

Fibrinogen as a replacement therapy in bleeding disorder.

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Fibrinogen by its role in clot formation and stabilization via its conversion to fibrin catalyzed by thrombin and also by induction of platelet activation and aggregation by binding to the platelet fibrinogen receptor glycoprotein **GP1Ib/IIIa** strengthening the clot formed .⁽¹¹⁾

Its supplementation is indicated as prophylaxis and therapy of haemorrhage in congenital and acquired fibrinogen deficiency ⁽¹⁸⁾.

Supplementation of fibrinogen can be provided by transfusion of fresh-frozen plasma (FFP), cryoprecipitate and fibrinogen concentrate.⁽¹⁶⁾

FFP has several limitations including a low fibrinogen content, so large volumes to be given, and the risk of transfusion-related complications (e.g., transfusion-related acute lung injury [TRALI] and viral transmission).

Fibrinogen concentrate its content of fibrinogen is standardized, cross-matching is not required In contrast to FFP and cryoprecipitate .⁽⁴⁾

Haemocomplettan (commercialised in the USA as RiaSTAP) ⁽⁸⁾, is the type which is widely used and was effective in both the treatment of spontaneous bleeding episodes and as prophylaxis before surgical procedures or against spontaneous bleeding in patients with congenital fibrinogen deficiency .⁽¹⁾

Fibrinogen can be dosed based on the level of bleeding and initial fibrinogen concentration. perioperatively, 1 to 2 g should be administered initially if bleeding is accompanied by suspected low fibrinogen concentrations or function⁽⁹⁾

The fibrinogen dose can be calculated as follows: Fibrinogen concentrate dose (g) = [target FIBTEM MCF (**maximum clot firmness**) (mm) – actual FIBTEM MCF (mm)] × [body weight (kg)/70] × 0.5 g/mm.

Normal MCF values are 9 to 25 mm that correlate with normal fibrinogen levels; however, a target MCF of 22 mm has been used in aortic surgery patients (achieved using mean fibrinogen doses of 5.7 g ⁽¹³⁾.

25 mg/kg fibrinogen concentrate is recommended if EXTEM A10 and FIBTEM A10 are below 40 mm and 8 mm, respectively. If FIBTEM A10 is <6 mm and EXTEM A10 is <40 mm, the recommended dose increases to 50 mg/kg.⁽²⁰⁾

Thromboembolic event associated with administering excessive fibrinogen, particularly with high thrombin generation, may increase the risk of systemic microthrombogenicity.

However, no reports of hypercoagulability or thromboembolism following treatment with fibrinogen levels up to 600 mg/kg.⁽¹⁰⁾

To be highlighted that recombinant activated factor VII, used for the treatment or prevention of bleeding in patients with acquired and congenital haemophilia with inhibitors or with other inherited bleeding disorders, requires a fibrinogen level of ≥ 1 g/L as a pre-condition for optimal haemostatic activity.⁽¹²⁾

Acquired hypofibrinogenaemia, such as following trauma, Fibrinogen and other factor concentrates are increasingly being studied and reported in surgical and trauma algorithms as a management protocol for treating hemorrhage. Goal-directed coagulation management using fibrinogen concentrates and PCCs improved survival rates as compared with those predicted by the **Trauma Injury Severity Score** in a retrospective report of 131 patients.⁽¹⁴⁾

A study evaluating 144 patients with major blunt trauma reported coagulation factor concentrates corrected coagulopathy and reduced RBC and platelet transfusion compared with those receiving FFP, and fewer patients developed multiorgan failure.⁽⁶⁾

However, overall mortality was not reduced with fibrinogen concentrates in another retrospective study of 294 trauma patients.⁽¹⁹⁾

More recent European trauma guidelines from 2013 recommend fibrinogen administration at levels <1.5 to 2.0 g/L.⁽¹⁵⁾

In cardiothoracic surgery Preoperative fibrinogen concentrations <3 g/L are reported to increase perioperative blood loss and transfusion requirements after coronary artery bypass grafting.⁽⁷⁾⁽⁵⁾

Fibrinogen repletion will reduce bleeding and the need for allogeneic blood products. Other prospective and retrospective cardiac surgical studies, including high-risk ascending aortic replacement surgery, report that fibrinogen repletion with concentrates reduces postoperative bleeding and allogeneic blood product administration.⁽¹⁷⁾

In obstetric haemorrhage as an important cause of maternal mortality, Multiple studies reported reduced levels of fibrinogen associated with the progression of PPH (postpartum hemorrhage) in study of 356 women even **lower fibrinogen** and **FIBTEM A5** values were associated with more prolonged bleeds, especially when FIBTEM was <10 mm or fibrinogen <2 g/L.⁽²⁾

Patients with severe **PPH** had significantly lower fibrinogen and prolonged PT. Fibrinogen was the only laboratory value associated with severe PPH, and the risk was 2.63-fold higher for each 1-g/L decrease. ⁽³⁾

In study of orthopaedic patients receiving volume replacement, fibrinogen concentrate restored clotting function, reversing the effects of dilutional coagulopathy. ⁽⁴⁾

