From Life-Blood Streaming to Hemostasis

Richard B. Weiskopf, MD

"And Life-blood streaming fresh; wide was the wound,
But suddenly with flesh fill'd up and heal'd"

—John Milton, *Paradise Lost*[1]

Thus, in perhaps the greatest single piece of literature in the English language, described John Milton the elective surgery performed on Adam, the resultant hemorrhage, and the method by which hemostasis was secured.

More than 2 centuries later, in 1910, Duke[2] provided hemostasis by the transfusion of fresh whole blood. Whole blood continued to be the standard therapy through the 1970s and at very few institutions into the 1980s when the ability to fractionate blood,[3] the advent of other technological developments, such as plastic storage bags and preservative and storage conditions specific for components,[4] and the transfer of blood collection from individual hospitals to regional centers, resulted in the near pervasive separation of whole blood into red cells, platelets, and plasma in the United States (US), Canada, and Western Europe. Whereas this has been of benefit to those in need of only one component, it likely has been detrimental to those who require all components, as do those suffering substantial hemorrhage. The US Army has used whole blood in conflicts dating from World War I through the present day in Iraq and Afghanistan.[5]

A spate of retrospective database analyses have attempted, some prospective observations, and now active and planned prospective randomized trials are seeking, to determine whether greater use of plasma and platelets than has generally been transfused since the development of separately stored components, or the use of whole blood, provides superior hemostasis for trauma than does component therapy.[6] The US military and civilian practice have already instituted these paradigms as standard transfusion practice for trauma.[6]

In this issue of *Anesthesia & Analgesia*, Levy et al.[7] highlight what we do and do not know about the critical role of fibrinogen for providing hemostasis for surgery.

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We have learned much about coagulation in the ensuing nearly 450 years since Milton's description of surgical hemostasis. The concept of a "coagulation cascade"[8] with intrinsic and extrinsic pathways did much to advance our understanding. More recently, the obvious omission (to Duke[2] in 1910 and to us, now) of a cellular element, the platelet, has been included in a modified schema.[9,10] We have come to understand that the platelet provides the biological and structural base for several zymogens to be converted to active proteases,[9,10] and for the essential thrombin burst for converting fibrinogen to fibrin.[10–12] For many years it was thought that a critical concentration of each and every coagulation factor was required sequentially to eventually produce fibrin from fibrinogen. Then, Hedner, in a remarkable revelation, discovered that "supraphysiologic" concentrations of activated coagulation factor VII (FVIIa) could "push" the reactions in the absence of coagulation factor VIII.[13,14] This "bypass" therapy proved superb for patients with hemophilia A and antibodies to factor VIII, providing them with a hemostatic, including for surgery, where they had none until then, and with little in the way of adverse events.[13,14] The concept of a bypass therapy was expanded later to that of a "universal hemostatic."[15,16] Phase II trials in intracerebral hemorrhage (ICH)[17] and trauma[18] provided proof of concept for this thought. However, both phase III trials for these conditions, although providing proof of hemostasis (as demonstrated by computed tomography–measured decreased hematoma growth in ICH[19] and reduced blood use in trauma[20]), failed to meet their primary regulatory clinical efficacy end points of improved neurologic outcome in ICH and mortality in trauma.

Such single coagulation factor use perhaps led to the thought that fibrinogen might provide hemostasis when administered by itself, especially inasmuch as it is the "final common pathway," if you will, on the way to the critical creation of fibrin. Although it is fibrinogen, and only fibrinogen, that is converted to the fibrin that is necessary for hemostasis, there are impediments to determining whether treatment with fibrinogen alone can provide hemostatic efficacy (i.e., function as a "universal hemostatic"), while at the same time have few, if any, adverse events.

First, it is of substantial importance that not all fibrin is created equally. Fibrin produced from fibrinogen absent a substantial thrombin burst results in a coarse, rather than fine, structure that is easily degraded by plasmin.[21–23] The same thrombin burst is also necessary for the full activation of thrombin-activable fibrinolysis inhibitor (TAFI).[24] Additionally, the resistance of fibrin to degradation and deformation

is further enhanced by molecular cross-linking induced by coagulation factor XIII.[12,25–29] In my view, such failure to produce a proper fibrin and fully activated TAFI may be responsible for what many may regard as "hyperfibrinolysis," when the etiology may be an inadequate concentration of one or more coagulation factors, or thrombocytopenia or deranged platelet function (the surface on which thrombin is generated), causing the production of a fibrin that is easily lysed with a concomitant failure of full activation of TAFI further enabling such lysis.[30]

Second, we don't know the minimum in vivo concentration of fibrinogen required to produce adequate amounts of fibrin with a structure that resists fibrinolysis. The single observational report that with blood loss fibrinogen reaches "critical" concentrations earlier than do platelets, prothrombin, or coagulation factors V or VII, assumed the values for critical concentration.[31] Other coagulation factors were not evaluated. The differences may not have been statistically significant, and small changes in the assumptions would have produced substantially different results and conclusions. There may be several reasons for the lack of this knowledge. We don't know: (a) the proper method of measurement of fibrinogen for all clinical circumstances. The several methods agree in some, but not all, clinical conditions[32]; (b) the dose of the various fibrinogen-containing products necessary to reach the unknown adequate in vivo concentration.[7] There is an absence of prospective, randomized, dose-finding clinical studies. Whereas the concentration of fibrinogen in specific fibrinogen products is controlled, the concentration in cryoprecipitate is variable; and (c) the appropriate clinical settings and end point(s) for clinical trials to assess the efficacy of these products.

It might seem strange to posit that the appropriate setting for a clinical trial to test a systemic hemostatic agent might be problematic. However, the numbers of elective surgical procedures that are associated with routine, predictable, substantial hemorrhage have decreased, making any potential clinical trial somewhat difficult to contemplate and design. Although major trauma is associated with substantial bleeding, because of the unpredictable nature and intensity of the clinical circumstances, trauma trials are difficult and expensive to perform, and most frequently require a waiver of informed consent (under regulation 21CFR50.24),[33] substantially increasing the complexity and expense. Of further substantial importance, the appropriate primary efficacy end point has been sufficiently unclear as to prompt a National Institutes of Health–Food and Drug Administration (FDA) sponsored workshop in December 2010. For many years, I and others have advocated that the efficacy end point of 30-day all-cause mortality frequently recommended by the FDA is not consistent with the pharmacodynamics or pharmacokinetics of agents that act within a very few minutes and for a very limited time to reduce or stop hemorrhage. The panel at the workshop agreed with this thought, indicating that a 6- to 24-hour period is more sensible.[34] The panel agreed that an appropriate end point for a hemostatic agent is hemostasis, but acknowledged the difficulty in establishing this objectively. Although clinicians may "know it when they see it," that is insufficient for an objective end point required by regulatory authorities. Reduction or avoidance of transfusion has been accepted as a surrogate end point for systemically administered proposed hemostatic agents,[35,36] and likely continues to be the most achievable of those discussed, although it should be noted that the 3 separate centers of the FDA seem to have differing criteria for efficacy end points for hemostatic agents. An efficacy end point of reduction of transfusion implies the need to study a patient population with sufficient hemorrhage to require a sufficient amount of transfusion to make reduction both feasible and clinically meaningful.

Beyond the issue of efficacy, the current data related to the safety of systemically administered fibrinogen rests largely on its use in patients with congenital deficiencies and self-reported use in the 2 countries (Germany and Austria) where it is approved for surgical hemostasis. There are few comprehensive rigorously assessed data from prospective randomized trials in surgical populations. If one is to draw an analogy from the clinical development experience of recombinant FVIIa (rFVIIa), where adverse event rates differ in differing populations,[30] more remains to be learned.

In a larger sense, one may ask whether it is reasonable to expect any one of the elements necessary for coagulation to stand out as a universal hemostatic. Our current understanding of coagulation is that at least 3 separate elements are required: (1) sufficient concentrations of the zymogens to produce the thrombin burst that is necessary to convert fibrinogen to an appropriately structured fibrin and to fully activate TAFI; (2) a sufficient concentration of functional platelets to provide the surface for zymogen activity and binding; and (3) a sufficient concentration of fibrinogen. We do not understand why so many zymogens and proteases are needed, nor do we know fully the concentrations required in a dynamic in vivo, rather than in a static in vitro, setting. An attempt to test 1 of these 3 elements for hemostasis related to surgery or trauma, while controlling the other 2, is likely to be exceedingly difficult. Clinical trials incorporating interventions for all 3 (e.g., administration of several doses of platelets, multiple doses of several coagulation factors or supraphysiologic concentrations of rFVIIa, and fibrinogen, each) would not seem possible at this juncture. Despite these considerations, it should be noted that rFVIIa did provide evidence of hemostasis in 2 phase II and 2 phase III trials of widely differing causes of hemorrhage.[19,20]

Nevertheless, clinical trials with fibrinogen offer the exciting possibility of testing our understanding of static coagulation as it applies to the dynamics of surgery and further quantifying the necessary constituents for the unspoken intervening steps between a "wide wound"/"streaming life-blood" and it being "with flesh fill'd up and heal'd."[1]

