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)

From the Department of Anesthesiology, Emory University School of Medicine, Cardiothoracic Anesthesiology and Critical Care, Emory Healthcare, Atlanta, Georgia.

Accepted for publication July 11, 2011.

Funding: Funded by Department of Anesthesiology at the Emory University School of Medicine.

Conflict of Interest: See Disclosures at the end of the article.

Reprints will not be available from the authors.

Address correspondence to Jerrold H. Levy, MD, FAHA, Department of Anesthesiology, Emory University School of Medicine, Cardiothoracic Anesthesiology and Critical Care, Emory Healthcare, Atlanta, GA. Address e-mail to jlevey01@emory.edu.

Copyright © 2012 International Anesthesia Research Society. DOI: 10.1213/ANE.0b013e31822e1853

Fibrinogen is a plasma protein critical to hemostasis and clot formation. 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. Structurally, human fibrinogen comprises 2 outer D domains, which are both linked by a central E domain. 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. 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). 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. Furthermore, recent preliminary data have suggested that fibrinogen may be heme associated and could play a role in carbon monoxide sensing.

Studies from our laboratory and others have demonstrated the importance of thrombin generation and hemostatic activation for clot formation. 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). 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. Such derangements are associated with...
significantly increased mortality rates in trauma patients.\textsuperscript{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).\textsuperscript{16} Because of its relatively high initial plasma concentration, fibrinogen was the first clotting factor to decrease to critically low levels.\textsuperscript{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.\textsuperscript{16}

The maintenance of hemostasis relies on a series of complex interactions between both the cellular and protein components of coagulation.\textsuperscript{17} Importantly, platelets play a key role in many of these interactions; the platelet surface is the primary site for thrombin generation,\textsuperscript{17} and platelets aggregate to form the primary hemostatic plug,\textsuperscript{18} as well as stabilizing clot formation.\textsuperscript{1} Circulating platelet concentrations reduce in a similar manner to the observed depletion of clotting factors during major surgery.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{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.\textsuperscript{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

---

**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.
Fibrinogen Management in Acquired Bleeding

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

<table>
<thead>
<tr>
<th>Coagulation factor</th>
<th>FFP, relative content (%) in comparison with normal plasma(^{26,28})</th>
<th>Cryoprecipitate, relative content (%) in comparison with normal plasma: per single donor unit (20–50 mL)(^{26})</th>
<th>Fibrinogen concentrates</th>
<th>Clottafact(^{27}) (per 100-mL vial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen</td>
<td>2.0 mg/mL (0.9–3.2)(^{34a}) 92 (72–108)(^{34b})</td>
<td>388 mg(^{c}) (range: 120–796 mg)</td>
<td>Ristap®/Haemocomplettan P/HS(^{c,e}) (per 50-mL vial) (CSL Behring, Marburg, Germany)</td>
<td>~15 mg/mL</td>
</tr>
<tr>
<td>FII</td>
<td>88 (72–108)(^{34b}) 90 (59–120)(^{34b})</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>FVII</td>
<td>90 (59–120)(^{34b}) 90 (59–120)(^{34b})</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>FVIII</td>
<td>53 (32–92)(^{34b}) 68 (45–87)(^{34b}) 88 (72–108)(^{34b})</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>FIX</td>
<td>100(^{28}) 83(^{28})</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>FX</td>
<td>100(^{28}) 83(^{28})</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Antithrombin III</td>
<td>100(^{28})</td>
<td>20%–30%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>VWF</td>
<td>80(^{28c})</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>FVIII and VWF(^a)</td>
<td>—</td>
<td>40%–70%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fibronectin</td>
<td>—</td>
<td>20%–25%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IgG</td>
<td>—</td>
<td>5%–8%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>IgM</td>
<td>—</td>
<td>1%–2%</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Albumin</td>
<td>—</td>
<td>5%–8%</td>
<td>8–14 mg/mL</td>
<td>—</td>
</tr>
<tr>
<td>L-arginine</td>
<td>—</td>
<td>—</td>
<td>7.5–13.2 mg/mL</td>
<td>—</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>—</td>
<td>—</td>
<td>4–7 mg/mL</td>
<td>—</td>
</tr>
<tr>
<td>Sodium citrate</td>
<td>—</td>
<td>—</td>
<td>1–2 mg/mL</td>
<td>—</td>
</tr>
</tbody>
</table>

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.

