Fibrinogen replacement therapy: a critical review of the literature

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Introduction

Fibrinogen is a plasma glycoprotein with a molecular weight of 340 kDa; it is synthesised by the liver. The conversion of fibrinogen to fibrin is catalysed by thrombin and plays a key role in clot formation and stabilisation. In addition, fibrinogen induces platelet activation and aggregation by binding to the platelet fibrinogen receptor glycoprotein GPIIb/IIIa[1].

Fibrinogen replacement therapy is currently indicated as prophylaxis and therapy of haemorrhage in congenital and acquired fibrinogen deficiency, this latter being associated with liver failure, disseminated intravascular coagulation, massive transfusion and cardiac surgery)[2,3]. Hypofibrinogenaemia is defined by a decreased level of normal fibrinogen between 0.5 g/L and the lower limit of the normal range for the local laboratory (usually 1.5 g/L)[4]. Fibrinogen supplementation can be provided by transfusion of fresh-frozen plasma (FFP), cryoprecipitate and fibrinogen concentrate[5,6]. However, as FFP has several limitations including a low fibrinogen content, which means that large volumes must be given, and the risk of transfusion-related complications (e.g., transfusion-related acute lung injury [TRALI] and viral transmission), this critical analysis is focused on the role of cryoprecipitate and fibrinogen concentrate.

Cryoprecipitate

Cryoprecipitate is prepared by controlled thawing of frozen plasma to precipitate high molecular weight proteins, which include factor VIII (FVIII), von Willebrand factor (VWF) and fibrinogen. The precipitated proteins are separated by centrifugation, re-suspended in a small volume of plasma (typically 10-20 mL) and stored frozen at –20 °C[7]. Cryoprecipitate is usually administered as a pool of four to six units.

Although cryoprecipitate contains a higher concentration of fibrinogen than FFP, usually around 15 g/L, it shares many of the disadvantages of FFP (see Table I) as its fibrinogen concentration is not standardised and blood group matching is needed prior to transfusion. Time is also required to thaw cryoprecipitate, and this aspect represents a clear disadvantage in the setting of massive haemorrhage. Furthermore, it carries a risk of viral transmission similar to that of FFP. Indeed, as it can be produced from plasma that has undergone treatment with methylene blue or psoralen/ultraviolet light, viral inactivation procedures are not usually employed as they can reduce functional fibrinogen content significantly[7]. Indeed, it is well documented that methylene blue treatment reduces coagulation factor levels, with fibrinogen being one of the factors most sensitive to depletion (the loss of fibrinogen in methylene blue-inactivated cryoprecipitate compared with cryoprecipitate derived from untreated plasma ranges between 18 and 41%)[8,9]. Cryoprecipitate is not available in most western European countries but it is still used in the US and UK[6,10,11].

Table I - Cryoprecipitate versus fibrinogen concentrate as fibrinogen replacement therapy.

Cryoprecipitate	Fibrinogen concentrate
No viral inactivation, potential risk of pathogen transmission	Viral inactivation, minimal risk of pathogen transmission
Variable fibrinogen levels, accurate dosing not possible	Standardised fibrinogen content, accurate and consistent dosing
Infusion volume lower than fresh-frozen plasma but higher than fibrinogen concentrate	Low infusion volume
Must be thawed before infusion, ABO compatibility is required	Rapidity of reconstitution, no cross-matching required

Fibrinogen concentrate

Fibrinogen concentrate is produced from pooled human plasma using the Cohn/Oncley cryoprecipitation procedure[12]. The concentration of fibrinogen is standardised; the product is stored as a lyophilised powder at room temperature and can be reconstituted quickly with sterile water and infusion volumes are low, allowing for rapid administration without delays for thawing or cross-matching[13]. In contrast to FFP and cryoprecipitate, viral inactivation steps by solvent/detergent exposure or pasteurisation are routinely included in the manufacturing process for fibrinogen concentrate, thus minimising the risk of viral transmission (Table I)[14].