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REFERENCES

1. Milton J. Paradise Lost. Originally, Book VII, Lines 1106–7. Later editions as of 1674 (e.g., Baskerville Press for J. and R. Tonson, London, 1758): Book VIII, Lines 467–8. London: Samuel Simmons, 1667
2. Duke WW. The relation of blood platelets to hemorrhagic disease. JAMA 1910;55:1185–92
3. Cohn EJ. The separation of blood into fractions of therapeutic value. Ann Intern Med 1947;26:341–52
4. Klein HG. It seemed a pity to throw away the red cells: selective component collection. Transfusion 1993;33:788–90
5. Spinella PC. Warm fresh whole blood transfusion for severe hemorrhage: U.S. military and potential civilian applications. Crit Care Med 2008;36:S340–5
6. Weiskopf R. Reconstructing deconstructed blood for trauma. Anesthesiology (in press)
7. Levy JH, Szlam F, Tanaka KA, Sniecienski RM. Fibrinogen and hemostasis: a primary hemostatic target for the management of acquired bleeding. Anesth Analg 2012;114:261–74
8. Davie E, Ratnoff O. Waterfall sequence for intrinsic blood clotting. Science 1964;145:1310–2
9. Roberts HR, Monroe DM, Escobar M. Current concepts of hemostasis: implications for therapy. Anesthesiology 2004;100:722–30
10. Roberts HR, Monroe DM, Oliver JA, Chang JY, Hoffman M. Newer concepts of blood coagulation. Haemophilia 1998;4:331–4
11. Monroe DM, Hoffman M, Roberts HR. Platelets and thrombin generation. Arterioscler Thromb Vasc Biol 2002;22:1381–9
12. Roberts HR, Monroe DM III, Hoffman M. Molecular biology and biochemistry of the coagulation factors and pathways of hemostasis. In: Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT, eds. Williams Hematology. 7th ed. New York: McGraw-Hill, 2006
13. Hedner U, Glazer S, Pingel K, Alberts K, Blomback M, Schulman S, Johnson H. Successful use of recombinant factor VIIa in a patient with severe hemophilia A during synovectomy. Lancet 1988;2:1193
14. Hedner U, Kisiel W. Use of human factor VIIa in the treatment of two hemophilia A patients with high-titer inhibitors. J Clin Invest 1983;71:1836–41
15. Hedner U. Recombinant activated factor VII as a universal haemostatic agent. Blood Coagul Fibrinolysis 1998;9:S147–52
16. Hedner U. NovoSeven as a universal haemostatic agent. Blood Coagul Fibrinolysis 2000;11:S107–11
17. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T. Recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med 2005;352:777–85
18. Boffard KD, Riou B, Warren B, Choong PI, Rizoli S, Rossaint R, Axelsen M, Kluger Y. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. J Trauma 2005;59:8–15
19. Mayer SA, Brun NC, Begtrup K, Broderick J, Davis S, Diringer MN, Skolnick BE, Steiner T. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. N Engl J Med 2008;358:2127–37
20. Hauser CJ, Boffard K, Dutton R, Bernard GR, Croce MA, Holcomb JB, Leppaniemi A, Parr M, Vincent JL, Tortella BJ, Dimsits J, Bouillon B. Results of the CONTROL trial: efficacy and safety of recombinant activated factor VII in the management of refractory traumatic hemorrhage. J Trauma 2010;69:489–500
21. Gabriel DA, Muga K, Boothroyd EM. The effect of fibrin structure on fibrinolysis. J Biol Chem 1992;267:24259–63
22. Collet J, Lesty C, Montalescot G, Weisel J. Dynamic changes of fibrin architecture during fibrin formation and intrinsic fibrinolysis of fibrin-rich clots. J Biol Chem 2003;278:21331–5
23. Collet J, Park D, Lesty C, Soria J, Montalescot G, Weisel J. Influence of fibrin network conformation and fibrin diameter on fibrinolysis speed: dynamic and structural approaches by confocal microscopy. Arterioscler Thromb Vasc Biol 2000;20:1354–61
24. Bajzar L, Manuel R, Nesheim ME. Purification and characterization of TAFI, a thrombin-activable fibrinolysis inhibitor. J Biol Chem 1995;270:14477–84
25. Ichinose A. Physiopathology and regulation of factor XIII. Thromb Haemost 2001;86:57–65
26. Chen R, Doolittle RF. Identification of the polypeptide chains involved in the cross-linking of fibrin. Proc Natl Acad Sci U S A 1969;63:420–7
27. Pisano JJ, Finlayson JS, Peyton MP. Cross-link in fibrin polymerized by factor 13: epsilon-(gamma-glutamyl)lysine. Science 1968;160:892–3
28. Matacic S, Loewy AG. The identification of isopeptide cross-links in insoluble fibrin. Biochem Biophys Res Commun 1968;30:356–62
29. Mosesson MW. Hereditary fibrinogen abnormalities. In: Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Kaushansky K, Prchal JT, eds. Williams Hematology. 7th ed. New York: McGraw-Hill, 2006
30. Weiskopf RB. Recombinant-activated coagulation factor VIIa (NovoSeven): current development. Vox Sang 2007;92:281–8
31. Hiippala ST, Myllyla GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. Anesth Analg 1995;81:360–5
32. Solomon C, Cadamuro J, Ziegler B, Schochl H, Varvenne M, Sorensen B, Hochleitner G, Rahe-Meyer N. A comparison of fibrinogen measurement methods with fibrin clot elasticity assessed by thromboelastometry, before and after administration of fibrinogen concentrate in cardiac surgery patients. Transfusion 2011;51:1695–706
33. Food and Drug Administration. 21CFR50.24. Protection of Human Subjects: Informed Consent. Exception from informed consent requirements for emergency research, 2007
34. Center for Biologics Evaluation and Research. Product development program for interventions in patients with severe bleeding due to trauma or other causes. December 9, 2010 (day 1). Rockville, MD: Center for Biologics Evaluation and Research, 2010:308–54
35. Center for Biologics Evaluation and Research USFDA. Draft guidance for industry: efficacy evaluation of hemoglobin- and perfluorocarbon-based oxygen carriers. September 8, 1997. Rockville, MD: Center for Biologics Evaluation and Research, 1997
36. Center for Biologics Evaluation and Research USFDA. Draft guidance for industry: criteria for safety and efficacy evaluation of oxygen therapeutics as red blood cell substitutes. October 2004. Rockville, MD: Center for Biologics Evaluation and Research, 2004

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REVIEW ARTICLE

CME

Fibrinogen and Hemostasis: A Primary Hemostatic Target for the Management of Acquired Bleeding

Jerrold H. Levy, MD, FAHA, Fania Szlam, MMSc, Kenichi A. Tanaka, MD, and Roman M. Sniecienski, MD

Fibrinogen plays several key roles in the maintenance of hemostasis. Its cleavage by thrombin and subsequent polymerization to form fibrin strands provides the structural network required for effective clot formation. During cases of acute blood loss, attempts to maintain circulating volume and tissue perfusion often involve the infusion of crystalloids, colloids, and red blood cells. Intravascular volume resuscitation, although vital, frequently results in dilution of the remaining clotting factors and onset of dilutional coagulopathy. In such cases, fibrinogen is the first coagulation factor to decrease to critically low levels. There currently is a lack of awareness among physicians regarding the significance of fibrinogen during acute bleeding and, at many centers, fibrinogen is not monitored routinely during treatment. We reviewed current studies that demonstrate the importance of considering fibrinogen replacement during the treatment of acquired bleeding across clinical settings. If depleted, the supplementation of fibrinogen is key for the rescue and maintenance of hemostatic function; however, the threshold at which such intervention should be triggered is currently poorly defined. Although traditionally performed via administration of fresh frozen plasma or cryoprecipitate, the use of lyophilized fibrinogen (concentrate) is becoming more prevalent in some countries. Recent reports relating to the efficacy of fibrinogen concentrate suggest that it is a viable alternative to traditional hemostatic approaches, which should be considered. The prospective study of fibrinogen supplementation in acquired bleeding is needed to accurately assess the range of clinical settings in which this management strategy is appropriate, the most effective method of supplementation and a comprehensive safety profile of fibrinogen concentrate used for such an approach. (Anesth Analg 2012;114:261–74)

Fibrinogen is a plasma protein critical to hemostasis and clot formation.[1] The blood plasma concentration of fibrinogen ranges between 1.5 and 4.0 g/L but it can be higher, particularly in certain conditions such as pregnancy.[2] Structurally, human fibrinogen comprises 2 outer D domains, which are both linked by a central E domain.[3] Each D domain is made up of 3 polypeptide chains (α, β, and γ), which together form a coiled-coil configuration. These domains are linked at the *N*-terminus to the central E domain via a series of disulfide bonds.[4] Thrombin cleavage occurs at specific amino-acid sequences present on the α and β polypeptide chains, removing the *N*-terminal peptides (fibrinopeptides) and exposing the polymerization sites (Fig. 1).[3] Fibrin polymerization then occurs via noncovalent interaction of the exposed polypeptide chain with complementary binding sites present on the D domain of a neighboring molecule.[3] Furthermore, recent preliminary data have suggested that fibrinogen may be heme associated and could play a role in carbon monoxide sensing.[5]

Studies from our laboratory and others have demonstrated the importance of thrombin generation and hemostatic activation for clot formation.[6–11] Functionally, fibrinogen molecules act during both cellular and fluid phases of coagulation. In the cellular phase, it facilitates the aggregation of platelets via binding of glycoprotein IIb/IIIa receptors on platelet surfaces. In the fluid phase, it is cleaved by thrombin to produce fibrin monomers, which polymerize to form the basis of the clot (Fig. 2).[4,12–14] Fibrinogen also plays other important roles, functioning in vivo as an acute phase reactant, helping modulate inflammatory cellular reactions and also increasing in plasma concentration after injury.

When acute hemorrhage occurs, the resulting blood loss and consumption of procoagulants combine to reduce the circulating concentration of multiple clotting factors. Derangement in common measures of coagulation (prothrombin time and activated partial thromboplastin time) can develop in cases of acute trauma, before administration of fluid therapy.[15] Such derangements are associated with

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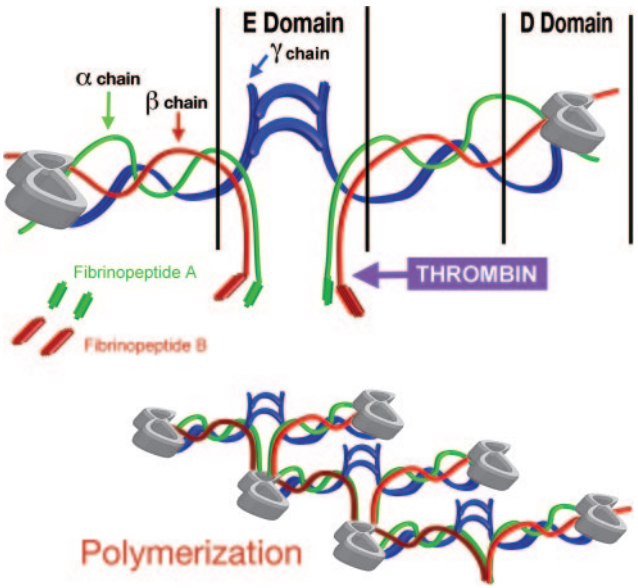

Figure 1. The thrombin cleavage of fibrinogen and polymerization of fibrin monomers to fibrin. A schematic representation of the thrombin cleavage of fibrinogen, followed by the polymerization of fibrin monomers to form fibrin strands is illustrated.

