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Summary

Maintaining the plasma fibrinogen concentration is important to limit excessive perioperative blood loss. In this review, we consider the evidence for this statement, and question the justification for using cryoprecipitate rather than virus-inactivated fibrinogen concentrate to support plasma fibrinogen levels. Haemophilia was historically treated with cryoprecipitate, but specific coagulation factor concentrates are now preferred. In contrast, primary fractions of allogeneic donor blood, including cryoprecipitate, are still commonly used to treat perioperative bleeding.

When compared with cryoprecipitate and fresh-frozen plasma (FFP), freeze-dried fibrinogen concentrate offers standardised fibrinogen content, faster reconstitution and improved efficacy. Pasteurisation and purification processes employed in the preparation of fibrinogen concentrate reduce the risk of pathogen transmission and immune-mediated complications, in comparison with cryoprecipitate and FFP. When all costs associated with administration are taken into consideration, the cost of fibrinogen concentrate is not substantially different to that of cryoprecipitate.

In conclusion, wider availability and use of fibrinogen concentrate may improve the management of perioperative bleeding. Further benefits may accrue from more rapid and accurate techniques for monitoring fibrinogen levels. Clinical studies are needed to evaluate methods of measuring fibrinogen and assessing fibrin polymerisation, and to define critical haemostatic plasma fibrinogen concentrations in different perioperative situations.

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Introduction

In patients without pre-existing haemostatic disorders, coagulation defects that occur during surgery and/or massive haemorrhage are caused by loss, consumption and dilution of coagulation factors, collectively referred to as 'dilutional coagulopathy'. Some types of surgery disturb haemostasis in other ways: during cardiopulmonary bypass (CPB), interactions with the extracorporeal circuit activates the coagulation and fibrinolytic systems, resulting in platelet dysfunction, which is exacerbated by parallel induction of an inflammatory enzymatic cascade (Dietrich 2000). In liver surgery, portal hypertension results in splenic platelet sequestration and thrombocytopenia (Gorlinger 2006).

Current responses to severe perioperative bleeding include transfusion of allogeneic blood products such as red blood cell concentrates, fresh frozen plasma (FFP), platelets, and, in a few countries, cryoprecipitate. Transfusion of fibrinogen concentrate is not yet a standard component of such protocols in either the UK or the USA. In the past 5 years, several studies, which are reviewed below, have revealed the importance of supplementing fibrinogen levels in correcting coagulopathy associated with surgery. Fibrinogen plays an important role in the coagulation process and clot stabilisation via its cleavage by thrombin to form fibrin polymers capable of binding factor XIII (Velik-Salchner, *et al* 2007), with consequent cross-linkage to form a robust fibrin network. In addition, it induces platelet activation and aggregation by binding to the platelet fibrinogen receptor, the $\alpha_2\beta_3$ integrin GPIIb/IIIa.

Cryoprecipitate is a good source of fibrinogen prepared by controlled thawing of frozen plasma to precipitate high molecular weight proteins. These include factor VIII, von Willebrand factor (vWF), and fibrinogen. The precipitated proteins are separated by centrifugation, resuspended in a small volume of plasma (typically 10–20 mL) and stored frozen at -20°C (Poon 1993). In those countries that still use cryoprecipitate, the current rationale is solely to provide fibrinogen. Although cryoprecipitate is prepared as single units, these are pooled prior to administration – a typical adult dose is 10 units (Stanworth 2007). Alternatively, pasteurised human fibrinogen concentrates are available. In Europe, fibrinogen concentrate is well established for treatment of congenital fibrinogen deficiency, and is increasingly

used for acquired fibrinogen deficiency (i.e. the management of perioperative bleeding) (Bundesaertzekammer 2009).

As initially stated almost a decade ago (Bevan 1999), the use of cryoprecipitate in the treatment of perioperative bleeding represents a double standard since it is contraindicated for the treatment of haemophilia, in preference for recombinant and pathogen-reduced plasma-fractionated products when available, on safety grounds. The present manuscript aims to explore: the historic reasons behind the discrepancy between treatment of acquired and hereditary bleeding disorders; the factors influencing the choice between cryoprecipitate and fibrinogen concentrate; and the potential for future improvements in perioperative bleeding management.

