and 32 placebo-treated participants were analyzed. The authors report a marked reduction in the total number of allogeneic units transfused between groups (median, 2 vs. 13; \( P \) value less than 0.0001 for fibrinogen and placebo, respectively), with significantly fewer units transfused for each of the blood components in the fibrinogen group. Although 45% of participants in the fibrinogen group avoided transfusion entirely, none avoided transfusion in the placebo group (\( P \) value less than 0.0001). The number of serious adverse events was similar between groups, with fewer deaths but a greater number of reoperations occurring in the fibrinogen-treated group. Fibrinogen levels were greater for the fibrinogen-treated group immediately after study drug administration but were similar by the day after surgery. One thrombotic complication occurred in each group.

Only two other prospective RCTs have been published examining the effect of fibrinogen administration on surgical bleeding. In a study of coronary bypass graft patients, 20 participants were randomized to receive 2 g of fibrinogen or no infusion immediately before surgery.\textsuperscript{9} Chest tube drainage was noted to be significantly lower (565 ± 150 vs. 830 ± 268 mL, \( P = 0.010 \)) and hemoglobin significantly higher (11.0 ± 1.2 vs. 9.8 ± 0.8 g/dl, \( P = 0.018 \)) in the fibrinogen-treated group on the day after surgery. One participant in the fibrinogen-treated and three in the control group received transfusions. In another study, patients undergoing cystectomy were randomized to receive fibrinogen infusion (45 mg/kg) or placebo after intraoperative bleeding, and volume resuscitation caused a 30% reduction in baseline hematocrit.\textsuperscript{10} Intraoperative transfusion of red cells and total red cell transfusion within 48 h of surgery were not different between groups, although transfusion in the postoperative phase alone was noted to be lower in the fibrinogen-treated group.

The reduction in transfusion from fibrinogen administration in the report by Rahe-Meyer et al.\textsuperscript{1} is impressive, and data from this study are consistent with other clinical and laboratory studies that examined the benefits of fibrinogen supplementation on hemostasis. However, enthusiasm for the administration of fibrinogen as a clinical therapy for bleeding in surgical patients must remain tempered at this time. Fewer than 100 total patients have thus far been studied in the setting of an RCT, and in one of the three trials, a clinically important reduction in transfusion was not identified. Although the study by Rahe-Meyer et al.\textsuperscript{1} is the most robust trial to date, it excluded patients who were at highest risk to bleed (e.g., recent antithrombotic therapy, more than 250 g of blood loss in 5 min) and at highest risk for thrombosis (e.g., recent myocardial infarction or stroke). Furthermore, both the criteria used to define clinical bleeding and the protocol used to guide transfusion management were of questionable clinical relevance. In addition, the authors did not design and analyze their study in accordance with true intention-to-treat principles. Thus, both the validity and generalizability of the authors’ findings cannot be determined with sufficient confidence at this time.

Several strategies have proven efficacy in reducing perioperative allogeneic blood transfusion including: use of intraoperative cell salvage,\textsuperscript{11} hemostasis testing-based transfusion algorithms,\textsuperscript{12–14} and antifibrinolytic agents.\textsuperscript{15,16} The efficacy of fibrinogen concentrate therapy remains unclear at this time. Nonetheless, the work of Rahe-Meyer et al.\textsuperscript{1} marks an important advance in the search for alternatives to allogeneic blood transfusion in management of acquired bleeding disorders. The administration of fibrinogen concentrates demonstrates clear potential to improve hemostasis more rapidly and at lower risk of immunologic reactions, infection, and volume overload than conventional allogeneic blood products. Future studies should develop more clinically relevant treatment algorithms and use modern randomization strategies that adhere to intention-to-treat principles. Larger, multicenter RCTs should now move forward to determine whether the administration of fibrinogen concentrate improves clinical outcomes in surgical patients at an acceptable level of safety and cost.

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References