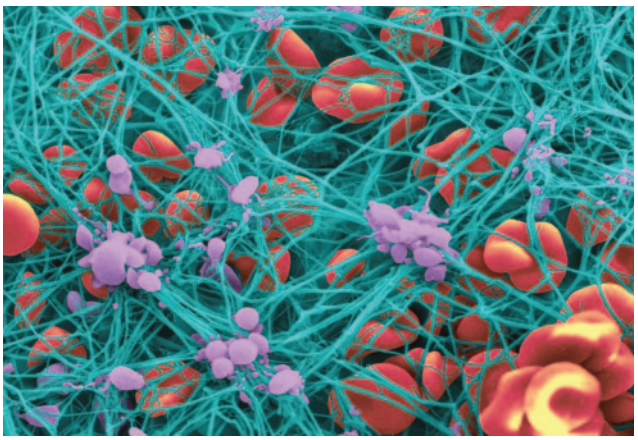

Figure 2. A fibrin blood clot: the constituent parts of a blood clot are shown (red blood cells, red; fibrin fibers, blue; platelet aggregates, purple). From John W. Weisel, PhD, University of Pennsylvania, with permission.

significantly increased mortality rates in trauma patients.[15] The dilution of clotting factors during intravascular volume replacement can result in further coagulopathy; however, such hemostatic intervention is essential for the restoration of circulating volume and tissue perfusion. A prospective observation of plasma concentrations of clotting factors in patients undergoing major urologic or abdominal surgery (n = 60) showed that levels of prothrombin, factor V, factor VII and fibrinogen were all significantly reduced after blood loss and subsequent fluid replacement (red blood cells [RBCs] and colloids).[16] Because of its relatively high initial plasma concentration, fibrinogen was the first clotting factor to decrease to critically low levels.[16] In noncardiac major surgery, it has been shown that fibrinogen reaches plasma concentrations of 1 g/L when 142% (95% confidence interval [CI], 117 to 169%) of the circulating blood volume has been lost.[16]

The maintenance of hemostasis relies on a series of complex interactions between both the cellular and protein components of coagulation.[17] Importantly, platelets play a key role in many of these interactions; the platelet surface is the primary site for thrombin generation,[17] and platelets aggregate to form the primary hemostatic plug,[18] as well as stabilizing clot formation.[1] Circulating platelet concentrations reduce in a similar manner to the observed depletion of clotting factors during major surgery.[16] As such, the development of thrombocytopenia in critically bleeding patients is a significant challenge to hemostasis. In vitro analysis of platelet-poor plasma showed a positive correlation of viscoelastic measurements of clot strength with increasing fibrinogen concentration,[1] a result that was corroborated by a retrospective analysis of 904 thrombocytopenic patients. As such, the maintenance of fibrinogen concentrations is crucial in cases of thrombocytopenia.[1]

The clinical relevance of plasma fibrinogen concentrations in bleeding patients is not widely recognized and, as a result, physicians may not routinely measure fibrinogen levels or consider supplementation options when treating major bleeding. In this review we will discuss the importance of fibrinogen in clot formation and the therapeutic approaches for replacing fibrinogen in acquired bleeding states.

ACUTE BLOOD LOSS AND MASSIVE TRANSFUSION COAGULOPATHY

In cases of acute blood loss, restoring circulatory volume is a primary objective often addressed with volume expanders such as crystalloids, colloids, or a combination of both.[19,20] The ideal volume expander has been the subject of significant debate; however, the administration of any volume expander will result in the reduction of platelets and plasma clotting factor concentrations.[21] In such cases, the commonly observed change is dilutional thrombocytopenia, but continuing blood loss can lead to a more complex coagulopathy. Neither concentrates of RBCs or platelets contain enough plasma to supplement the depleted factors sufficiently to maintain hemostatic balance.[16] Thus, continued consumption of clotting factors coupled with their dilution with volume expanders can lead to the development of dilutional coagulopathy.

The critical role of fibrinogen deficiency and fibrinolysis in cases of major bleeding is increasingly described.[1,22,23] The preoperative measurement of plasma fibrinogen concentration was found to be predictive of postoperative bleeding volume and transfusion requirements in a prospective observation of coronary bypass grafting surgical patients (n = 170).[24] In another example, a multivariate analysis of postpartum hemorrhage (n = 128) reported that fibrinogen concentration was the only hemostatic marker consistently associated with the occurrence of severe postpartum hemorrhage. It was concluded that the early measurement of fibrinogen was able to detect reductions in plasma fibrinogen concentration, allowing the risk of severe bleeding to be predicted. As such, monitoring of this kind is recommended during the management of obstetric-related bleeding events.[25]

A greater understanding of the predictive value of plasma fibrinogen concentrations has led to the potential for laboratory-guided, prophylactic supplementation of coagulation factors in cases of elective procedures. Thus, in

Table 1. A Comparison of the Constituent Components of the Transfusion Options for Fibrinogen Supplementation

Coagulation factor	FFP, relative content (%) in comparison with normal plasma[28,34]	Cryoprecipitate, relative content (%) in comparison with normal plasma: per single donor unit (20–50 mL)[38]	Fibrinogen concentrates	
			Riastap™[d]/ Haemocomplettan P/HS®[e] (per 50-mL vial) (CSL Behring, Marburg, Germany)	Clottafact®[f] (LFB-biomedicaments) (per 100-mL vial) (LFB-biomedicaments, Paris, France)
Fibrinogen	2.0 mg/mL (0.9–3.2)[34b]	388 mg[c] (range: 120–796 mg)	18–26 mg/mL	~15 mg/mL
FII	90 (72–108)[34b]	—	—	—
FV	88 (72–108)[34b]	—	—	—
FVII	90 (59–120)[34b]	—	—	—
FVIII	53 (32–92)[34b]	—	—	—
FIX	68 (45–87)[34b]	—	—	—
FX	88 (72–108)[34b]	—	—	—
FXI	100[28]	—	—	—
FXII	83[28]	—	—	—
FXIII	100[28]	20%–30%	—	—
Antithrombin III	100[28]	—	—	—
VWF	80[28c]	—	—	—
FVIII and VWF[a]	—	40%–70%	—	—
Fibronectin	—	20%–25%	—	—
IgG	—	5%–8%	—	—
IgM	—	1%–2%	—	—
Albumin	—	5%–8%	8–14 mg/mL	—
L-arginine	—	—	7.5–13.2 mg/mL	—
Sodium chloride	—	—	4–7 mg/mL	—
Sodium citrate	—	—	1–2 mg/mL	—

F = factor; FFP = fresh frozen plasma; Ig = immunoglobulin; VWF = Von Willebrand factor.
[a] Reported jointly. [b] Median (reported range). [c] With some loss of high molecular weight multimers, particularly if solvent/detergent treated. [d] Licensed in European countries and the United States for congenital fibrinogen deficiency. [e] Licensed in Austria, Brazil, Bulgaria, Germany, the Czech Republic, Hungary, Kuwait, the Netherlands, Portugal, Romania, Switzerland, Taiwan, and Turkey for acquired bleeding. [f] Licensed in France for acquired bleeding.

events when hemorrhage is likely, the onset of coagulopathy can be delayed and the extent of bleeding reduced. A recent prospective randomized controlled pilot study (n = 20) investigating prophylactic fibrinogen supplementation before coronary artery bypass grafting showed that postoperative bleeding was reduced by 32% in patients receiving 2 g fibrinogen concentrate preoperatively in comparison with the control group (565 ± 150 vs 830 ± 268 mL; P = 0.010), without any evidence of hypercoagulability.[26] Recognizing the emerging evidence, which highlights the importance of maintaining adequate plasma fibrinogen concentrations, European guidelines now include the administration of fibrinogen concentrate among their recommendations for the treatment of trauma-related, life-threatening hemorrhage; however, it should be noted that this recommendation is based upon the lowest level of evidence available to the guideline authors.[19,27]

FIBRINOGEN REPLACEMENT

There are 3 main approaches to fibrinogen supplementation, which involve the infusion of fresh frozen plasma (FFP), cryoprecipitate, or fibrinogen concentrate.

Fresh Frozen Plasma

FFP contains all proteins present in human plasma, including albumin, immunoglobulins, and coagulation and fibrinolytic elements, which are at or below physiological concentrations (Table 1).[28] It is commonly transfused for the reversal of oral anticoagulation therapy,[29] but is also used for coagulation factor supplementation during acute bleeding.[30] Although extensively used during massive transfusion protocols, FFP preparations have been associated with the potential risk of pathogen transmission.[31,32] Commercially available plasma can be virally inactivated using 1 of 4 major treatment processes to minimize the risk of pathogen contamination: solvent-detergent (SD), methylene blue, amotosalen, or riboflavin. All 4 methods demonstrate effectiveness against common pathogens, including human immunodeficiency virus.[33] With the exception of SD-treated plasma, these methods are designed for small-volume use at blood banks,[33] and the availability of such plasmas is limited to certain regions and countries. Immunological reactions, including allergic reactions, and transfusion-related acute lung injury can also result from FFP administration.[32]

FFP contains approximately 2.0 g/L[34] of fibrinogen, but fibrinogen concentrations do vary between units; thus predicting the increase in patient plasma fibrinogen concentrations after transfusion is difficult.[28] When the in vivo fibrinogen concentration was measured in patients transfused with 30 mL/kg of FFP (approximating to 2.1 L of FFP for a 70-kg patient), a median increase of 1.0 g/L (range, 0.9 to 2.4 g/L) was observed.[35] Thus, large volumes of FFP are required to increase plasma fibrinogen concentrations in bleeding patients, increasing the risk of hypervolemia and transfusion-related circulatory overload.[36] FFP is used increasingly in situations such as massive transfusion coagulopathy; however, a recent systematic review of massive plasma transfusion found very-low-quality evidence that such treatment reduces the risk of patient death.[36]

Cryoprecipitate

Cryoprecipitate is a human plasma concentrate that was first described in the 1960s.[37] It is manufactured from FFP, and the processes involved have changed little since it was

first discovered. In short, the thawing (between 1°C and 6°C) and subsequent centrifugation of FFP is followed by the removal of the supernatant.[38] The remaining 5 to 15 mL of plasma is refrozen and can be stored in this way for up to 12 months.[38] According to recent testing, each unit of cryoprecipitate contains a median fibrinogen concentration of 388 mg (range, 120 to 796 mg), whereas the minimum requirements of the American Association of Blood Banks (AABB) is 150 mg per unit.[38] The typical concentrations of other constituents contained in each unit are displayed in Table 1.