Fibrinogen Management in Acquired Bleeding

- **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\(^{26,28}\) | Cryoprecipitate, relative content (%) in comparison with normal plasma: per single donor unit (20–50 mL)\(^{26}\) | Fibrinogen concentrates | Clottafact\(^{27}\) (per 100-mL vial) |
  | Fibrinogen         | 2.0 mg/mL (0.9–3.2)\(^{34a}\) 92 (72–108)\(^{34b}\) | 388 mg\(^{c}\) (range: 120–796 mg) | Ristap®/Haemocomplettan P/HS\(^{c,e}\) (per 50-mL vial) (CSL Behring, Marburg, Germany) | ~15 mg/mL |
  | FII                | 88 (72–108)\(^{34b}\) 90 (59–120)\(^{34b}\) | — | — | — |
  | FVII               | 90 (59–120)\(^{34b}\) 90 (59–120)\(^{34b}\) | — | — | — |
  | FVIII              | 53 (32–92)\(^{34b}\) 68 (45–87)\(^{34b}\) 88 (72–108)\(^{34b}\) | — | — | — |
  | FIX                | 100\(^{28}\) 83\(^{28}\) | — | — | — |
  | FX                 | 100\(^{28}\) 83\(^{28}\) | — | — | — |
  | Antithrombin III   | 100\(^{28}\) | 20%–30% | — | — |
  | 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.

**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,\(^{34}\) 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. The remaining 5 to 15 mL of plasma is refrozen and can be stored in this way for up to 12 months. 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. 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. Cryoprecipitate is unsuitable for viral inactivation processes in its native form, though plasma derivatives that have been pretreated with methylene blue or SD can be used for its production. Unfortunately, such pretreatment processes can reduce the concentration of functional fibrinogen present. 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. 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. Doses as high as 6 g infused in as little as 1 to 2 minutes have been reported in critical bleeding. A summary of fibrinogen concentrates currently available is shown in Table 1. Commericially 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. This inherent viral reduction capacity also minimizes the risk of transmitting new emerging viruses. 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. 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.