Fibrinogen concentrate is considered the mainstay of treatment of bleeding episodes in patients with congenital afibrinogenaemia[15]. In addition, a number of studies have documented its effectiveness as secondary prophylaxis in cases in which there has been potentially life-threatening bleeding at high risk of recurrence (e.g., intracranial haemorrhage)[15]. Fibrinogen concentrate is also being increasingly used for acquired hypofibrinogenaemia[3]. Fibrinogen deficiency can develop in the event of massive transfusions in the context of loss and dilution coagulopathy, because primary replacement by crystalloids, colloids and red blood cell concentrates is performed almost exclusively without plasma. In such situations fibrinogen, the coagulation factor most quantitatively represented, is the first procoagulant factor to decline, dropping to a critical level of 1.5-2 g/L[16].

Four fibrinogen concentrates are currently available: Haemocomplettan (CSL Behring, Marburg, Germany), FIBRINOGENE T1 and Clottagen (LFB, Les Ulis, France), Fibrinogen HT (Benesis, Osaka, Japan) and FibroRAAS (Shangai RAAS, Shangai, China)[13,17]. However, the most widely used is Haemocomplettan (commercialised in the USA as RiaSTAP)[18], a human pasteurised, highly purified, plasma-derived fibrinogen concentrate, and a number of studies have evaluated the effects of fibrinogen supplementation with this agent in patients suffering from various forms of congenital or acquired hypofibrinogenaemia[19-31]. By contrast, no clinical studies have been published so far on the other fibrinogen concentrates. In a multicentre open, uncontrolled, retrospective study, Haemocomplettan 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[19]. The median post-infusion fibrinogen levels were 1.45 g/L and reductions in both thrombin and activated partial thromboplastin time were observed after infusion. The median single and total doses per episode were 2.0 and 4.0 g per patient, respectively, and the median duration of treatment was 1 day[19]. A number of retrospective and prospective clinical studies have been published on patients with acquired hypofibrinogenaemia, such as following trauma, cardiothoracic surgery and obstetric haemorrhage, all documenting that this agent is able to improve clotting function and reduce blood loss. For example, in a retrospective analysis of 131 massively traumatised and bleeding patients, thromboelastometry-guided haemostatic therapy with fibrinogen concentrate as first-line haemostatic therapy and additional prothrombin complex concentrate was goal-directed, efficacious, quick to administer and produced a favourable survival rate[28]. In a prospective clinical study of orthopaedic patients receiving volume replacement, fibrinogen concentrate restored clotting function, reversing the effects of dilutional coagulopathy[20]. Similarly, Fenger-Eriksen and colleagues found that the coagulopathy induced by dilution with modern hydroxyethylstarch was completely corrected by ex vivo addition of fibrinogen[32]. The same authors, in a small randomised, placebo-controlled study assessing the efficacy of peri-operatively administered fibrinogen concentrate for excessive bleeding during radical cystectomy found that this haemostatic agent increased maximum clot firmness and reduced the need for post-operative transfusion of red blood cells[24]. In an observational study of 69 patients suffering from various forms of acquired severe hypofibrinogenemia, after a median dose of 4 g of fibrinogen concentrate, there was a mean absolute increase of 1.09 g/L of plasma fibrinogen and coagulation parameters were significantly improved ($P<0.001$)[21]. Furthermore, there was an association between plasma fibrinogen concentrations after treatment and patients' survival at 7 days[21]. In another retrospective study of 43 patients, a similar increase in fibrinogen levels (1.01 g/L) was achieved but with half the average dose of fibrinogen[23]. A randomised study tested the efficacy of pre-operative fibrinogen infusion on post-operative bleeding in 20 patients

undergoing coronary artery bypass surgery and found that this prophylactic regimen significantly reduced blood loss[25]. In another study in aortic valve surgery and ascending aorta replacement, thromboelastometry-guided haemostatic therapy with fibrinogen concentrates (aimed at reaching high baseline fibrinogen plasma levels) was compared with conventional treatment[26]. The authors found that fibrinogen concentrate administration was associated with reduced transfusion requirements and 24-hour postoperative bleeding. The same conclusions (i.e., reduced blood loss and transfusion requirements after fibrinogen concentrate) were made by Thorarinsdottir and colleagues in a retrospective study on the administration of fibrinogen concentrate in 37 patients, most of whom were suffering from severe haemorrhage following open heart surgery[30].

Finally, it should be highlighted that recombinant activated factor VII, which is 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[33].

Table II - The use of the fibrinogen concentrate Haemocomplettan in congenital and acquired hypofibrinogenaemic states: results of the main clinical studies.