History of the development of blood products

Haemophilia

Haemophilia A and B are caused by deficiency of factors VIII and IX, respectively (Figure 1). The first successful treatment of perioperative bleeding in a haemophiliac using blood transfusion was reported as early as 1840, but modern transfusion history really began in 1900 when Landsteiner discovered ABO histocompatibility antigens (Starr 2002).

Figure 1 shows a timeline of developments in the treatment of haemophilia. In the 1940s and 50s, transfusion for haemophilia involved the use of 'antihaemophilic globulin', a crude preparation of fibrinogen and factor VIII. This was followed by the development of cryoprecipitate (Pool, *et al* 1964, Pool and Shannon 1965), which allowed an effective dose of factor VIII in a tolerable volume and led to a dramatic increase in life expectancy (Josephson and Abshire 2006).

However, treatment with plasma-derived products brought infection with diseases such as hepatitis, with multiple transfusions increasing the risk of infection (Alter and Klein 2008). In 1982, three cases of acquired immunodeficiency syndrome (AIDS) were observed among patients with haemophilia A in whom transfusion was the most likely source of infection. It is estimated that, tragically, around 90% of concentrate-treated patients with severe haemophilia were already infected with the human immunodeficiency virus (HIV) before the first case of AIDS was recognised in 1981 (Alter and Klein 2008). Assays to screen blood for contamination with HIV

were introduced in 1985, significantly reducing the risk of transfusion-transmitted HIV (Alter and Klein 2008).

Although reduced by more rigorous donor screening and more sensitive viral detection tests such as polymerase chain reaction testing for viral genomes, the residual risk of viral transmission by plasma-derived products drove the development of more purified preparations of factor VIII with better safety profiles (Poon 1993). A method to produce virally-inactivated factor VIII concentrates was developed in 1985 (Heimburger 2002). Most recently in the development of haemophilia A treatments, recombinant factor VIII products became available in the early 1990s. The World Federation of Hemophilia supports use of coagulation factor concentrates in preference to cryoprecipitate, because cryoprecipitate is not subjected to viral inactivation procedures (World Federation of Hemophilia 2005).

Perioperative bleeding

Initially, whole blood was used in the management of perioperative bleeding, but this evolved to the use of blood components including red blood cells, FFP, cryoprecipitate and platelets. It was the needs of those wounded in war that led to advances in blood transfusion: blood storage was introduced during World War I; and fractionation of blood during World War II. Primary allogeneic blood components remain the mainstay of therapy for perioperative bleeding. At the same time, there is general agreement that transfusion of blood components, in particular plasma-rich blood components, should be avoided if possible (The Serious Hazards of Transfusion Steering Group 2004). Crystalloid and colloid solutions can be used to provide volume, and concentrates are available for replacement of coagulation factors (fibrinogen concentrate, factor XIII concentrate, and prothrombin complex concentrates containing three or four coagulation factors). Other ongoing developments include haemoglobin- or perfluorocarbon-based artificial oxygen carriers (Henkel-Honke and Oleck 2007).

During the era of whole-blood transfusion, thrombocytopenia was the first haemostatic abnormality observed during blood loss. However, in the modern era of intravenous fluids and red cell concentrates, fibrinogen deficiency is the first defect observed (Hiippala, *et al* 1995). In a pig model of dilutional coagulopathy, even with moderate loss (35% of blood volume), the limited increase in fibrinogen synthesis

cannot compensate for the concomitantly increased breakdown (Martini, *et al* 2005). Necessary fluid replacement using crystalloid and colloid solutions not only further reduces fibrinogen concentration by dilution, but colloids such as hydroxyethyl starch also impair fibrin polymerisation (Fenger-Eriksen, *et al* 2009b, Fries, *et al* 2002, Innerhofer, *et al* 2002).

A further indication of the importance of fibrinogen comes from the observation that patients with high fibrinogen levels experience fewer bleeding complications than those with low levels (Blome, *et al* 2005, Fries, *et al* 2005, Pothula, *et al* 2004, Ucar, *et al* 2007a). Thus, the threshold level for treatment may be substantially higher than the 'historical' 1 g/L, particularly in patients suffering from postpartum bleeding [4 g/L; (Charbit, *et al* 2007)] or excessive blood loss during cardiac surgery [3.8 g/L; (Karlsson, *et al* 2008)]. Low preoperative levels of fibrinogen are associated with increased postoperative blood loss (Blome, *et al* 2005, Karlsson, *et al* 2008, Ucar, *et al* 2007b). In postpartum bleeding, low levels of fibrinogen are associated with severe bleeding, with a positive predictive value of 100% (Charbit, *et al* 2007). Based on this work, some current guidelines recommend transfusing fibrinogen concentrate in massive bleeding. Administration of fibrinogen is supported by recent studies including one prospective clinical trial (Fenger-Eriksen, *et al* 2009a, Fenger-Eriksen, *et al* 2009b).