Because cryoprecipitate contains higher concentrations of fibrinogen than does FFP, it is the therapy option often used for fibrinogen supplementation in the United States (US) and United Kingdom. However, the existing risk of immunological reactions and the transmission of infectious agents has led to its withdrawal in several European countries.[39] Cryoprecipitate is unsuitable for viral inactivation processes in its native form,[40] though plasma derivatives that have been pretreated with methylene blue or SD can be used for its production.[39] Unfortunately, such pretreatment processes can reduce the concentration of functional fibrinogen present.[39,40] As with FFP, cryoprecipitate requires blood type matching and thawing before infusion, delaying administration in time-critical situations.

Fibrinogen Concentrate

Fibrinogen concentrate is derived from human plasma and is stored at room temperature as a pasteurized, lyophilized powder.[41] It does not require blood type matching or thawing; thus it is available immediately when required. It can be reconstituted in low-volume concentrations of up to 20 g/L.[41] Doses as high as 6 g infused in as little as 1 to 2 minutes have been reported in critical bleeding.[42] A summary of fibrinogen concentrates currently available is shown in Table 1. Commercially available fibrinogen concentrates are primarily licensed for the treatment of congenital fibrinogen deficiency across the US and Europe, and a license for the treatment of acquired bleeding has been granted for only 1 of these products in some European countries (Table 1).

The risk of viral infection with fibrinogen concentrates is significantly reduced because of viral inactivation and removal processes.[43] This inherent viral reduction capacity also minimizes the risk of transmitting new emerging viruses.[43] Although fibrinogen concentrate is manufactured using human plasma from a large pool of donors, the production processes involved remove antibodies and antigens, largely mitigating the risk of immunological and allergic reactions resulting from its administration.[39] It should be noted that although this risk is much reduced, as with all blood products, fibrinogen concentrate administration will always have the theoretical potential for transmission of new emerging infectious agents.[44]

Historically, the occurrence of thromboembolic events has been a concern surrounding the administration of clotting factor concentrates. With respect to fibrinogen concentrate specifically, there are currently no results from large prospective randomized controlled clinical trials on which any firm judgments can be based. Although an increase in the amount of available prospective data would provide valuable evidence for fully evaluating the thrombotic potential of fibrinogen concentrate, reviews of published clinical data and a recent pharmacovigilance report have demonstrated no significant thrombogenic concerns with fibrinogen concentrate.[45,46] Furthermore, a study of 151 separate infusions administered to 12 patients with congenital fibrinogen deficiencies showed that the supplementation of fibrinogen using fibrinogen concentrate for prophylaxis, as well as during bleeding episodes and surgery, was both efficient (with a median in vivo fibrinogen recovery of 59.8% [n = 8; range: 32.5 to 93.9]) and generally well tolerated.[47] In support of the clinical data, animal models of venous stasis have found that fibrinogen concentrates demonstrated no thrombogenic activity.[22,45] It should be noted, however, that the use of fibrinogen concentrate in patients exhibiting disseminated intravascular coagulation is potentially hazardous because of the risk of accelerated fibrin formation and should be avoided.[41] Current opinion still remains divided regarding what constitutes the correct and appropriate administration of fibrinogen concentrate in the critical care setting.[44,48] Surveillance data may not provide reliable estimates of thrombotic adverse events, which can occur up to 3 months postsurgery at the doses used.[44] It is also important to consider that there is no current prospective comparison of the safety profiles of FFP, cryoprecipitate, and fibrinogen concentrate, when administered for fibrinogen supplementation.

CURRENT UNDERSTANDING OF FIBRINOGEN REPLACEMENT

Preclinical Data

In a porcine model of thrombocytopenia, fibrinogen concentrate was shown to better improve hemostatic function and survival times than platelet transfusion alone after blunt liver injury.[22] A second porcine model of blunt liver trauma has compared bleeding and subject outcomes among animals receiving varying concentrations of fibrinogen concentrate. When compared with placebo, the administration of fibrinogen concentrate (70 or 200 mg/kg) after severe dilutional coagulopathy both significantly improved coagulation and attenuated blood loss.[49] Although the proper dosing cannot be determined from the studies involving nonhuman species, in vitro clinical data using human blood also demonstrate that increased fibrinogen concentration improves clot strength independently of platelet count.[1,50] Taken together, these results suggest that restoration of plasma fibrinogen concentrations using fibrinogen concentrate could be an effective hemostatic treatment in cases of acquired bleeding.

Clinical Data

Since fibrinogen supplementation in cases of major bleeding was established as a potentially useful treatment approach, the efficacy of fibrinogen concentrate has been assessed by many retrospective and some prospective studies. Its administration for the treatment of acquired bleeding has been studied in heterologous cohorts of patients across a range of critical care settings (summarized in Table 2).

Table 2. A Summary of Clinical Studies Detailing Fibrinogen Administration

Study	Indication	Data source	Fibrinogen dose	Number of patients treated with fibrinogen	Treatment and results	Key findings
Trauma						
M. Brenni et al. 2010[68] (*N* = 1)	Severe abdominal trauma	Case report	16 g	1	A total of 1 g of tranexamic acid, 7 U RBCs, 16 g of fibrinogen concentrate, 3500 mL of colloids and 5500 mL of lactated Ringer's solution were administered. Together with surgical intervention, bleeding was stopped and the patient stabilized	Fibrinogen concentrate was administered as primary hemostatic therapy. Coagulopathy was corrected without the need for FFP or platelet administration
Schöchl et al. 2010[69] (*N* = 1)	Polytrauma induced coagulopathy	Case report	13 g	1	Hemostatic therapy was guided by EXTEM® and FIBTEM®. MCF ≥10 mm was maintained following 9 g fibrinogen concentrate administration intraoperatively and 4 g postoperatively	The combined use of fibrinogen concentrate and PCC infusion allowed extended emergency hemihepatectomy without the need for FFP and platelets, and reduced the need for RBCs
Schöchl et al. 2010[70] (*N* = 131)	Trauma-induced coagulopathy	Retrospective database analysis	6.0 g[a] (IQR, 4–9 g) until ICU admission; 7.0 g[a] (IQR, 5–11 g) total after 24 hours	128	Excluding traumatic brain injury, a 14% mortality rate was observed in patients receiving fibrinogen concentrate (*n* = 128) and PCCs (*n* = 98), in comparison with rates of 27.8% and 24.3% predicted by TRISS or RISC, respectively	Goal-directed, ROTEM®-guided administration of fibrinogen concentrate and PCC was fast (within 30 minutes of admission to the ER in most cases) and correlated with a favorable survival rate
Schöchl et al. 2011[71] (*N* = 681)	Trauma-induced coagulopathy	Retrospective database analysis	6.0 g[a] (IQR, 3–9 g)	73	RBC and platelet transfusion avoided in 29% and 91% of fibrinogen-PCC patients, respectively, in comparison with 3% and 56%, respectively, in the FFP (no clotting factor concentrates) group Mortality was comparable between groups	TEM-guided hemostatic combination therapy with fibrinogen concentrate and PCC reduced the exposure of trauma patients to allogeneic blood products in comparison with patients receiving FFP (without clotting factor concentrates)

(*Continued*)

Table 2. (Continued)

Study	Indication	Data source	Fibrinogen dose	Number of patients treated with fibrinogen	Treatment and results	Key findings
Cardiovascular surgery						
Karlsson et al. 2009[26] (*N* = 20)	Elective CABG	Prospective randomized phase I/II study	2.0 g	10	Fibrinogen infusion reduced postoperative bleeding (12 hours) by 32% (565 ± 150 vs 830 ± 268 mL; *P* = 0.01). No clinically detectable adverse events were recorded in the fibrinogen group	Fibrinogen concentrate was administered prior to CABG (fibrinogen group). Reduced bleeding without evidence of hypercoagulability was observed in the fibrinogen group in comparison with the control group
Rahe-Meyer et al. 2009[74] (*N* = 15)	Aortic valve operation and ascending aorta replacement	Prospective, nonrandomized pilot study	5.7 (±0.7) g[b]	10	Total transfusion requirements (fibrinogen group vs control) were 0.7 U (±1.5) vs 8.2 U (±2.3), and postoperative drainage volume was 716 mL (±219 mL) vs 366 mL (±199 mL)	The perioperative administration of fibrinogen concentrate prior to the instigation of the established blood product transfusion algorithm was investigated in bleeding patients. Fibrinogen concentrate infusion reduced transfusion requirements and 24-hour postoperative bleeding
Rahe-Meyer et al. 2009[80] (*N* = 18)	Thoracoabdominal aortic aneurysm surgery	Retrospective control group vs prospective fibrinogen group	7.8 g[b] (±2.7 g)	6	Total transfusion requirements (fibrinogen group *vs* control) were 2.5U (SD, ±4.3) *vs* 16.4U (SD, ±4.8). 4 of 6 patients receiving fibrinogen concentrate required no transfusion of allogeneic blood products	Prophylactic administration of fibrinogen concentrate significantly reduced transfusion of allogeneic blood products and postoperative bleeding
Solomon et al. 2010[42] (*N* = 39)	Postcardiopulmonary bypass surgery	Open-label, uncontrolled, retrospective study	6.5 g[b] (±1.6 g) (78 [±20] mg/kg)	39	Mean fibrinogen level increased to 2.29 (±0.7) mg/dL per mg/kg body weight of fibrinogen concentrate administered. Maximum clot firmness increased from 10 to 21 mm	Administration of fibrinogen concentrate raised plasma fibrinogen concentration and contributed to the correction of postoperative bleeding

(*Continued*)

Table 2. (Continued)

Study	Indication	Data source	Fibrinogen dose	Number of patients treated with fibrinogen	Treatment and results	Key findings
Perioperative bleeding						
C. Fenger-Eriksen et al. 2009[98] (*N* = 20)	Radical cystectomy	Single-center, prospective, double-blind, placebo-controlled, randomized clinical trial	45 mg/kg	10	Significant increase in maximum clot firmness. Two of 10 patients who received fibrinogen concentrate required pos to perative RBCs vs 8 of 10 in placebo group	Randomized placebo-controlled administration of fibrinogen concentrate significantly improved maximum clot firmness and reduced the requirement for postoperative transfusion
Mittermayr et al. 2007[82] (*N* = 66)	Orthopedic surgery	Prospective observational study	30 mg/kg	13	MCF and fibrinogen polymerization significantly decreased in the patients receiving HES (area under the curve minus baseline (− 5 [− 9 to − 2]), followed by gelatin solution (− 3 [− 8 to 0]), with the smallest reductions seen for Ringer's lactate solution (− 2 [− 4 to 1])	Disturbance of fibrinogen/fibrin polymerization is the primary problem triggering dilutional coagulopathy. Fibrinogen concentrate administration maintained clot firmness in these cases, even in the presence of continued bleeding
Bell et al. 2010[87] (*N* = 6)	Obstetric hemorrhage	Collection of 6 case reports	N/A	6	Laboratory assessed coagulation was rapidly normalized and severe hemorrhage improved following fibrinogen concentrate administration	Fibrinogen concentrate could effectively reduce peripartum blood loss associated with hypofibrinogenemia
Cross-setting administration						
Danes et al. 2008[51] (*N* = 69)	Surgery, trauma and gastrointestinal hemorrhage. Hepatic dysfunction and hematological malignancies	Open-label, noncontrolled retrospective study	3.52g[a] (range,0.5–8.0g)	69	Mean absolute increase in plasma fibrinogen was 1.09 g/L 24 hours after treatment; coagulation variables significantly improved; mortality rates of 32.3% and 44.2% after 24 hours and 72 hours	Fibrinogen concentrate administration improved laboratory coagulation measures and may be life saving in patients with life-threatening, unresponsive coagulopathy

