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Review Article

# Clinical Significance of Fibrinogen Concentrate for Haemostatic Therapy in Patients with Massive Haemorrhage

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**Abstract**

Coagulopathy due to massive haemorrhage and hyperfibrinolysis is a major cause of mortality in many clinical settings. The primary cause of coagulopathy is hypofibrinogenemia. As fibrinogen is the precursor to fibrin and a mediator of platelet aggregation, it is the principal target for haemostasis and plays a critical role in massive bleeding. Although frozen plasma is usually transfused for fibrinogen supplementation, it cannot increase the fibrinogen level to the haemostatic threshold in cases of critical hypofibrinogenemia (fibrinogen concentration < 1.0 g/L). Moreover, preparation and administration of frozen plasma is time consuming and therefore unsuitable for emergencies.

Fibrinogen concentrate is available for administration almost immediately and contains fibrinogen at a concentration of 20 g/L, which is 10 times higher than its concentration in frozen plasma. Therefore, it can be administered in very small volumes, allowing the fibrinogen level to reach the haemostatic threshold (fibrinogen concentration > 1.5-2.0 g/L) immediately, even in cases of critical hypofibrinogenemia. Fibrinogen concentrate is reportedly effective and well tolerated for haemostasis in cases of massive bleeding due to critical coagulopathy. In cases of severe trauma, major obstetric haemorrhage, and aortic replacement surgery, in particular, fibrinogen concentrate has the potential to reduce allogeneic blood transfusion and improve outcomes without increasing the risk of adverse events. Although fibrinogen concentrate is highlighted for its significant therapeutic effects in patients with critical coagulopathy, further prospective randomized control trials are needed to establish strong evidence for its clinical use.

**Keywords:** Trauma-induced coagulopathy; Obstetric haemorrhage; Hypofibrinogenemia; Hyperfibrinolysis; Massive bleeding

## Abbreviations

FC: Fibrinogen Concentrate; RCT: Randomized Controlled Trial; CPB: Cardiopulmonary Bypass; FIB-PPH: FIBrinogen concentrate as initial treatment for Post Partum Haemorrhage

## Introduction

Transfusion therapy for haemostasis has been an important issue in critical care, including trauma, obstetric haemorrhage, and massive bleeding during major cardiovascular surgery (e.g. aortic replacement). Coagulopathy due to massive haemorrhage and hyperfibrinolysis is a major cause of mortality in critical patients. Conventional transfusion therapy, which involves transfusion of frozen plasma to patients with critical coagulopathy, shows insufficient haemostatic effects, because frozen plasma cannot increase the concentration of coagulation factors, especially fibrinogen, up to the threshold level required for haemostasis [1].

Recently, Fibrinogen Concentrate (FC) has been highlighted for its effectiveness in transfusion therapy for haemostasis. FC is a plasma-derived blood-component product that is reconstituted in 50 mL of sterile water to a final concentration of 20 g/L, at which it contains 10 times more fibrinogen than frozen plasma. FC shows significant effects on the recovery of plasma fibrinogen levels and subsequent haemostasis in both hereditary [2] and acquired hypofibrinogenemic conditions [3,4], including trauma-induced coagulopathy [5,6], major obstetric haemorrhage [7,8], and severe dilutional coagulopathy during major aortic replacement surgery [9,10]. Moreover, analysis of decades of pharmacovigilance data shows a promising safety profile of FC [11]. Therefore, in this review, we discuss the therapeutic significance of FC in critical situations.

### Critical hypofibrinogenemia as the primary coagulopathy in massive haemorrhage

Fibrinogen is a crucial haemostatic factor for sustaining platelet aggregation via glycoprotein IIb/IIIa receptors during primary haemostasis. Fibrinogen is the first coagulation factor to be affected by massive bleeding and haemodilution, during which its concentration decreases below a critical haemostatic value [12]; thus, it should be the first protein to be supplied to critical patients. Recently, fibrinogen has been highlighted as a target for evaluation of coagulation potential and haemostatic therapy in cases of massive bleeding [13,14]. For example, critical hypofibrinogenemia (fibrinogen concentration< 1.0-1.5 g/L) occurs early during major