In a porcine model of uncontrolled haemorrhage (induced by inflicting a standardised liver injury), administration of fibrinogen concentrate improved clot firmness and slowed down blood loss (Fries, *et al* 2006, Fries, *et al* 2005). In this model, fibrinogen concentrate was significantly more effective than platelet concentrate transfusion in the presence of thrombocytopenia [average platelet count = 30 x 10^9/L; (Velik-Salchner, *et al* 2007)]. Thus, substitution of fibrinogen may act at more than one level in clot formation, compensating for low thrombin generation and decreased platelet function. High fibrinogen levels may compensate for a low concentration of thrombin because it only takes a single thrombin molecule to cleave up to 1,680 molecules of fibrinogen (Elodi and Varadi 1979). Similarly, the number of platelets present may not be the limiting factor in clot formation if fibrinogen levels are high as there are 40,000–80,000 copies of GPIIb/IIIa receptors on a single activated platelet (Kestin, *et al* 1993). This is supported by the observation that the effect of platelet-blocking substrates like clopidogrel can be antagonised by

increasing the concentration of fibrinogen (Li, *et al* 2001). In patients undergoing thoracoabdominal aortic aneurysm surgery, fibrinogen supplementation with concentrate was more effective than transfusion of FFP and platelet concentrate in achieving effective haemostasis and reducing postoperative bleeding (Rahe-Meyer, *et al* 2009b).

Current sources of fibrinogen

Today's therapeutic options for supplementing plasma fibrinogen are FFP, cryoprecipitate and fibrinogen concentrate. FFP is the most widely available source of fibrinogen, but it has several significant drawbacks such as extended administration time, transfusion-related complications and questionable efficacy (Stanworth 2007). Blood group matching is required and, as FFP is stored at -20°C, thawing time needs to be taken into account. High volumes are needed for effective fibrinogen supplementation as the concentration in FFP is low (typically around 2.5 g/L (O'Shaughnessy, *et al* 2004), although this is variable). These factors all contribute to extending the time for administering FFP, a clear disadvantage in the setting of massive haemorrhage. Also, the low concentration limits the extent to which the fibrinogen level can be raised. FFP is not typically subjected to viral inactivation procedures, so there are risks of viral transmission. Treatment with methylene blue or solvent–detergent can be employed, but this can reduce the level of fibrinogen in the end-product (particularly in the case of methylene-blue treatment, where the reduction is around 30%) (Cardigan, *et al* 2009). Other potential complications associated with the use of FFP include volume overload and transfusion-related acute lung injury (TRALI) (Stanworth 2007). Perhaps the most notable consideration with FFP, however, is the lack of robust evidence supporting its efficacy (Heim, *et al* 2009, Stanworth 2007).

Cryoprecipitate contains a higher concentration of fibrinogen than FFP, typically around 15 g/L (Stinger, *et al* 2008). However, it shares many of the disadvantages of FFP. The risk of viral transmission is similar to that with FFP, the fibrinogen concentration is variable, and blood group matching is needed (Danes, *et al* 2008). Time is also required for thawing cryoprecipitate. The product was withdrawn from most European countries some years ago, on the basis of safety concerns, though it remains available in the UK and the USA. Cryoprecipitate is unsuitable for pathogen

reduction steps, but it can be produced from plasma that has undergone treatment with methylene blue or psoralen/ultraviolet light. However, as previously mentioned, these methods can reduce functional fibrinogen content.

In contrast to FFP and cryoprecipitate, viral inactivation steps are routinely included in the manufacturing process for fibrinogen concentrate, therefore the risk of viral transmission is minimal (Groner 2008). The concentration of fibrinogen is standardised, and the administration volume is low (Fenger-Erikson, *et al* 2009). The administration time is short as there is no requirement for thawing (Rahe-Meyer, *et al* 2009a). Fibrinogen concentrate has been shown to be effective and well tolerated, in a variety of clinical settings. The risk of thrombosis has been shown in a 22-year pharmacovigilance study to be low (Dickneite, *et al* 2008).