(*Continued*)

Table 2. (Continued)

Study	Indication	Data source	Fibrinogen dose	Number of patients treated with fibrinogen	Treatment and results	Key findings
Weinkove et al. 2008[46] (*N* = 30)	Placental abruption, massive blood loss and transfusion, liver failure, cardiac surgery	Retrospective database analysis	4.0 (range, 2.0–14.0 g)[a]	30	Median absolute increase in plasma fibrinogen per 1 g of fibrinogen concentrate was 0.25 g/L (0.65–2.01 g). Bleeding stopped in 46% of patients treated with fibrinogen and blood components alone	Fibrinogen concentrate appears to be effective in the management of acquired bleeding, being able to provide a consistent dose in the emergency setting
Fenger-Eriksen et al.[52] 2008 (*N* = 43)	Serious acquired bleeding; primarily obstetric complications, cardiothoracic and intra-abdominal bleeding	Retrospective database analysis	Adults: 2.0 g[a] (range, 1–5 g); children: 0.35 g[a] (range, 0.2–0.5 g)	43	Median increase in plasma fibrinogen concentration was 1.0 g/L (from 1.4 [1.0–1.8] to 2.4 [2.1–2.6]). In adults, median total blood loss decreased significantly from 4000 ml (1500–7750 mL) to 50 mL (0–425 mL)	Off-label fibrinogen concentrate administration led to significant reductions in both bleeding and the requirement for transfusion of RBCs, platelets, and FFP

CABG = coronary artery bypass graft; ER = emergency room; FFP = fresh frozen plasma; ICU = intensive care unit; PCC = prothrombin complex concentrate; RBCs = red blood cells; RISC = revised injury severity classification; ROTEM = rotational thromboelastometry; TRISS = trauma injury severity score; MCF = maximum clot firmness; HES = hydroxyethyl starch; N/A = not applicable; IQR = interquartile range.
[a] Median. [b] Mean.

Retrospective analyses (n = 30) of fibrinogen concentrate administration to treat acquired hypofibrinogenemia and life-threatening bleeding found it was effective in the management of such events,[46] improving laboratory coagulation measures and survival rates in unresponsive coagulopathy.[51] Laboratory monitoring of plasma fibrinogen concentrations has shown significant increases after fibrinogen concentrate administration (median dose, 3.52 g [range: 0.5 to 8.0]; mean increase [± SD] in plasma fibrinogen, 1.09 [±0.68] g/L),[51] with associated improvements in both prothrombin time and activated partial thromboplastin time.[51,52] Retrospective analysis of such laboratory coagulation measurements, in bleeding patients (n = 43) treated with fibrinogen concentrate, demonstrated that such improvements have led to reduced blood loss and lower requirements for RBCs (~12 U vs ~2 U), FFP (~8 U vs ~2 U), and platelets (~2.5 U vs ~0.5 U).[53] These blood-sparing effects indicate that fibrinogen concentrate could potentially challenge traditional hemostatic approaches using FFP and platelet concentrates.

Trauma

The significant loss of blood volume associated with trauma-related bleeding often precipitates the "lethal triad" of acidosis, hypothermia, and coagulopathy. Coagulopathy in trauma patients results from the rapid depletion of circulating coagulation factors because of consumption and blood loss. Although acidemia, hypothermia, and subsequent dilution all interact to contribute to trauma-related coagulopathy, the interplay between these mechanisms is yet to be fully elucidated.[54] Importantly, trauma-related coagulopathy is a leading cause of mortality,[55,56] and is responsible for up to 40% of trauma-related deaths.[19] In such cases, the need for effective and rapid hemostasis management is important, in addition to the rapid surgical control of bleeding. In cases of trauma-related massive bleeding, European transfusion guidelines recommend the primary restoration of circulating volume and secondary hemostatic measures via transfusion of blood products or pharmaceutical agents.[19,27] Recent military experience of trauma has strongly influenced transfusion practices in US trauma centers.[57,58] Several observational studies have suggested that transfusion of high ratios of FFP to RBCs (1:1) is key to improving survival rates in patients with major trauma.[59–61] Consequently, many civilian trauma centers are now adopting massive transfusion protocols, which include the transfusion of FFP in high volumes.[62] Although this approach is not universally accepted,[63–65] and the complete restoration of circulating volume is not recommended in the US, it is becoming clear that the timely supplementation of coagulation factors during major trauma-related bleeding is important for the improvement of patient outcomes.[66] A retrospective review of battlefield trauma reported 252 patients receiving massive transfusion, in which the total amount of fibrinogen infused within all administered blood products (FFP, RBCs, and platelets) correlated with reductions in mortality.[67]

There are increasing reports of fibrinogen replacement using concentrates administered as a first-line treatment of trauma. Brenni et al. detailed a case study in which fibrinogen concentrate was used in combination with RBCs

as a primary hemostatic agent for the treatment of coagulopathy resulting from major abdominal trauma.[68] Coagulopathy was corrected without the use of allogeneic blood products, highlighting the potential efficacy and safety benefits of such management protocols. The coadministration of fibrinogen concentrate with other prohemostatic agents is an effective management protocol for trauma patients. A separate case study details the administration of fibrinogen concentrate, in combination with prothrombin complex concentrate (PCC), for the successful treatment of polytrauma.[69] The combined use of these coagulation factor concentrates, guided by point-of-care assessment (rotational thromboelastometry [ROTEM®; TEM Innovations GmbH, Munich, Germany]), eliminated the need for allogeneic factors (including FFP and platelet transfusion) and reduced the need for RBCs. A larger, retrospective analysis of a patient cohort with acquired bleeding (n = 131 total) receiving similar transfusion protocols adds weight to the conclusions drawn by these case studies.[70] Patients infused with fibrinogen concentrates (n = 128) and PCCs (n = 98), using ROTEM-guided goal-directed coagulation management, displayed favorable survival rates in relation to those predicted by the trauma injury severity score (TRISS).[70] A similar retrospective analysis compared a group of trauma patients (n = 80) receiving TEM-guided fibrinogen concentrate (median 6 g [range: 0 to 15 g]) and PCC administration (median 1200 U [range: 0 to 6600]) with trauma patients administered FFP in the absence of coagulation factor concentrates (n = 601, median 6 U [range: 2 to 51]).[71] The need for RBC and platelet transfusion was avoided in 29% and 91% of fibrinogen-PCC patients, respectively, in comparison with 3% and 56%, respectively, in the FFP group. The study authors concluded that the TEM-guided administration of coagulation factor concentrates reduced the exposure level of trauma patients to allogeneic blood products; however, it should be noted that mortality rates between groups remained broadly comparable (7.5% vs.10.0% [fibrinogen-PCC versus FFP; P = 0.69]).

These studies highlight the potentially useful combination of modern, real-time, coagulation monitoring with the administration of clotting factor concentrates capable of rapidly increasing the plasma concentrations of procoagulants in a goal-directed fashion. Currently, evidence, which demonstrates the efficacy of this approach, is restricted to case studies and retrospective analyses. There are concerns that highlight the limitations in study design that are inherent in such retrospective analyses, and care should be taken regarding the strength of conclusions that can be drawn on the basis of their results.[72] It is clear that though promising, further prospective studies are required to better establish the dosing efficacy and safety of this approach.

Perioperative Bleeding

Fibrinogen concentrate is now used across a range of surgical settings to maintain patient hemostasis and control bleeding. There follows an overview of recent studies that examines the efficacy of fibrinogen concentrate administered perioperatively.

Cardiovascular and Vascular Surgery

Cardiovascular and vascular surgical procedures are often accompanied by excessive bleeding.[73–75] Perioperative bleeding is a serious problem that can lead to increases in both morbidity and mortality rates.[76,77] The effective management of such bleeding is the key to improved patient outcomes, and a variety of approaches are now available to physicians.[78] Increasing numbers of both prospective and retrospective studies allow analysis of the impact of coagulation management in surgical procedures typically associated with excessive hemorrhage.

A retrospective study investigating mortality rates in patients (n = 128) undergoing ruptured abdominal aortic aneurysm repair found a significant reduction in mortality rates (15% vs 39%; $P < 0.03$) in patients receiving RBC:FFP ratio of ≤2:1 (high FFP cohort) in comparison with those receiving >2:1 ratios (low FFP cohort).[79] These results suggest that high volumes of FFP can effectively aid hemostatic function and improve patient outcomes during high-risk procedures. Fibrinogen concentrate may also be of benefit during such procedures. A study comparing both retrospective and prospective data investigated the use of fibrinogen concentrate during aortic valve and ascending aorta surgery. Eight of 10 patients (prospective group) receiving fibrinogen concentrate before surgery required no transfusion of RBCs during cardiopulmonary bypass or within the subsequent 24 hours. In comparison, 41 of 42 patients (retrospective group) receiving conventional hemostatic therapy did require RBC transfusion within the same period ($P < 0.05$).[74] A follow-up study evaluated prospective fibrinogen replacement using concentrates in 6 patients as an initial treatment of postbypass bleeding during thoracoabdominal aortic aneurysm repair in comparison with a retrospective cohort of patients receiving no prophylaxis (n = 20).[80] The need for transfusion of allogeneic blood products was reduced in patients receiving fibrinogen concentrate in comparison with those who did not (2.5 ± 4.3 U vs 16.4 ± 4.8 U), as was both the amount of bleeding during the following 24 hours, and the average length of treatment in the intensive care unit.[80] These preliminary data have led to the initiation of a prospective randomized clinical trial to further elucidate the potential of fibrinogen concentrate in this setting (ClinicalTrials.gov identifier number NCT00701142).