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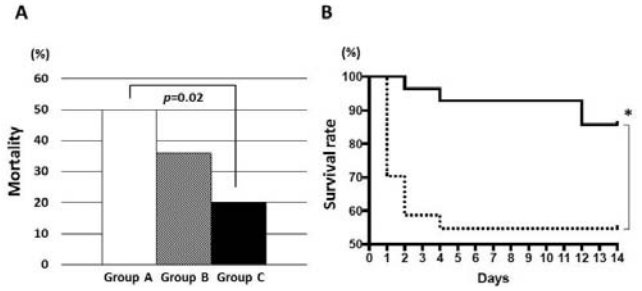


**Figure 1:** Mortality of severe trauma patients.
**A**: Mortality of patients with ISS ≥41. Group A (open columns), no administration of FC (*n*=30); Group B (hatched columns), administration of 3 g FC when plasma fibrinogen level is<1.5 g/L (*n*=22); and Group C (closed columns), pre-emptive administration of 3 g FC immediately at arrival at the hospital before measurement of fibrinogen levels (*n*=25).A significant difference is seen between Groups A and C (*p*=0.02) after evaluation by Pearson's chi-square test. **B**: Fourteen-day survival curves evaluated using Cox's multivariate proportional hazard model in pelvic fracture patients with ISS ≥41 compared between the group that received FC treatment and the group that did not. Solid line, group with early administration of FC (*n*=109); dashed line, group treated without FC (*n*=115). **p*<0.05 evaluated by the Mann-Whitney's *U*-test. ISS, injury severity score.

blood loss and causes uncontrollable oozing at multiple sites. Critical hypofibrinogenemia results from dilutional coagulopathy caused by fluid supplementation and red blood cell transfusion as well as fibrinogenolysis due to hyperfibrinolysis induced by the tissue-type plasminogen activator released from injured endothelial cells [15].

A prospective observational study reported that the fibrinogen level at presentation is an independent predictor of mortality for trauma patients [16]. Early clinical data suggest that fibrinogen supplementation, as a part of an algorithm for haemostatic therapy based on point-of-care guided coagulation factor concentrates, improves outcomes for traumatic haemorrhage by improving clot strength and reducing blood loss [6]. In addition, there is strong evidence to show that the decrease in fibrinogen concentration is an early predictor of the severity of postpartum haemorrhage [17]. Importantly, fibrinogen levels after Cardiopulmonary Bypass (CPB) are related to large volume red cell transfusion in cardiovascular surgery [18]. Thus, fibrinogen is a key molecule in transfusion therapy for trauma-induced coagulopathy [16,19], severe postpartum haemorrhage [7,20], and massive bleeding during major cardiovascular surgery such as aortic replacement [21,22]. The experts currently recommend a target fibrinogen level of at least 1.5-2.0 g/L in patients with active bleeding [14,23].

## Clinical effectiveness of FC in massive hemorrhage

FC has been effective and well tolerated in many clinical trials [9,23-25], and studies in a variety of settings have reported its excellent safety profile [26,27]. Despite the small number of studies on its outcomes associated with its perioperative administration, studies consistently reported its benefit over both frozen plasma and crystalloids and colloids with regard to numerous outcome measures including reduction of blood loss and allogeneic transfusions. In terms of clinical effectiveness, perioperatively, the use of FC in an early, goal-directed, coagulation-management strategy may be preferred over the use of frozen plasma [28]. The results of clinical studies on the therapeutic effectiveness of FC for massive haemorrhage in the systematic review [25] are summarized in Table 1 [3,4,6,7,9,20, 21,22,25,29-65].

Several studies reported a change in plasma fibrinogen levels in response to different doses of frozen plasma and FC. A good response was achieved with FC: 2–4 g FC typically increased the plasma fibrinogen levels by approximately 1.0 g/L [22,66]. According to recent measurements, 1 L frozen plasma [67] contains 2 g fibrinogen; the same amount of fibrinogen is present in only 100 mL FC [24]. Thus, the use of FC is more favorable than frozen plasma for fibrinogen substitution. This reduced infusion volume may help avoid dilutional coagulopathy and the risk of volume overload associated with massive transfusion with frozen plasma.