Author, year (reference)	N. of patients	Clinical condition	Main clinical results
Kreuz, 2005 (19)	12	Congenital fibrinogen deficiency	Clinical efficacy was good in all events (26 bleeding episodes, 11 operations; 89 prophylaxis). One anaphylactic reaction and 1 DVT were recorded.
Mittermayr, 2007 (20)	66	Major orthopaedic surgery	Haemostatic changes after colloid/crystalloid fluid administration were reversed by using fibrinogen concentrate.
Danes, 2008 (21)	69	Acquired severe fibrinogen deficiency associated with bleeding	Fibrinogen administration improved coagulation parameters. A direct relationship between plasma fibrinogen levels and survival was also observed.
Weinkove, 2008 (22)	33	Acquired fibrinogen deficiency	Forty-six percent of patients stopped bleeding with blood components and fibrinogen concentrate alone and a further 29% stopped bleeding with surgical or endoscopic intervention. No adverse thrombotic events were recorded.
Fenger-Eriksen, 2008 (23)	43	Acquired fibrinogen deficiency associated with severe bleeding	Fibrinogen administration improved coagulation parameters and reduced transfusion requirements.
Fenger-Eriksen, 2009 (24)	20	Elective radical cystectomy	Fibrinogen administration completely reversed the dilutional coagulopathy.
Karlsson, 2009 (25)	20	CABG	Pre-operative fibrinogen concentrate infusion reduced bleeding after CABG.
Rahe-Meyer, 2009 (26)	42	AV-AA replacement	Fibrinogen concentrate administration was associated with reduced transfusion requirements and 24-hour postoperative bleeding.
Manco-Johnson, 2009 (27)	14	Congenital afibrinogenaemia	Fibrinogen concentrate administered at a dose of 70 mg/kg demonstrated a favourable PK and safety profile and was effective in promoting clot formation.
Schöchl, 2010 (28)	131	Major trauma	A mortality of 24.4% was observed after the use of fibrinogen concentrate as first-line haemostatic therapy and additional PCC.
Solomon, 2010 (29)	39	Diffuse bleeding after CPB surgery	Fibrinogen concentrate was effective in increasing plasma fibrinogen level and contributed to the correction of bleeding after cardiovascular surgery.
Thorarinsdottir, 2010 (30)	37	Acquired fibrinogen deficiency associated with severe bleeding	Fibrinogen administration improved coagulation parameters and reduced transfusion requirements.
Bell, 2010 (31)	6	Acquired fibrinogen deficiency associated with obstetric haemorrhage	In all cases fibrinogen concentrate led to normalisation of coagulation parameter and to improvement of severe haemorrhage.

Abbreviations: DVT=deep venous thrombosis; PCC=prothrombin complex concentrate; CABG=coronary artery bypass graft; AV-AA=aortic valve-ascending aorta; CPB=cardiopulmonary bypass; PK=pharmacokinetics.

Table II summarises the results of the most important studies on the use of the fibrinogen concentrate Haemocomplettan. Although limited, the literature data available also suggest the low thrombogenic potential of fibrinogen supplementation, according to the findings by Dickneite and colleagues[34].

Conclusions

Although no comparative studies have been conducted so far, the literature data document that fibrinogen concentrate has several advantages over cryoprecipitate as fibrinogen replacement therapy: its better safety profile with regards to blood-borne pathogen transmission as a result of viral inactivation techniques and its accurate and consistent dosing and rapidity of administration. In addition, although cryoprecipitate is cheaper than fibrinogen concentrate, a recent cost-effective analysis showed that the overall costs (i.e., including compatibility testing, thawing and administration) of cryoprecipitate and fibrinogen concentrate are quite similar[21]. In conclusion, while there is increasing published 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 hypofibrinogenaemic state need to confirmed by additional prospective phase II/III clinical trials focusing on dosing, efficacy and safety.

Keywords: cryoprecipitate, fibrinogen concentrate, hypofibrinogenaemia; bleeding, replacement therapy.

Conflict of interest

Massimo Franchini acts as a consultant for CSL Behring and Bayer Healthcare. He has received honoraria from CSL Behring, Bayer Healthcare and Kedrion. Giuseppe Lippi has no conflicts of interest.

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