A retrospective analysis (n = 39) of fibrinogen concentrate infusion after cardiopulmonary bypass showed it to be an effective method of increasing the plasma fibrinogen concentration (mean dose [±SD]: 6.5 [±1.6]; absolute increase: 1.7 [±0.5] g/L).[42] As was mentioned previously, serious intraoperative bleeding was treated successfully using rapid fibrinogen concentrate infusion in some cases (~6 g in 1 to 2 minutes). The study authors concluded that the use of fibrinogen concentrate contributed to the correction of bleeding after surgery.[42]

Noncardiovascular Surgery

Patients undergoing orthopedic surgery are at risk of significant bleeding and developing dilutional coagulopathy, which may be influenced by the solution used for intravascular volume replacement.[21,81,82] A prospective study compared patients receiving colloids (either hydroxyethyl starch [HES]

[n = 19] or a modified gelatin solution [n = 21]) with those receiving Ringer's lactate solution (n = 21) for volume replacement during major orthopedic surgery, and examined coagulation variables using ROTEM.[82] Fibrinogen polymerization was significantly impaired in patients receiving colloid rather than crystalloid. Different HES solutions variably impede fibrinogen polymerization, resulting in reduced clot firmness. The administration of fibrinogen concentrate led to the restoration and maintenance of clot firmness, even during continued blood loss and further colloid administration.[82]

A prospective, placebo-controlled, randomized study (n = 20) of patients undergoing elective radical cystectomy investigated the ability of fibrinogen concentrate to restore hemostasis in patients experiencing excessive blood loss.[83] Patients received HES for volume replacement when required as part of the established blood replacement regimen; treatment with fibrinogen concentrate was triggered once 30% volume dilution had occurred. In comparison with placebo, fibrinogen supplementation significantly improved both whole blood clot firmness and the rate of clot formation. Additionally, the requirement for postoperative transfusion of RBCs was significantly reduced.[83]

Obstetric Hemorrhage

Obstetric hemorrhage remains a major cause of mortality and morbidity associated with childbirth.[84,85] The increase in uterine arterial bloodflow during labor means that massive obstetric hemorrhage (>1500 mL) can rapidly result in life-threatening blood loss, occurring in approximately 0.67% of all deliveries.[86] Such events require volume resuscitation and allogeneic transfusion; however, this approach can contribute to coagulopathy because of further dilution of coagulation factors. A review of 6 cases of severe obstetric hemorrhage suggested that the addition of fibrinogen concentrate to traditional therapies was effective in the treatment of peripartum blood loss associated with hypofibrinogenemia.[87] Fibrinogen administration in combination with other blood products can control bleeding even during continuing consumption and hemodilution.

These initial studies detail potential mechanisms by which severe obstetric hemorrhage could be both predicted and attenuated. However, it should be noted that there is currently little published evidence conclusively showing fibrinogen concentrate to be effective in preventing obstetric bleeding. Further prospective studies are needed to elucidate the full potential of this treatment option.

RECOMMENDED TRIGGER CONCENTRATIONS FOR FIBRINOGEN

Fibrinogen Detection Assays

Quantitative fibrinogen detection can be performed immunologically, measuring both functional and nonfunctional fibrinogen molecules. Functional assays that measure fibrinogen-dependent clot formation are used most often and utilize spectroscopic or viscoelastic detection. The Clauss method is a frequently used functional fibrinogen assay, whereby diluted citrated plasma is activated with thrombin and the time-to-clot formation is recorded spectroscopically.[41] Viscoelastic detection is performed using whole blood. When tested this way, the blood is housed in a cup (maintained at 37°C) and a pin is suspended within the sample. The cup and pin are oscillated in relation to each other and any subsequent impedance to this oscillation provides a measure of clot formation.[88] Point-of-care testing using viscoelastic measures of clot strength (TEG®; Hemonetics®, Braintree, MA, or ROTEM) allow patient-specific, rapid, and guided supplementation of depleted coagulation elements.[69,70,89,90] The extent of fibrin polymerization in whole blood can be estimated by inhibiting platelet-fibrin(ogen) interactions on the TEG-based Functional Fibrinogen Test or ROTEM-based FIBTEM. The latter is commonly used in European countries to titrate the dosing of fibrinogen concentrates.[69,70,89]

When deciding which functional test is most appropriate for fibrinogen detection, several considerations must be made. One advantage of using viscoelastic testing for fibrinogen determination is the inherent variability of Clauss-based fibrinogen assays. Clauss-based fibrinogen measurements may be falsely decreased in the presence of direct thrombin inhibitors,[91] and falsely increased in the presence of HES solutions.[92] In general, the turbidimetric (optical) detection method is affected more than mechanical detections by these agents.[93] However, it should be noted that the viscoelastic methodology described has not been prospectively validated for the measurement of fibrinogen-dependent clot formation during acute bleeding. It is not universally available, and furthermore, recent evidence suggests that the measurement of fibrinogen levels using FIBTEM can vary after hemostatic therapy, depending upon the type of coagulometer being used.[93]

Treatment Thresholds and Dosing of Fibrinogen

Although there are increasing data on the importance of plasma fibrinogen levels to prevent profuse bleeding, the threshold levels for transfusing either cryoprecipitate or fibrinogen concentrates have not been agreed on universally because of a lack of prospective evidence or consistent observations across different clinical settings. There has been some concern over iatrogenic hyperfibrinogenemia because increased plasma fibrinogen concentrations have been linked to an increased risk of coronary heart disease and myocardial infarction.[94] However, a study by Reinhart demonstrated that fibrinogen is a marker rather than a mediator of coronary heart disease.[95]

The revised European trauma guidelines published in 2010 recommend a trigger fibrinogen concentration of 1.5 to 2.0 g/L,[27] which was increased from below 1.0 g/L in earlier guidelines.[96] This change is in agreement with other in vitro evidence that concentrations larger than 2.0 g/L are required to produce effective clot formation.[50] Importantly, fibrinogen concentrations can vary among patients, as well as during incidences of acquired bleeding. Although the target plasma fibrinogen concentration that should be reached in a bleeding patient is not known, and the optimum dose of fibrinogen has not been established by dose-ranging trials, bleeding increases for each 1.0 g/L decrease in plasma fibrinogen in parturients.[25] In vitro viscoelastic analysis of whole blood shows clot strength increases linearly up to a fibrinogen concentration of 3.0 g/L, with a minimum threshold of 2.0 g/L required for the optimal rate of clot formation.[50,97]

Because of the large variability in fibrinogen concentrations among bleeding patients, increasing fibrinogen levels

should be individualized and based upon both the level of bleeding and the plasma fibrinogen concentration.[41] An initial dose of 10 U of cryoprecipitate, or 2.0 to 4.0 g of fibrinogen concentrate is recommended for a 70-kg patient,[41] with subsequent administration dependent upon an individual's bleeding status. For fibrinogen concentrates, the required dose can be estimated as follows[41,74]:

$$\text{Fibrinogen dose} = \text{desired increase (g/L)} \times \text{plasma volume (L)}.$$

Thus, administration of 3 g of fibrinogen concentrate in a 70-kg patient approximates to an overall increase in plasma fibrinogen concentration of 1.0 g/L (assuming 0.04 L/kg plasma volume). Predicting the increase in plasma fibrinogen concentrations that will result after cryoprecipitate administration is troublesome, because of the wide variation in fibrinogen concentration between units.[39]

SUMMARY

Fibrinogen is critical for effective clot formation, and its monitoring and guided supplementation in the treatment of major bleeding is increasingly recognized. A growing number of reports note the importance of fibrinogen replacement in the treatment of massive bleeding across a broad range of clinical settings.[1,22,42,51,68–70,74,80,82,87,98] Available sources of fibrinogen for supplementation include FFP, cryoprecipitate, and fibrinogen concentrates. Coagulation factor concentrates offer potential advantages over allogeneic blood products, such as decreased immunogenic and infectious complications, as well as rapid availability. Studies of the efficacy and safety of fibrinogen supplementation during acute bleeding has been most often retrospective or performed in prospective trials with limited participant numbers owing to ethical and practical constraints. This must be considered when evaluating the evidence on the administration of fibrinogen in bleeding patients. As such, further prospective, randomized controlled studies on the use of fibrinogen concentrate are essential to help define the breadth of clinical settings in which fibrinogen supplementation may be beneficial. Additional evidence would also help further define optimal trigger concentrations and doses for fibrinogen supplementation.

RECUSE NOTE

Jerrold H. Levy is section Editor of Hemostasis and Transfusion Medicine for *Anesthesia & Analgesia*. This manuscript was handled by Steve Shafer, Editor-in-Chief, and Dr. Levy was not involved in any way with the editorial process or decision.

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Name: Fania Szlam.
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Contribution: Reviewed manuscript, added additional information, references, and developed figures for manuscript.
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REFERENCES