During radical cystectomy efficacy of peri-operatively administered fibrinogen concentrate for excessive bleeding was found, by increasing clot firmness with reduced post-operative transfusion of red blood cells. ⁽⁴⁾

Finally, evidence documenting the benefit of fibrinogen concentrate as treatment/prophylaxis of bleeding in congenital fibrinogen deficiency, the preliminary results suggesting its potential role in haemorrhagic conditions associated with an acquired hypofibrinogenemic state confirmed by additional prospective phase II/III clinical trials focusing on dosing, efficacy and safety ⁽⁹⁾

| Clinical setting | Trigger for administering fibrinogen concentrate | Fibrinogen dosing |
|-----------------------|---|---|
| Cardiac surgery | Using conventional laboratory measures: <200 mg/dL (<2 g/L) | 25 mg/kg |
| | <150 mg/dL (<1.5 g/L) | 50 mg/kg |
| | Using POC: EXTEM A10 <40 mm and FIBTEM A10 <8 mm | 25 mg/kg |
| | EXTEM A10 <40 mm and FIBTEM A10 <6 mm | 50 mg/kg |
| | EXTEM A10 <40 mm and FIBTEM A10 <4 mm | 75 mg/kg |
| | EXTEM A10 <30 mm and FIBTEM A10 <4 mm | 75 mg/kg + 2 PC + 0.4 µg/kg DDAVP |
| Trauma | FIBTEM CA10 <7 mm | 2-6 g |
| | EXTEM CA10 <30 mm | 6-8 g and PCC 20-30 U/kg BW |
| Liver transplantation | Massive diffuse bleeding and EXTEM MCF <25 mm | Fibrinogen concentrate, PC and PCC |
| | EXTEM MCF <35 mm and FIBTEM MCF <8 mm | 25 mg/kg (or cryoprecipitate); 50 mg/kg if FIBTEM MCF <4 mm |
| | EXTEM MCF <45 mm and FIBTEM MCF <8 mm | 25 mg/kg (or cryoprecipitate); 50 mg/kg if FIBTEM MCF <4 mm |

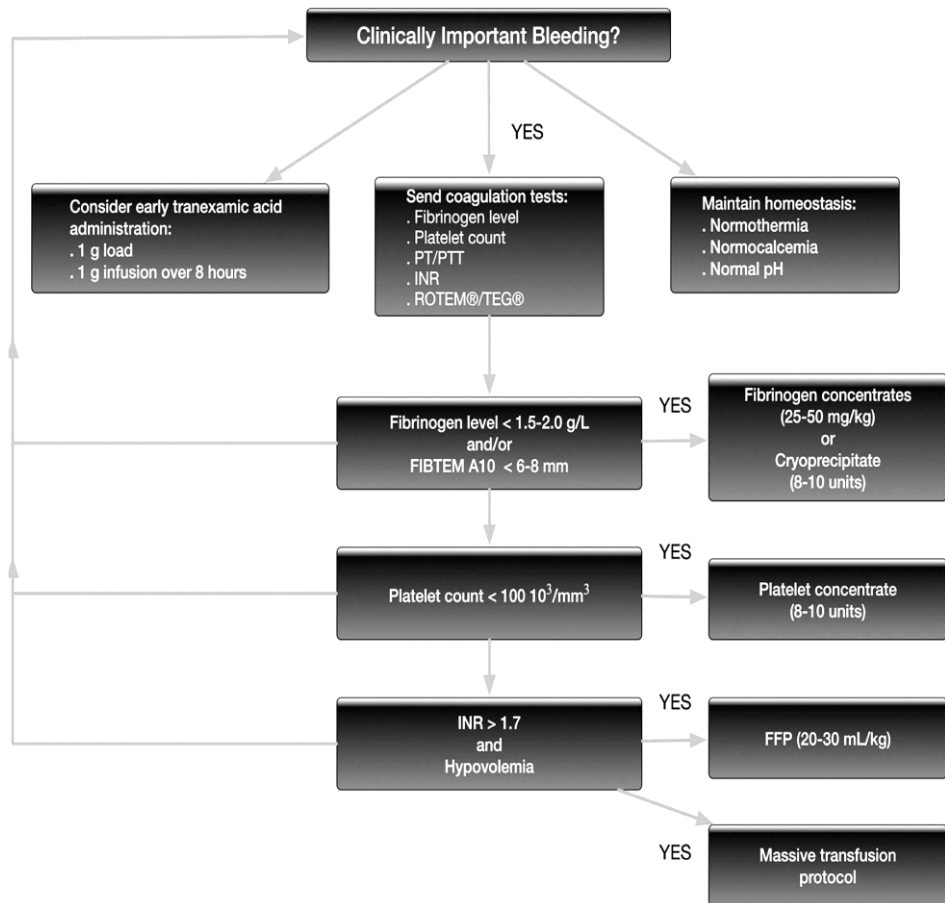


Fig (1) Fibrinogen algorithm. Suggested management strategy for the bleeding patient and repletion strategies.

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