## Trauma

The lethal triad of coagulopathy, acidosis, and hypothermia develops early after traumatic injury and is associated with increased mortality [19]. Trauma-induced coagulopathy is primarily diagnosed as hypofibrinogenemia, which is accelerated by acidosis, hypothermia [68,69], and hyperfibrinolysis [70]. Conventional approaches for trauma patients with massive haemorrhage, including damage control resuscitation using blood component therapy, have been shown to result in persistent coagulopathy, bleeding, and poor outcomes [71]. Although haemostatic resuscitation offers advantages over previous strategies, it does not correct coagulopathy during the acute phase of traumatic haemorrhage without a high total fibrinogen load [72]. On the other hand, early treatment with FC could control active bleeding and oozing at multiple injury sites in trauma patients with hypofibrinogenemia [6]. Therefore, FC administration is recommended for initial coagulation resuscitation in the latest European guidelines on management of major bleeding and coagulopathy following trauma [73].

Two cohort studies reported low mortality rates for among patients receiving high doses of fibrinogen during traumatic haemorrhage [74,75]. Recently, a randomized feasibility trial demonstrated that infusion of 6g FC within 1 hour of arrival at the hospital was feasible and improved the plasma fibrinogen concentration by approximately 1.0 g/L in a population of trauma patients at risk for significant haemorrhage [64]. Another Randomized Controlled Trial (RCT) of FC for trauma patients is currently underway [65].

In a case-control study performed at a single center for emergency and critical care, pre-emptive administration of FC contributed to improved prognosis for survival in severe trauma patients (Figure 1) [60], especially in those with pelvic fracture (Figure 2) [61]. Among trauma patients with an injury severity score ≥26 who were transfused with ≥ 10 units of red blood cell concentrates, upon arrival at the hospital (n=180), approximately 56% showed hypofibrinogenemia (fibrinogen concentration <1.5 g/L) and 26% showed critical hypofibrinogenemia (fibrinogen concentration <1.0 g/L). Primary haemostasis, accomplished by pre-emptive administration of FC, enables surgeons to perform early mobilization of patients for imaging diagnosis to detect bleeding sites, which leads to definitive surgical fixation and haemostasis. Together, such time-saving, aggressive supplementation with fibrinogen may contribute to improved outcomes and prevent death due to massive haemorrhage, especially during the acute phase of trauma.

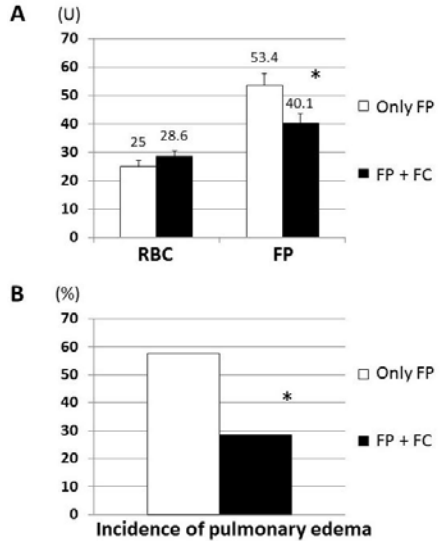


**Figure 2:** Transfusion volumes and incidence of pulmonary edema in patients with major postpartum haemorrhage.
**A**: Transfusion volume of RBC and FP in patients with the most severe postpartum haemorrhage who received≥18 units of RBCs. The indicated numbers are the average units in each group. **B**: Incidence of pulmonary edema in the patients mentioned above in panel **A**. Open columns, patients treated with FP only ($n$=14); Closed columns, patients treated with FP plus FC ($n$=25). *$p$<0.05 evaluated by the chi-square test. RBC: Red Blood Cell; FP: Frozen Plasma; FC: Fibrinogen Concentrate.

## Obstetric haemorrhage

Multiple studies have reported that fibrinogen is an important predictor of major obstetric haemorrhage and progression to severe postpartum haemorrhage [17], which is an important cause of maternal mortality. Obstetric haemorrhage is characterized by hypofibrinogenemia and hyperfibrinolysis, which is evaluated by elevation in the levels of fibrin/fibrinogen degradation products and exacerbates coagulopathy by accelerating fibrinogenolysis. Importantly, accelerated fibrinolysis and critical hypofibrinogenemia (fibrinogen concentration < 1.0 g/L) are frequently observed in amniotic fluid embolism [76,77].