1. Lang T, Johanning K, Metzler H, Piepenbrock S, Solomon C, Rahe-Meyer N, Tanaka KA. The effects of fibrinogen levels on thromboelastometric variables in the presence of thrombocytopenia. Anesth Analg 2009;108:751–8
2. Simon L, Santi TM, Sacquin P, Hamza J. Pre-anaesthetic assessment of coagulation abnormalities in obstetric patients: usefulness, timing and clinical implications. Br J Anaesth 1997;78:678–83
3. Kollman JM, Pandi L, Sawaya MR, Riley M, Doolittle RF. Crystal structure of human fibrinogen. Biochemistry 2009;48:3877–86
4. Mosesson MW. Fibrinogen and fibrin structure and functions. J Thromb Haemost 2005;3:1894–904
5. Nielsen VG, Cohen JB, Malayaman SN, Nowak M, Vosseller K. Fibrinogen is a heme-associated, carbon monoxide sensing molecule: a preliminary report. Blood Coagul Fibrinolysis 2011;22:443–7
6. He S, Blomback M, Jacobsson Ekman G, Hedner U. The role of recombinant factor VIIa (FVIIa) in fibrin structure in the absence of FVIII/FIX. J Thromb Haemost 2003;1:1215–9
7. Johansson PI, Jacobsen N, Viuff D, Olsen EH, Rojkjaer R, Andersen S, Petersen LC, Kjalke M. Differential clot stabilising effects of rFVIIa and rFXIII-A2 in whole blood from thrombocytopenic patients and healthy volunteers. Br J Haematol 2008;143:559–69
8. Kjalke M, Ezban M, Monroe DM, Hoffman M, Roberts HR, Hedner U. High-dose factor VIIa increases initial thrombin generation and mediates faster platelet activation in thrombocytopenia-like conditions in a cell-based model system. Br J Haematol 2001;114:114–20
9. Roberts HR, Hoffman M, Monroe DM. A cell-based model of thrombin generation. Semin Thromb Hemost 2006;32(suppl 1):32–8
10. Tanaka KA, Key NS, Levy JH. Blood coagulation: hemostasis and thrombin regulation. Anesth Analg 2009;108:1433–46
11. Bolliger D, Gorlinger K, Tanaka KA. Pathophysiology and treatment of coagulopathy in massive hemorrhage and hemodilution. Anesthesiology 2010;113:1205–19
12. Weisel JW, Veklich Y, Gorkun O. The sequence of cleavage of fibrinopeptides from fibrinogen is important for protofibril formation and enhancement of lateral aggregation in fibrin clots. J Mol Biol 1993;232:285–97
13. Gorkun OV, Veklich YI, Weisel JW, Lord ST. The conversion of fibrinogen to fibrin: recombinant fibrinogen typifies plasma fibrinogen. Blood 1997;89:4407–14
14. Weisel JW, Nagaswami C, Vilaire G, Bennett JS. Examination of the platelet membrane glycoprotein IIb-IIIa complex and its interaction with fibrinogen and other ligands by electron microscopy. J Biol Chem 1992;267:16637–43
15. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma 2003;54:1127–30
16. Hiippala ST, Myllyla GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. Anesth Analg 1995;81:360–5
17. Hoffman M, Monroe DM 3rd. A cell-based model of hemostasis. Thromb Haemost 2001;85:958–65
18. Ruggeri ZM. The role of von Willebrand factor and fibrinogen in the initiation of platelet adhesion to thrombogenic surfaces. Thromb Haemost 1995;74:460–3
19. Stainsby D, MacLennan S, Thomas D, Isaac J, Hamilton PJ. Guidelines on the management of massive blood loss. Br J Haematol 2006;135:634–41
20. Donaldson MD, Seaman MJ, Park GR. Massive blood transfusion. Br J Anaesth 1992;69:621–30

21. Fenger-Eriksen C, Anker-Moller E, Heslop J, Ingerslev J, Sorensen B. Thrombelastographic whole blood clot formation after ex vivo addition of plasma substitutes: improvements of the induced coagulopathy with fibrinogen concentrate. Br J Anaesth 2005;94:324–9
22. Velik-Salchner C, Haas T, Innerhofer P, Streif W, Nussbaumer W, Klingler A, Klima G, Martinowitz U, Fries D. The effect of fibrinogen concentrate on thrombocytopenia. J Thromb Haemost 2007;5:1019–25
23. Kashuk JL, Moore EE, Sawyer M, Wohlauer M, Pezold M, Barnett C, Biffl WL, Burlew CC, Johnson JL, Sauaia A. Primary fibrinolysis is integral in the pathogenesis of the acute coagulopathy of trauma. Ann Surg 2010;252:434–42
24. Karlsson M, Ternstrom L, Hyllner M, Baghaei F, Nilsson S, Jeppsson A. Plasma fibrinogen level, bleeding, and transfusion after on-pump coronary artery bypass grafting surgery: a prospective observational study. Transfusion 2008;48:2152–8
25. Charbit B, Mandelbrot L, Samain E, Baron G, Haddaoui B, Keita H, Sibony O, Mahieu-Caputo D, Hurtaud-Roux MF, Huisse MG, Denninger MH, de Prost D. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. J Thromb Haemost 2007;5:266–73
26. Karlsson M, Ternstrom L, Hyllner M, Baghaei F, Flinck A, Skrtic S, Jeppsson A. Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. Thromb Haemost 2009;102:137–44
27. Rossaint R, Bouillon B, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, Hunt BJ, Komadina R, Nardi G, Neugebauer E, Ozier Y, Riddez L, Schultz A, Stahel PF, Vincent JL, Spahn DR. Management of bleeding following major trauma: an updated European guideline. Crit Care 2010;14:R52
28. O'Shaughnessy DF, Atterbury C, Bolton Maggs P, Murphy M, Thomas D, Yates S, Williamson LM. Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. Br J Haematol 2004;126:11–28
29. Stanworth SJ, Brunskill SJ, Hyde CJ, Murphy MF, McClelland DB. Appraisal of the evidence for the clinical use of FFP and plasma fractions. Best Pract Res Clin Haematol 2006;19:67–82
30. Shaz BH, Dente CJ, Harris RS, MacLeod JB, Hillyer CD. Transfusion management of trauma patients. Anesth Analg 2009;108:1760–8
31. Sarani B, Dunkman WJ, Dean L, Sonnad S, Rohrbach JI, Gracias VH. Transfusion of fresh frozen plasma in critically ill surgical patients is associated with an increased risk of infection. Crit Care Med 2008;36:1114–8
32. Holness L, Knippen MA, Simmons L, Lachenbruch PA. Fatalities caused by TRALI. Transfus Med Rev 2004;18:184–8
33. Rock G. A comparison of methods of pathogen inactivation of FFP. Vox Sang 2011;100:169–78
34. Theusinger OM, Baulig W, Seifert B, Emmert MY, Spahn DR, Asmis LM. Relative concentrations of haemostatic factors and cytokines in solvent/detergent-treated and fresh-frozen plasma. Br J Anaesth 2011;106:505–11
35. Chowdhury P, Saayman AG, Paulus U, Findlay GP, Collins PW. Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients. Br J Haematol 2004;125:69–73
36. Murad MH, Stubbs JR, Gandhi MJ, Wang AT, Paul A, Erwin PJ, Montori VM, Roback JD. The effect of plasma transfusion on morbidity and mortality: a systematic review and meta-analysis. Transfusion 2010;50:1370–83
37. Pool JG, Gershgold EJ, Pappenhagen AR. High-potency antihaemophilic factor concentrate prepared from cryoglobulin precipitate. Nature 1964;203:312
38. Callum JL, Karkouti K, Lin Y. Cryoprecipitate: the current state of knowledge. Transfus Med Rev 2009;23:177–88
39. Sorensen B, Bevan D. A critical evaluation of cryoprecipitate for replacement of fibrinogen. Br J Haematol 2010;149:834–43
40. Seghatchian J, Krailadsiri P. What's happening? The quality of methylene blue treated FFP and cryo. Transfus Apher Sci 2001;25:227–31
41. Fenger-Eriksen C, Ingerslev J, Sorensen B. Fibrinogen concentrate—a potential universal hemostatic agent. Expert Opin Biol Ther 2009;9:1325–33
42. Solomon C, Pichlmaier U, Schoechl H, Hagl C, Raymondos K, Scheinichen D, Koppert W, Rahe-Meyer N. Recovery of fibrinogen after administration of fibrinogen concentrate to patients with severe bleeding after cardiopulmonary bypass surgery. Br J Anaesth 2010;104:555–62
43. Pereira A. Cryoprecipitate versus commercial fibrinogen concentrate in patients who occasionally require a therapeutic supply of fibrinogen: risk comparison in the case of an emerging transfusion-transmitted infection. Haematologica 2007;92:846–9
44. Ozier Y, Hunt BJ. Against: Fibrinogen concentrate for management of bleeding: against indiscriminate use. J Thromb Haemost 2011;9:6–8
45. Dickneite G, Pragst I, Joch C, Bergman GE. Animal model and clinical evidence indicating low thrombogenic potential of fibrinogen concentrate (Haemocomplettan P). Blood Coagul Fibrinolysis 2009;20:535–40
46. Weinkove R, Rangarajan S. Fibrinogen concentrate for acquired hypofibrinogenaemic states. Transfus Med 2008;18:151–7
47. Kreuz W, Meili E, Peter-Salonen K, Haertel S, Devay J, Krzensk U, Egbring R. Efficacy and tolerability of a pasteurised human fibrinogen concentrate in patients with congenital fibrinogen deficiency. Transfus Apher Sci 2005;32:247–53
48. Rahe-Meyer N, Sorensen B. For: Fibrinogen concentrate for management of bleeding. J Thromb Haemost 2011;9:1–5
49. Grottke O, Braunschweig T, Henzler D, Coburn M, Tolba R, Rossaint R. Effects of different fibrinogen concentrations on blood loss and coagulation parameters in a pig model of coagulopathy with blunt liver injury. Crit Care 2010;14:R62
50. Bolliger D, Szlam F, Molinaro RJ, Rahe-Meyer N, Levy JH, Tanaka KA. Finding the optimal concentration range for fibrinogen replacement after severe haemodilution: an in vitro model. Br J Anaesth 2009;102:793–9
51. Danes AF, Cuenca LG, Bueno SR, Mendarte Barrenechea L, Ronsano JB. Efficacy and tolerability of human fibrinogen concentrate administration to patients with acquired fibrinogen deficiency and active or in high-risk severe bleeding. Vox Sang 2008;94:221–6
52. Fenger-Eriksen C, Lindberg-Larsen M, Christensen AQ, Ingerslev J, Sørensen B. Fibrinogen concentrate substitution therapy in patients with massive haemorrhage and low plasma fibrinogen concentrations. Br J Anaesth 2008;101:769–73
53. Fenger-Eriksen C, Lindberg-Larsen M, Christensen AQ, Ingerslev J, Sorensen B. Fibrinogen concentrate substitution therapy in patients with massive haemorrhage and low plasma fibrinogen concentrations. Br J Anaesth 2008;101:769–73
54. Hess JR, Brohi K, Dutton RP, Hauser CJ, Holcomb JB, Kluger Y, Mackway-Jones K, Parr MJ, Rizoli SB, Yukioka T, Hoyt DB, Bouillon B. The coagulopathy of trauma: a review of mechanisms. J Trauma 2008;65:748–54
55. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. Lancet 1997;349:1269–76
56. Krug EG, Sharma GK, Lozano R. The global burden of injuries. Am J Public Health 2000;90:523–6
57. Geeraedts LM Jr, Demiral H, Schaap NP, Kamphuisen PW, Pompe JC, Frolke JP. 'Blind' transfusion of blood products in exsanguinating trauma patients. Resuscitation 2007;73:382–8
58. Gonzalez EA, Moore FA, Holcomb JB, Miller CC, Kozar RA, Todd SR, Cocanour CS, Balldin BC, McKinley BA. Fresh frozen plasma should be given earlier to patients requiring massive transfusion. J Trauma 2007;62:112–9
59. Borgman MA, Spinella PC, Perkins JG, Grathwohl KW, Repine T, Beekley AC, Sebesta J, Jenkins D, Wade CE, Holcomb JB. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. J Trauma 2007;63:805–13
60. Gunter OL Jr, Au BK, Isbell JM, Mowery NT, Young PP, Cotton BA. Optimizing outcomes in damage control resuscitation: identifying blood product ratios associated with improved survival. J Trauma 2008;65:527–34