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. 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. In support of the clinical data, animal models of venous stasis have found that fibrinogen concentrates demonstrated no thrombogenic activity. 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. Current opinion still remains divided regarding what constitutes the correct and appropriate administration of fibrinogen concentrate in the critical care setting. Surveillance data may not provide reliable estimates of thrombotic adverse events, which can occur up to 3 months postsurgery at the doses used. 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. 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. 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. 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>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Data source</th>
<th>Fibrinogen dose</th>
<th>Number of patients treated with fibrinogen</th>
<th>Treatment and results</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td>Severe abdominal trauma</td>
<td>Case report</td>
<td>16 g</td>
<td>1</td>
<td>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.</td>
<td>Fibrinogen concentrate was administered as primary hemostatic therapy. Coagulopathy was corrected without the need for FFP or platelet administration.</td>
</tr>
<tr>
<td>Schöchl et al. 2010</td>
<td>Polytrauma induced coagulopathy</td>
<td>Case report</td>
<td>13 g</td>
<td>1</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Schöchl et al. 2010</td>
<td>Trauma-induced coagulopathy</td>
<td>Retrospective database analysis</td>
<td>6.0 g*(IQR, 4–9 g) until ICU admission; 7.0 g*(IQR, 5–11 g) total after 24 hours</td>
<td>128</td>
<td>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.</td>
<td></td>
</tr>
<tr>
<td>Schöchl et al. 2011</td>
<td>Trauma-induced coagulopathy</td>
<td>Retrospective database analysis</td>
<td>6.0 g*(IQR, 3–9 g)</td>
<td>73</td>
<td>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).</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Study</th>
<th>Indication</th>
<th>Data source</th>
<th>Fibrinogen dose</th>
<th>Number of patients treated with fibrinogen</th>
<th>Treatment and results</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Karlsson et al. 2009(^{26}) (N = 20)</td>
<td>Cardiovascular surgery</td>
<td>Prospective randomized phase I/II study</td>
<td>2.0 g</td>
<td>10</td>
<td>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.</td>
<td>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.</td>
</tr>
<tr>
<td>Rahe-Meyer et al. 2009(^{74}) (N = 15)</td>
<td>Aortic valve operation and ascending aorta replacement</td>
<td>Prospective, nonrandomized pilot study</td>
<td>5.7 (± 0.7) g(^b)</td>
<td>10</td>
<td>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).</td>
<td>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.</td>
</tr>
<tr>
<td>Rahe-Meyer et al. 2009(^{80}) (N = 18)</td>
<td>Thoracoabdominal aortic aneurysm surgery</td>
<td>Retrospective control group vs prospective fibrinogen group</td>
<td>7.8 g(^b) (± 2.7 g)</td>
<td>6</td>
<td>Total transfusion requirements (fibrinogen group vs control) were 2.5 U (SD, ± 4.3) vs 16.4 U (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 24-hour postoperative bleeding.</td>
<td>Prophylactic administration of fibrinogen concentrate significantly reduced transfusion of allogeneic blood products and 24-hour postoperative bleeding.</td>
</tr>
<tr>
<td>Solomon et al. 2010(^{62}) (N = 39)</td>
<td>Postcardiopulmonary bypass surgery</td>
<td>Open-label, uncontrolled, retrospective study</td>
<td>6.5 g(^b) (± 1.6 g) (78 [± 20] mg/kg)</td>
<td>39</td>
<td>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.</td>
<td>Administration of fibrinogen concentrate raised plasma fibrinogen concentration and contributed to the correction of postoperative bleeding.</td>
</tr>
<tr>
<td>Study</td>
<td>Indication</td>
<td>Data source</td>
<td>Fibrinogen dose</td>
<td>Number of patients treated with fibrinogen</td>
<td>Treatment and results</td>
<td>Key findings</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>-------------------------------------</td>
<td>-------------------------------------------------</td>
<td>-----------------</td>
<td>--------------------------------------------</td>
<td>--------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>C. Fenger-Eriksen et al. 2009** (N = 20)</td>
<td>Radical cystectomy</td>
<td>Single-center, prospective, double-blind, placebo-controlled, randomized clinical trial</td>
<td>45 mg/kg</td>
<td>10</td>
<td>Significant increase in maximum clot firmness. Two of 10 patients who received fibrinogen concentrate required peroperative RBCs vs. 8 of 10 in placebo group</td>
<td>Randomized placebo-controlled administration of fibrinogen concentrate significantly improved maximum clot firmness and reduced the requirement for postoperative transfusion</td>
</tr>
<tr>
<td>Mittermayr et al. 2007** (N = 66)</td>
<td>Orthopedic surgery</td>
<td>Prospective observational study</td>
<td>30 mg/kg</td>
<td>13</td>
<td>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]),</td>
<td>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</td>
</tr>
<tr>
<td>Bell et al. 2010** (N = 6)</td>
<td>Obstetric hemorrhage</td>
<td>Collection of 6 case reports</td>
<td>N/A</td>
<td>6</td>
<td>Laboratory assessed coagulation was rapidly normalized and severe hemorrhage improved following fibrinogen concentrate administration</td>
<td>Fibrinogen concentrate could effectively reduce peripartum blood loss associated with hypofibrinogenemia</td>
</tr>
<tr>
<td>Cross-setting administration Daines et al. 2008** (N = 69)</td>
<td>Surgery, trauma and gastrointestinal hemorrhage. Hepatic dysfunction and hematological malignancies</td>
<td>Open-label, noncontrolled retrospective study</td>
<td>3.52g (range, 0-5-8.0g)</td>
<td>69</td>
<td>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</td>
<td>Fibrinogen concentrate administration improved laboratory coagulation measures and may be life saving in patients with life-threatening, unresponsive coagulopathy</td>
</tr>
</tbody>
</table>
Fibrinogen concentrate appears to be effective in the management of acquired bleeding, being able to provide a consistent dose in the emergency setting.

### Table 2. (Continued)

<table>
<thead>
<tr>
<th>Number of patients treated with fibrinogen</th>
<th>Value described</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fenger-Eriksen et al. 2008 (N = 30)</td>
<td>4.0 (range, 2.0–14.0 g)</td>
</tr>
<tr>
<td>Off-label fibrinogen concentrate administration led to significant reductions in both bleeding and the requirement for transfusion of RBCs, platelets, and FFP</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Number of patients treated with fibrinogen</th>
<th>Value described</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weinkove et al. 2008 (N = 46)</td>
<td>2.0 g</td>
</tr>
<tr>
<td>Median increase in plasma fibrinogen concentration was 1.0 g/L (from 1.4–2.6)</td>
<td></td>
</tr>
<tr>
<td>Retrospective database analysis</td>
<td></td>
</tr>
</tbody>
</table>

### Key findings
- Fibrinogen concentrate appears to be effective in the management of acquired bleeding, providing a consistent dose in the emergency setting.