Reduced levels of fibrinogen are associated with prolonged bleeding, need for invasive procedures, and early transfusion, especially when the fibrinogen level is < 2.0 g/L. The fibrinogen level is the only laboratory parameter associated with severe postpartum haemorrhage, and the risk of severe postpartum haemorrhage is 2.6-fold higher for each 1.0 g/L decrease in the fibrinogen level [17]. A case-control study observed that fibrinogen levels <2.0 g/L were independently associated with a significant risk of severe postpartum haemorrhage [78]. An additional report evaluating the specificity of fibrinogen levels lower than 2.0 g/L for predicting severe postpartum haemorrhage was approximately 99%, and the odds ratio was approximately 12 [79]. A prospective analysis on the need for embolization or surgical interventions for severe postpartum haemorrhage on admission to the intensive care unit reported that a fibrinogen level < 2.0 g/L was an independent predictor of severe postpartum haemorrhage [80]. Thus, the target threshold for fibrinogen substitution may be 2.0 g/L in cases of major obstetric haemorrhage.

Further studies on postpartum haemorrhage reported that FC therapy is indispensable in patients with hypofibrinogenemia [7]. In such emergency settings, FC allows rapid therapy without blood-type matching; however, there are limited data and no published randomized clinical trials in such a setting. A single-center retrospective analysis for maternal and neonatal medicine showed the therapeutic effectiveness of FC in major obstetric haemorrhage with severe hypofibrinogenemia [56]; in the study, administration of 3g FC to postpartum haemorrhagic patients with hypofibrinogenemia (i.e., fibrinogen concentration < 1.5 g/L) not only increased the rate of fibrinogen supplementation by 5-fold, but also reduced the frozen plasma dosage and the incidence of pulmonary edema. On the contrary, one such RCT—the FIB rinogen concentrate as initial

**Table 1:** Summary of the systematic review showing the clinical effectiveness of FC for massive haemorrhage.

| | Total number of reports | Number of enrolled patients | Number of reports in which the therapeutic significance* of FC was observed |
|---|---|---|---|
| **RCT** | **15** | **1366** | |
| Cardiovascular surgery [9,29-37] | 10 | 712 | Decreases in blood loss and transfusion:2<br>Decrease in blood loss:2<br>Decrease in transfusion:2<br>Recovery from hypofibrinogenemia:1 |
| Other types of surgery [38-41] | 4 | 407 | Decrease in transfusion: 1 |
| Postpartum haemorrhage [42] | 1 | 247 | |
| Observational study<br>(prospective)<br>(retrospective) | 25<br>6<br>19 | 3268 | |
| Cardiovascular surgery [3,4,21,22,43-47] | 9 | 1636 | Decrease in transfusion: 2<br>Recovery from hypofibrinogenemia: 4 |
| Other types of surgery [43,48-51] | 5 | 286 | Recovery from hypofibrinogenemia: 3 |
| Postpartum hemorrhage [3,47,20,52-56] | 9 | 382 | Recovery from hypofibrinogenemia: 8<br>Decrease in transfusion: 1 |
| Trauma [6,57-61] | 6 | 964 | Decrease in transfusion : 2<br>Decrease in mortality: 2 |
| Registered Ongoing RCT [25,62-65] | 11 | 1105 | |

*Significant effectiveness of FC compared with placebo or frozen plasma; FC: Fibrinogen Concentrate; RCT: Randomized Control Trial