61. Zink KA, Sambasivan CN, Holcomb JB, Chisholm G, Schreiber MA. A high ratio of plasma and platelets to packed red blood cells in the first 6 hours of massive transfusion improves outcomes in a large multicenter study. Am J Surg 2009;197:565–70
62. Schuster KM, Davis KA, Lui FY, Maerz LL, Kaplan LJ. The status of massive transfusion protocols in United States trauma centers: massive transfusion or massive confusion? Transfusion 2010;50:1545–51
63. Dirks J, Jorgensen H, Jensen CH, Ostrowski SR, Johansson PI. Blood product ratio in acute traumatic coagulopathy—effect on mortality in a Scandinavian level 1 trauma centre. Scand J Trauma Resusc Emerg Med 2010;18:65
64. Scalea TM, Bochicchio KM, Lumpkins K, Hess JR, Dutton R, Pyle A, Bochicchio GV. Early aggressive use of fresh frozen plasma does not improve outcome in critically injured trauma patients. Ann Surg 2008;248:578–84
65. Snyder CW, Weinberg JA, McGwin G Jr, Melton SM, George RL, Reiff DA, Cross JM, Hubbard-Brown J, Rue LW 3rd, Kerby JD. The relationship of blood product ratio to mortality: survival benefit or survival bias? J Trauma 2009;66:358–62
66. Riskin DJ, Tsai TC, Riskin L, Hernandez-Boussard T, Purtill M, Maggio PM, Spain DA, Brundage SI. Massive transfusion protocols: the role of aggressive resuscitation versus product ratio in mortality reduction. J Am Coll Surg 2009;209:198–205
67. Stinger HK, Spinella PC, Perkins JG, Grathwohl KW, Salinas J, Martini WZ, Hess JR, Dubick MA, Simon CD, Beekley AC, Wolf SE, Wade CE, Holcomb JB. The ratio of fibrinogen to red cells transfused affects survival in casualties receiving massive transfusions at an army combat support hospital. J Trauma 2008;64:S79–85
68. Brenni M, Worn M, Bruesch M, Spahn DR, Ganter MT. Successful rotational thromboelastometry-guided treatment of traumatic haemorrhage, hyperfibrinolysis and coagulopathy. Acta Anaesthesiol Scand 2010;54:111–7
69. Schöchl H, Forster L, Woidke R, Solomon C, Voelckel W. Use of rotation thromboelastometry (ROTEM) to achieve successful treatment of polytrauma with fibrinogen concentrate and prothrombin complex concentrate. Anaesthesia 2010;65:199–203
70. Schöchl H, Nienaber U, Hofer G, Voelckel W, Jambor C, Scharbert G, Kozek-Langenecker S, Solomon C. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM(R))-guided administration of fibrinogen concentrate and prothrombin complex concentrate. Crit Care 2010;14:R55
71. Schöchl H, Nienaber U, Maegele M, Hochleitner G, Primavesi F, Steitz B, Arndt C, Hanke A, Voelckel W, Solomon C. Transfusion in trauma: thromboelastometry-guided coagulation factor concentrate-based therapy versus standard fresh frozen plasma-based therapy. Crit Care 2011;15:R83
72. David J-S, Marchal V, Levrat A, Inaba K. Which is the most effective strategy: early detection of coagulopathy with thromboelastometry or use of hemostatic factors or both? Crit Care 2011;15:433
73. Nuttall GA, Oliver WC, Santrach PJ, Bryant S, Dearani JA, Schaff HV, Ereth MH. Efficacy of a simple intraoperative transfusion algorithm for nonerythrocyte component utilization after cardiopulmonary bypass. Anesthesiology 2001;94:773–81
74. Rahe-Meyer N, Pichlmaier M, Haverich A, Solomon C, Winterhalter M, Piepenbrock S, Tanaka KA. Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: a pilot study. Br J Anaesth 2009;102:785–92
75. Dacey LJ, Munoz JJ, Baribeau YR, Johnson ER, Lahey SJ, Leavitt BJ, Quinn RD, Nugent WC, Birkmeyer JD, O'Connor GT. Reexploration for hemorrhage following coronary artery bypass grafting: incidence and risk factors. Northern New Engl Cardiovascular Disease Study group. Arch Surg 1998;133:442–7
76. Levi M, Cromheecke ME, de Jonge E, Prins MH, de Mol BJ, Briet E, Buller HR. Pharmacological strategies to decrease excessive blood loss in cardiac surgery: a meta-analysis of clinically relevant endpoints. Lancet 1999;354:1940–7
77. Unsworth-White MJ, Herriot A, Valencia O, Poloniecki J, Smith EE, Murday AJ, Parker DJ, Treasure T. Resternotomy for bleeding after cardiac operation: a marker for increased morbidity and mortality. Ann Thorac Surg 1995;59:664–7
78. Sniecinski RM, Levy JH. Bleeding and management of coagulopathy. J Thora Cardio Surg 2011;142:662–7
79. Mell MW, O'Neil AS, Callcut RA, Acher CW, Hoch JR, Tefera G, Turnipseed WD. Effect of early plasma transfusion on mortality in patients with ruptured abdominal aortic aneurysm. Surgery 2010;148:955–62
80. Rahe-Meyer N, Solomon C, Winterhalter M, Piepenbrock S, Tanaka K, Haverich A, Pichlmaier M. Thromboelastometry-guided administration of fibrinogen concentrate for the treatment of excessive intraoperative bleeding in thoracoabdominal aortic aneurysm surgery. J Thorac Cardiovasc Surg 2009;138:694–702
81. Innerhofer P, Fries D, Margreiter J, Klingler A, Kuhbacher G, Wachter B, Oswald E, Salner E, Frischhut B, Schobersberger W. The effects of perioperatively administered colloids and crystalloids on primary platelet-mediated hemostasis and clot formation. Anesth Analg 2002;95:858–65
82. Mittermayr M, Streif W, Haas T, Fries D, Velik-Salchner C, Klingler A, Oswald E, Bach C, Schnapka-Koepf M, Innerhofer P. Hemostatic changes after crystalloid or colloid fluid administration during major orthopedic surgery: the role of fibrinogen administration. Anesth Analg 2007;105:905–17
83. Fenger-Eriksen C, Jensen TM, Kristensen BS, Jensen KM, Tonnesen E, Ingerslev J, Sørensen B. Fibrinogen substitution improves whole blood clot firmness after dilution with hydroxyethyl starch in bleeding patients undergoing radical cystectomy: a randomized, placebo-controlled clinical trial. J Thromb Haemost 2009;7:795–802
84. Hazra S, Chilaka VN, Rajendran S, Konje JC. Massive postpartum haemorrhage as a cause of maternal morbidity in a large tertiary hospital. J Obstet Gynaecol 2004;24:519–20
85. Zhang WH, Alexander S, Bouvier-Colle MH, Macfarlane A. Incidence of severe pre-eclampsia, postpartum haemorrhage and sepsis as a surrogate marker for severe maternal morbidity in a European population-based study: the MOMS-B survey. BJOG 2005;112:89–96
86. Waterstone M, Bewley S, Wolfe C. Incidence and predictors of severe obstetric morbidity: case-control study. BMJ 2001;322:1089–93
87. Bell SF, Rayment R, Collins PW, Collis RE. The use of fibrinogen concentrate to correct hypofibrinogenaemia rapidly during obstetric haemorrhage. Int J Obstet Anesth 2010;19:218–23
88. Luddington RJ. Thrombelastography/thromboelastometry. Clin Lab Haematol 2005;27:81–90
89. Holcomb JB. Traditional transfusion practices are changing. Crit Care 2010;14:162
90. Kalina U, Stohr HA, Bickhard H, Knaub S, Siboni SM, Mannucci PM, Peyvandi F. Rotational thromboelastography for monitoring of fibrinogen concentrate therapy in fibrinogen deficiency. Blood Coagul Fibrinolysis 2008;19:777–83
91. Molinaro RJ, Szlam F, Levy JH, Fantz CR, Tanaka KA. Low plasma fibrinogen levels with the Clauss method during anticoagulation with bivalirudin. Anesthesiology 2008;109:160–1
92. Fenger-Eriksen C, Moore GW, Rangarajan S, Ingerslev J, Sorensen B. Fibrinogen estimates are influenced by methods of measurement and hemodilution with colloid plasma expanders. Transfusion 2010;50:2571–6
93. Solomon C, Cadamuro J, Ziegler B, Schöchl H, Varvenne M, Sorensen B, Hochleitner G, Rahe-Meyer N. A comparison of fibrinogen measurement methods with fibrin clot elasticity assessed by thromboelastometry, before and after administration of fibrinogen concentrate in cardiac surgery patients. Transfusion 2011;51:1695–1706
94. Kannel WB, Wolf PA, Castelli WP, D'Agostino RB. Fibrinogen and risk of cardiovascular disease. The Framingham Study. JAMA 1987;258:1183–6
95. Reinhart WH. Fibrinogen—marker or mediator of vascular disease? Vasc Med 2003;8:211–6

96. Spahn DR, Cerny V, Coats TJ, Duranteau J, Fernandez-Mondejar E, Gordini G, Stahel PF, Hunt BJ, Komadina R, Neugebauer E, Ozier Y, Riddez L, Schultz A, Vincent JL, Rossaint R. Management of bleeding following major trauma: a European guideline. Crit Care 2007;11:R17
97. Nielsen VG, Cohen BM, Cohen E. Effects of coagulation factor deficiency on plasma coagulation kinetics determined via thrombelastography: critical roles of fibrinogen and factors II, VII, X and XII. Acta Anaesthesiol Scand 2005;49:222–31
98. Fenger-Eriksen C, Jensen TM, Kristensen BS, Jensen KM, Tonnesen E, Ingerslev J, Sorensen B. Fibrinogen substitution improves whole blood clot firmness after dilution with hydroxyethyl starch in bleeding patients undergoing radical cystectomy: a randomized, placebo-controlled clinical trial. J Thromb Haemost 2009;7:795–802