### 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. Importantly, trauma-related coagulopathy is a leading cause of mortality and is responsible for up to 40% of trauma-related deaths. 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. Recent military experience of trauma has strongly influenced transfusion practices in US trauma centers. 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. Consequently, many civilian trauma centers are now adopting massive transfusion protocols, which include the transfusion of FFP in high volumes. Although this approach is not universally accepted 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. A retrospective review of battlefield trauma reported 252 patients receiving massive transfusion, in which the total amount of fibrinogen infused was not statistically correlated with reductions in mortality.

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 coagu-
lopathy resulting from major abdominal trauma.68 Coagu-
lopathy was corrected without the use of allogeneic blood
products, highlighting the potential efficacy and safety
benefits of such management protocols. The coadministra-
tion 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 fac-
tor concentrates, guided by point-of-care assessment (rota-
tional thromboelastometry [ROTEM®; TEM Innovations
GmbH, Munich, Germany]), eliminated the need for allo-
geneic 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 manage-
dment, 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 concen-
trate (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 com-
parison with 3% and 56%, respectively, in the FFP group.
The study authors concluded that the TEM-guided admin-
istration 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 combina-
tion of modern, real-time, coagulation monitoring with the
administration of clotting factor concentrates capable of
rapidly increasing the plasma concentrations of procoagu-
lants 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 adminis-
tered 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 man-
agement 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 coagu-
lation management in surgical procedures typically associ-
ated 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 he-
mostatic 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 com-
parison with a retrospective cohort of patients receiving no
prophylaxis (n = 20).80 The need for transfusion of allogene-
ic 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 concen-
trate 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 in-
crease: 1.7 [±0.5] g/L).82 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 correc-
tion of bleeding after surgery.82

Noncardiovascular Surgery

Patients undergoing orthopedic surgery are at risk of signifi-
cant bleeding and developing dilutional coagulopathy, which
may be influenced by the solution used for intravascular
volume replacement.81,82 A prospective study compared
patients receiving colloids (either hydroxyethyl starch [HES]
Fibrinogen polymerization was significantly impaired in patients receiving colloid.89 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.93

### 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.

### 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 Reinart 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.90 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 yet 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.90,97

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:\(^{41,74}\):

Fibrinogen dose = desired increase (g/L) \times \frac{\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.\(^{1,2,22,42,51,68–70,74,80,82,87,98}\) 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.

**REFERENCES**


**DISCLOSURES**

Name: Jerrold H. Levy.

**Contribution:** Performed literature search and manuscript preparation, oversaw ongoing revisions and corrections.

**Conflict of Interest:** Dr. Levy receives research support from CSL Behring.

Name: Fania Szlam.

**Contribution:** Reviewed manuscript, added additional information and references.

**Conflict of Interest:** This author has no conflict to declare.

**DISCLOSURES**

Name: Kenichi A. Tanaka, MD.

**Contribution:** Reviewed manuscript, added additional information and references.

**Conflict of Interest:** Dr. Tanaka receives research support from CSL Behring and Octapharma.

**Name:** Roman M. Sniecienki, MD.

**Contribution:** Reviewed manuscript, added additional information, references, and developed figures for manuscript.

**Conflict of Interest:** This author has no conflict to declare.

**This manuscript was handled by:** Steven L. Shafer, MD.
30. Shaz BH, Dente CJ, Harris RS, MacLeod JB, Hillyer CD. Fibrinogen concentrate administration to patients with acquired fibrinogen deficiency and active or in high-risk severe bleeding. Vox Sang 2009;96:221–6
51. Danes AF, Cuenca LG, Bueno SR, Mandarte Barrechea 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
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
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
89. Holcomb JB. Traditional transfusion practices are changing. Crit Care Med 2010;38:1638–42
95. Reinhardt WH. Fibrinogen—marker or mediator of vascular disease? Vasc Med 2003;8:211–6


Nominations Sought for FAER Mentoring Excellence in Research Award

FAER is seeking nominations for the annual FAER Mentoring Excellence in Research Award. This award was created to ensure that the value of outstanding mentors is recognized and to encourage, develop, and retain these valuable individuals in our specialty.

The FAER Mentoring Excellence in Research Award recognizes mentorship rather than scientific accomplishment. Nominees must have mentored anesthesiologists or scientists who have worked in the U.S. and contributed significantly to the practice. The award is focused on the successful development of mentees, not the professional accomplishments of the mentor. Nominees should be superior mentors, seen as supporting the future of the specialty.

An overview of the award and the nomination process and a nomination form are posted on FAER’s website at faer.org/about/MentorResearchAward.html. The nomination form and supporting materials are due by March 31. Please submit all nomination materials by email to Mary Schrandt at MarySchrandt@faer.org.