The choice between cryoprecipitate and fibrinogen concentrate in therapy of congenital fibrinogen disorders

In addition to its important role in perioperative bleeding, fibrinogen supplementation is also indicated for congenital deficiencies. Inherited disorders that result in fibrinogen deficiency and/or aberrant function are rare but challenging therapeutic problems.

In afibrinogenaemia, homozygous or double heterozygous inheritance of lesions in the FGA, FGB or FGG genes encoding the paired Aα, Bβ and γ chains that form the hexameric fibrinogen molecule result in profound quantitative deficiency of fibrinogen (plasma concentration <0.1 g/L). This results in an episodic, sometimes life-threatening bleeding disorder. Replacement of fibrinogen is required to treat spontaneous bleeding (mucosal, cerebral, musculoskeletal, ovarian); to prevent bleeding after surgery (including poor wound healing); and in pregnancy, including prevention of early foetal loss. Afibrinogenaemia can also be associated with thrombosis, an unexplained complication possibly connected to the role of fibrin in binding and localising thrombin. There is marked heterogeneity in the frequency of these symptoms, but prophylactic fibrinogen replacement is clearly indicated in some individuals and is favoured by a long half-life of infused fibrinogen. The median plasma elimination half-life of Haemocomplettan® P (CSL Behring, Marburg, Germany) is 2.7 days (range: 2.5–3.7), with a median clearance of 0.91 ml/h/kg (range; 0.84 – 1.22) (Kreuz, *et al* 2005).

Hypofibrinogenaemia and dysfibrinogenaemia (usually associated with hypofibrinogenaemia, but sometimes with a normal plasma level) is caused by heterozygous inheritance of genes associated with afibrinogenaemia, and a wide variety of other mutations. Bleeding and/or poor wound healing usually follows surgical challenge, but venous and arterial thrombosis can occur spontaneously. In dysfibrinogenaemia, abnormal fibrin clot structure and delayed or disordered fibrinolysis can contribute to thrombogenesis. Simply elevating the plasma fibrinogen is enough to prevent bleeding and normalise wound healing, but effective treatment of thrombosis also requires suppression of endogenous synthesis and/or secretion of the thrombogenic dysfibrinogen. Many variants of dysfibrinogen are associated with hypofibrinogenaemia due to impaired hepatocytic secretion of the mutant protein.

Transfusion strategies and dose calculations in fibrinogen replacement and prophylaxis demand an infusion product that delivers a known, standardised content of fibrinogen. This is difficult to achieve with cryoprecipitate, in which fibrinogen content varies widely between samples (manual pooling before infusion may add to this variability). In contrast, freeze-dried fibrinogen concentrate provides a known quantity of fibrinogen (900–1400 mg per vial).

In terms of safety, cryoprecipitate retains, to a degree, the statistically low risk of pathogen transmission entailed by its single-donor origin. However, a mini-pool of 10–12 units has to be assembled to make a single effective dose of fibrinogen, and in an inherited disorder, cumulative exposure obviates this advantage compared to large pool-derived fibrinogen concentrates treated with standard pathogen-reduction methods. For all these reasons, appropriately treated fibrinogen concentrate, if available, offers clear advantages over cryoprecipitate as therapy for inherited deficiencies and disorders of fibrinogen.

The development of inhibitory antibodies in response to treatment with fibrinogen has been reported in three cases of afibrinogenemia: two cases following the use of cryoprecipitate (Bronnimann 1954, Ra'anani, *et al* 1991) and one case following treatment with Cohn fraction I (De Vries, *et al* 1961). These inhibitors reduced the

recovery and half-life of fibrinogen so that continuous infusion was required to maintain haemostasis. The patient who received Cohn fraction I developed anaphylaxis and giant urticaria, and eventually died as a result of anaphylaxis following subsequent infusion with whole blood (De Vries, *et al* 1961).

The choice between cryoprecipitate and fibrinogen concentrate for the management of perioperative bleeding

Efficacy

There is a clear consensus that treatment with FFP is inappropriate in cases of severe fibrinogen deficiency as it contains insufficient concentrations of fibrinogen (Chowdhury, *et al* 2004, Danes, *et al* 2008). Although scientific evidence regarding the clinical efficacy of fibrinogen concentrate is limited, this is even more the case for cryoprecipitate (Danes, *et al* 2008), with no published studies specifically addressing the efficacy of cryoprecipitate in the management of perioperative bleeding.