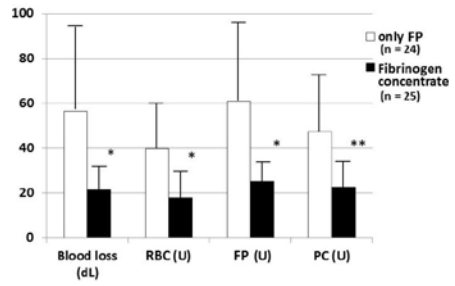


**Figure 3:** Volume of blood loss and transfusion during thoracic aortic replacement surgery.
Open columns: cases treated with only FP (*n*=24); closed columns: cases treated with FC and conventional transfusion (*n*=25). One unit (U) of RBC contains 130 mL of red blood cell concentrates derived from 200 mL whole blood. Five units of FP contain 400 mL whole plasma, whereas 10 units of PC contain 2-3 x $10^{11}$ of platelets. Data are presented as mean ± standard deviation. **p*< 0.05; ***p*< 0.01 (by unpaired *t*-test). RBC: Red Blood Cell; FP: Frozen Plasma; PC: Platelet Concentrate; FC: Fibrinogen Concentrate.

treatment for Post Partum Haemorrhage (FIB-PPH) trial—showed no significant reduction in bleeding and transfusion with pre-treatment of 2g FC for severe postpartum haemorrhagic patients with normofibrinogenemia [42]. Further RCTs of FC *vs.* placebo for the treatment of postpartum haemorrhage are currently underway [62,63].

### Cardiovascular surgery

Patients undergoing cardiovascular surgery bleed because of multiple coagulation defects associated with CPB, tissue injury, and dilutional changes [81]. Patients with cardiovascular surgery with CPB show haemostatic changes consistent with disseminated intravascular coagulation, including elevated D-dimer and low fibrinogen levels, leading to uncontrollable oozing and massive transfusion [82,83]. In aortic replacement surgery, particularly, blood that has leaked into the pleural cavity contains high amounts of tissue factor and is usually re circulated into the CPB through suction, which results in accelerated activation of the extrinsic coagulation pathway [84]. Therefore, activation of coagulation and consumption of fibrinogen progress continuously during CPB despite full heparinization, which leads to hypofibrinogenemia (fibrinogen concentration < 1.5 g/dL) at the end of CPB.

Several RCTs and systematic reviews have suggested that FC therapy may be effective in controlling perioperative bleeding and reducing transfusion requirements in cardiovascular surgery [9,33,34]. However, a few RCTs for cardiac surgery showed no significance of FC in blood loss and allogenic blood transfusion [35-37]; it is important to note that the appropriateness of the study design (e.g., type of surgical procedure, enrolment of patients, and trigger for FC infusion) used may be controversial in these studies. One retrospective study reported that administration of FC at the CPB termination sufficiently elevated the plasma fibrinogen concentration for haemostasis in patients with thoracic aortic replacement surgery, resulting in dramatic reduction of blood loss and allogeneic blood transfusion (Figure 3) [85]. Thus, timely administration of FC when the fibrinogen level is < 1.5 g/L after CPB termination may be an indispensable haemostatic therapy for aortic repair surgery. If confirmed in larger prospective randomized studies, FC could be an effective therapy for reducing transfusions and contributing to better prognosis of patients with thoracic aneurysm repair.

### Cost benefit of FC

Finally, we evaluate the economic advantage of FC base upon a couple of reports [86-88]. The management of patients with massive bleeding by FC was cost-effective because of a reduction of allogenic blood transfusion and a decrease in ICU length of stay. In the survey of 768 patients undergoing cardiac surgery in an Italian single-center, the point-of-care-based management with FC was associated with a saving of $300 per patient [87]. Although cryoprecipitate is estimated to be less expensive than FC in the United States [88], an economic benefit of FC is more highlighted in Japan where FC (Fibrinogen HT; Tokyo, Japan) costs only $220/g (i.e., 70% less price of FC in the United States and Europe) in spite of off-label usage.

## Conclusion

Severe hypofibrinogenemia is the primary cause of massive bleeding in critical patients and an independent risk factor of high mortality. Current research is focused on platelet alternatives for perioperative and peritraumatic haemostasis, and FC may be a "universal haemostatic agent" [24,89,90]. The therapeutic significance of FC should be highlighted in critical settings, including severe trauma, postpartum massive haemorrhage, and major aortic replacement surgery [91], wherein severe hypofibrinogenemia and hyperfibrinolysis coexist. Further prospective RCTs in a variety of clinical settings are necessary to establish strong evidence for the clinical use of FC.

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