There is evidence for the efficacy and safety of fibrinogen concentrate in congenital fibrinogen deficiency (Aygoren-Pursun, *et al* 2007, Kreuz, *et al* 2005, Rodriguez, *et al* 1988), and data on its use in patients with acquired deficiencies in a variety of surgical settings is beginning to emerge (Danes, *et al* 2008, Fenger-Eriksen, *et al* 2008, Fenger-Eriksen, *et al* 2009a, Haas, *et al* 2008, Heindl, *et al* 2005, Rahe-Meyer, *et al* 2009a, Rahe-Meyer, *et al* 2009b, Weinkove and Rangarajan 2008). In an observational study of 69 patients suffering from various forms of acquired severe hypofibrinogenaemia, most (62%) had consumptive hypofibrinogenaemia (Danes, *et al* 2008). After a median dose of 4 g of fibrinogen concentrate, a mean absolute increase of 1.09 g/L of plasma fibrinogen was measured. Coagulation parameters, PT and aPTT, were significantly improved ($p<0.001$) at 24 hours and 72 hours after fibrinogen concentrate administration (Danes, *et al* 2008). Furthermore, there was an association between plasma fibrinogen concentrations after treatment and 7-day patient survival. In another retrospective study of 43 patients, a similar increase in fibrinogen levels (1.01 g/L) was achieved with half the average dose of fibrinogen (Fenger-Eriksen, *et al* 2008). This may reflect differences between the two study populations including underlying clinical conditions and proportion of paediatric patients.

There are no published studies comparing the efficacy of fibrinogen concentrate with cryoprecipitate. The specification for cryoprecipitate in the UK requires that 75% of units contain at least 140 mg of fibrinogen, in other words, there can be wide variation in fibrinogen content between units (O'Shaughnessy, *et al* 2004). This confounds dose calculations in comparative studies.

Safety

In the past, nearly all patients with haemophilia who received factor VIII concentrates were exposed to transfusion-transmitted viruses, due to factor VIII being unable to withstand heating at 60°C during the standard pasteurisation process. The same is true for fibrinogen. In 1985, CSL Behring (then called Behringwerke), invented a pasteurisation process using stabilisers to protect fragile proteins (Heimburger 2002). A sterile filtration step also removes pathogens (Figure 2). As a result, the fibrinogen concentrate available today has a superior viral safety over cryoprecipitate, despite being plasma-derived. The overall reduction of titres during the production of fibrinogen concentrate is shown for some representative viruses in Table 1 (Groner 2008).

The introduction of viral testing of plasma has greatly reduced the risk of viral transmission with cryoprecipitate. It has been estimated that in the UK, where FFP is not manufactured from first-time or lapsed donors, the residual risks from a single unit of FFP are 1 in 10 million for HIV, 1 in 50 million for hepatitis C virus and 1 in 1.2 million for hepatitis B virus (Williamson, *et al* 2003). However, in the absence of pathogen inactivation processes, the potential remains for contamination of plasma with an emerging, potentially lethal agent, for example variant Creutzfeld-Jakob disease (vCJD) in the UK, and West Nile virus (WNV) in the USA. The first case of possible transmission of vCJD as a result of transfusion was reported in 2004 (Pincock 2004). Countermeasures taken to minimise the risk of vCJD transmission by transfusion, such as the use of leucocyte-depleted blood components and sourcing of FFP for neonates and children born after 1 January 1996 from outside the UK (O'Shaughnessy, *et al* 2004), increase the cost of blood products. By 2002, four transplant-associated cases and 23 transfusion-transmitted symptomatic cases of WNV had been identified. A test to detect genomic material of WNV was developed very rapidly, and transfusion-related transmission of WNV has been very rare since the implementation of testing in 2003 (Alter and Klein 2008).

There are two main methods available for viral inactivation of plasma: treatment with solvent/detergent or methylene blue. However, at present, cryoprecipitate available in the UK is all derived from untreated FFP (O'Shaughnessy, *et al* 2004). The use of methylene blue for viral inactivation of plasma was first described in 1991. Reactive oxygen species that are generated when methylene blue is exposed to visible light inactivate viruses. However, it is well documented that methylene blue treatment also reduces coagulation factor levels, with fibrinogen one of the factors most sensitive to depletion. Compared with cryoprecipitate derived from untreated plasma, the loss of fibrinogen in methylene blue-inactivated cryoprecipitate ranged from 18 to **41%** (Aznar, *et al* 2000, Hornsey, *et al* 2000, Seghatchian and Krailadsiri 2001). **A** retrospective analysis of blood product use before and after the introduction of methylene blue-inactivated plasma in a University hospital in Spain found that the demand for plasma and cryoprecipitate increased across all diagnostic categories (Atance, *et al* 2001). The authors proposed compensation for low fibrinogen content as the most plausible explanation for this increase. No loss of coagulation factors is associated with solvent/detergent treatment of plasma, but there have been batch withdrawals due to possible contamination with parvovirus B19 (O'Shaughnessy, *et al* 2004). Both the methylene-blue and solvent/detergent methods of inactivation are primarily effective against enveloped viruses. Therefore, agents that are inactivated by pasteurisation or removed by filtration during the processing of fibrinogen concentrates may still be transmitted by cryoprecipitate prepared from virally-inactivated plasma.

Aside from the risk of viral transmission, the same immune-mediated risks associated with transfusion of plasma exist for cryoprecipitate (MacLennan and Barbara 2006). These risks include anaphylactic or anaphyloid reactions, allergic reactions, haemolysis, and transfusion-related lung injury (TRALI). However, the non-specific allergic reactions associated with FFP transfusion are rarely seen with cryoprecipitate as only a small volume of plasma is used to resuspend the cryoprecipitated proteins (Ahrons, *et al* 1970, Reese, *et al* 1975). TRALI is believed to be caused by donor leukocyte antibodies, which are produced mainly as a result of pregnancy. Although it is under-diagnosed (Wallis 2003), not least because the same clinical features are seen in acute lung injury resulting from other causes such as sepsis, trauma and shock, TRALI is a common cause of transfusion-related death.

The UK's National Blood Service announced its decision not to supply FFP from female blood donors in an effort to reduce the risk of TRALI in 2003 (Anonymous 2003). A recent summary of 10 years of haemovigilance reports of TRALI in the UK suggested that this policy has been effective in reducing the incidence of TRALI due to FFP (Chapman, *et al* 2008). However, the report also found that, although low, the risk from cryoprecipitate seems to have increased (from 4.3 cases per 10^6 cryoprecipitate components issued from 1999–2004 to 9.6 cases per 10^6 from 2004–2006). This could be because there is now a greater proportion of female donor plasma being used to prepare cryoprecipitate (Chapman, *et al* 2008).

A further safety concern in the management of perioperative bleeding is the risk of a thrombogenic event occurring. Solvent/detergent-treated plasma has reduced activity of the anticoagulant protein S, and has been associated with deep vein thromboses when used to treat patients with thrombotic thrombocytopenic purpura (PLAS+SD®, VI Technologies, Melvin, NY, USA) (Flamholz, *et al* 2000). Increased fibrinogen levels are associated with increased risk of coronary heart disease and myocardial infarction (MI). However, there is evidence to suggest that in this instance fibrinogen is acting as a marker rather than a mediator (Reinhart 2003). For example, there is no increased risk of MI in people that have a polymorphism in the fibrinogen gene resulting in high fibrinogen levels (Reinhart 2003). There have been nine reports of thromboembolic events in patients with congenital or acquired afibrinogenaemia during postmarketing surveillance of a fibrinogen concentrate (Dickneite, *et al* 2008). Although the patients had additional risk factors in most of the cases, a causal relationship could not be definitely excluded. Nonetheless, fibrinogen concentrate appears to have a very low risk of thrombogenicity, corresponding to one case report for every 13,655 treatments of 8 g (Dickneite, *et al* 2008). Thrombin generation in plasma is inhibited by formation of fibrin (hence fibrin has been referred to as antithrombin I), and increased thrombin generation in afibrinogenaemic patients can be normalised by fibrinogen supplementation (Korte and Feldges 1994, Mosesson 2003). Cryoprecipitate is not subject to the same postmarketing surveillance as fibrinogen concentrate, but has been associated with thrombotic events (Nizzi, *et al* 2002). Administration of cryoprecipitate to substitute fibrinogen could cause thrombosis as a result of supraphysiological levels of other proteins present in the precipitate (e.g. von Willebrand factor).

Cost and availability

Fibrinogen concentrate is often perceived as much more expensive than cryoprecipitate. However, the true cost of cryoprecipitate may not be seen by operating theatre staff. Savings are made with fibrinogen concentrate as there is no need for compatibility testing or thawing and administration is simpler, meaning the net cost is not necessarily higher (Weinkove and Rangarajan 2008). Cryoprecipitate is not available in most European countries (Haas, *et al* 2008) but is still used in the US and the UK whereas fibrinogen concentrate is far more widely available than cryoprecipitate in Central Europe. These factors naturally affect treatment decisions.

Future improvements in management of perioperative bleeding

General uptake of fibrinogen concentrate in place of cryoprecipitate for the management of perioperative bleeding would bring about the benefits described above and summarised in Table 2. There is also scope for further improvement through clarification of critical fibrinogen levels and more rapid and reliable diagnostic tests.

Although fibrinogen levels of around 1 g/L are widely cited as a threshold for triggering supplementation, dating back to the late 1980s (Ciavarella, *et al* 1987), the optimal value for this is not clear (O'Shaughnessy, *et al* 2004, Stainsby, *et al* 2006). The critical threshold may vary with the clinical situation and patient characteristics, for example, normal fibrinogen levels increase with age (Balleisen, *et al* 1985, Coppola, *et al* 2000, Ishikawa, *et al* 1997, Laharrague, *et al* 1993, Oswald, *et al* 1983). Several authors consider a threshold of 1 g/L to be too low when blood loss is continuing (Haas, *et al* 2008). In an *in vitro* study, there was no clot formation at <0.5 g/L fibrinogen and at 0.75 g/L only weak clots were formed (Nielsen, *et al* 2005). In a study of postpartum haemorrhage (PPH), fibrinogen concentrations less than 2 g/L had a 100% positive predictive value for severe PPH (Charbit, *et al* 2007).

Point-of-care monitoring may further improve the management of patients with peri-operative bleeding. Certainly, evidence is growing that haemostasis management guided by thromboelastographic techniques is associated with a lower requirement for allogeneic transfusions (Kozek-Langenecker 2007, Royston and von Kier 2001, Shore-Lesserson, *et al* 1999, Spalding, *et al* 2007). Recently, assays that specifically measure the contribution of fibrinogen to clot formation by inhibiting platelets have

been developed for both available point-of-care systems – the TEG® Coagulation Analyzer and the ROTEM® Whole Blood Haemostasis Analyser. These methods provide faster results than the standard laboratory tests and also offer greater accuracy. The Clauss method for measuring fibrinogen may give falsely high fibrinogen levels if colloids have been used for volume replacement because they impair fibrin polymerisation (Fries, *et al* 2002, Hiippala 1995, Innerhofer, *et al* 2002, Mardel, *et al* 1998, Mittermayr, *et al* 2007).

Conclusions

There is evidence that effective fibrinogen supplementation in patients with perioperative bleeding can: reduce blood loss, lower the requirement for transfusion of other blood components such as FFP and platelet concentrates, restore coagulation, and improve survival. Where cryoprecipitate is still used, replacement with fibrinogen concentrate would offer improvements in efficacy and safety, bringing the standard of treatment for surgical patients in line with that offered to haemophilia patients. Additional improvements to perioperative bleeding management may be attained by the introduction of more rapid and reliable tests for monitoring fibrinogen levels, and by clarification of the level of fibrinogen at which therapy should be initiated.

In congenital fibrinogen deficiencies, the argument for using current pathogen-reduced fibrinogen concentrates as replacement therapy, in preference to cryoprecipitate, is very strong, although the current unlicensed status of this product in the UK is a significant impediment.

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Table 1. Mean reduction of virus titres during the production of Haemocomplettan® P/Riastap (CSL Behring, Marburg, Germany). Adapted from (Groner 2008)

Virus	Mean reduction of titre (log_{10})
Human immunodeficiency virus	≥9.6
Bovine viral diarrhoea virus[a]	≥11.2
Herpes simplex virus 1	≥9.1
Hepatitis A virus	≥7.6
Canine parvovirus[b]	6.1

[a]Model virus for hepatitis C virus; [b]model virus for human parvovirus B19.

Table 2. Attributes to consider when choosing between cryoprecipitate and fibrinogen concentrate for management of perioperative bleeding.

Attribute	**Cryoprecipitate**	**Fibrinogen concentrate**
Immunological reactions	Risk of ABO incompatibility, TRALI and severe anaphylaxis, albeit low because resuspended in small volume of plasma.	Negligible risk of immunological reactions because purification steps during preparation remove donor antibodies
Risk of viral/pathogen transmission	Usually not virally inactivated. Viral inactivation using MB or SD not as effective as pasteurisation	Manufacturing process includes pasteurisation* and filtration steps that minimise the risk
Accuracy of dosing	Inconsistent fibrinogen content between units. Reduced fibrinogen content in cryoprecipitate from MB-treated plasma	Standardised fibrinogen content
Number of units/vials required to provide 4g dose	29 units (based on 140 mg/unit)	4 vials
Reconstituted volume of 4g dose	Approximately 375 mL (based on 15 g/L)	200 mL
Time to administration	Must first be thawed in a water bath	Can be reconstituted rapidly
Cost	Perceived to be cheaper than fibrinogen concentrate	Cost-effective and overall cost may be similar to cryoprecipitate
Availability	Not available in many European countries. Mainly used in UK and USA	More widely available than cryoprecipitate in most European countries

MB, methylene blue; SD, solvent/detergent; TRALI, transfusion-related lung injury

*in Haemocomplettan® P/Riastap only

Figure 1. Timeline of developments in treatment of haemophilia

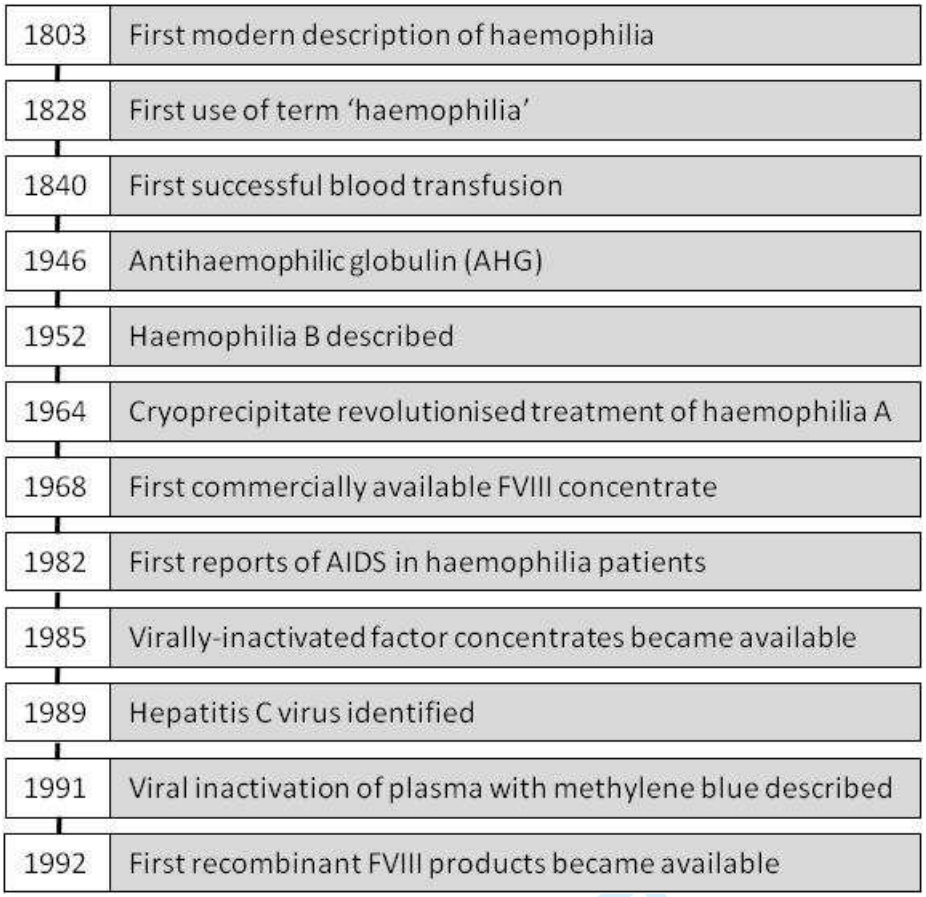

Figure 2. Schematic of production of pasteurised fibrinogen concentrate from frozen plasma.