

Efficacy and safety of fibrinogen concentrate in trauma patients— a systematic review ☆☆☆★



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ABSTRACT

Purpose: Uncontrolled bleeding is the main preventable cause of death in severe trauma patients. Fibrinogen is the first coagulation factor to decrease during trauma-induced coagulopathy, suggesting that pharmacological replacement might assist early hemorrhage control. Several sources of fibrinogen are available; however, fibrinogen concentrate (FC) is not routinely used in trauma settings in most countries. The aim of this review is to summarize the available literature evaluating the use of FC in the management of severe trauma.

Methods: Studies reporting the administration of FC in trauma patients published between January 2000 and April 2013 were identified from MEDLINE and from the Cochrane Library.

Results: The systematic review identified 12 articles reporting FC usage in trauma patients: 4 case reports, 7 retrospective studies, and 1 prospective observational study. Three of these were not restricted to trauma patients.

Conclusions: Despite methodological flaws, some of the available studies suggested that FC administration may be associated with a reduced blood product requirement. Randomized trials are warranted to determine whether FC improves outcomes in prehospital management of trauma patients or whether FC is superior to another source of fibrinogen in early hospital management of trauma patients.

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1. Introduction

Trauma is a major cause of mortality, with more than 5 million deaths annually worldwide. Young adults are particularly at risk, leading to many life-years lost or dependence on ongoing care. Hemorrhage is the most common cause of preventable death in trauma, with 55% of deaths due to prehospital bleeding [1]. Hemorrhage control is commonly thwarted by coagulopathy, which is present in more than 50% of trauma patients at emergency department (ED) admission [2]. Trauma patients who present to the hospital with coagulopathy already established, are 3

to 4 times more likely to die [3–6]. Prolonged hypotension and/or the adverse effects of massive blood product transfusion also lead to an increase in morbidity including acute kidney injury [4], multiple-organ failure [3], and an increased length of stay in the hospital and intensive care unit (ICU) [5,7]. Improving early hemorrhage control by optimizing treatment of coagulopathy might, therefore, lead to improved outcomes in severely injured trauma patients [1].

For many years, coagulopathy in trauma was thought to be attributable to 3 main mechanisms: (1) loss of coagulation factors due to bleeding and consumption, (2) dilution due to intravenous fluid and red blood cell (RBC) administration without sufficient clotting factors (in the form of fresh frozen plasma [FFP] and platelets), and (3) coagulation protease dysfunction due to hypothermia and acidemia. More recently, accumulating evidence has suggested that tissue hypoperfusion and direct tissue trauma initiate acute coagulopathy in trauma patients also called trauma-induced coagulopathy (TIC), in part through an increase of fibrinolysis [4,5,7,8].

Fibrinogen is the first coagulation factor to reach critically low levels during trauma, and hepatic synthesis is not sufficient to compensate for rapid massive consumption [9]. Although fibrinolysis secondary to activation of the coagulation cascade may be the primary reason for hypofibrinogenemia, other mechanisms play an important role in decreasing plasma fibrinogen. These include (i) increase in fibrinogen breakdown due to acidosis [10], (ii) dilution during fluid

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resuscitation [11], (iii) loss due to bleeding, and (iv) decrease in fibrinogen synthesis due to hypothermia [12] (Fig. 1). In addition, fibrinogen/fibrin polymerization is disturbed by colloid infusions [11]. Guidelines recommend replacement of fibrinogen if significant bleeding is associated with hypofibrinogenemia defined as plasma fibrinogen concentration less than 2 g/L or thromboelastometric signs of functional fibrinogen deficit, using the European guideline for management of bleeding and coagulopathy following major trauma [13,14]. Currently, there are 3 fibrinogen sources available to clinicians: fibrinogen concentrate (FC), FFP, and cryoprecipitate. Human fibrinogen concentrate is derived from human plasma and is currently manufactured as 4 different products: Haemocomplettan (CSL Behring, Marburg, Germany), Clotfact (LFB, Les Ulis, France), Fibrinogen HT (Benesis, Osaka, Japan), and FibroRAAS (Shanghai RAAS, Shanghai, China) [15]. Fibrinogen concentrate has several potential advantages over FFP or cryoprecipitate and is the only practical source of fibrinogen, which can be administered outside the hospital. Fibrinogen concentrate does not require ABO compatibility testing. Its lyophilized form allows FC to be stored in an ambulance for up to 5 years at 25°C and to be easily reconstituted and administered [16]. Fibrinogen concentrate avoids adverse effects associated with allogeneic blood products including transfusion-related acute lung injury and ABO incompatibility [14,17,18]. Although viral inactivation by heat treatment lessens the risk of pathogen transmission compared with other blood products, as a human plasma-derived product, transmission of infection cannot be completely excluded [16]. In addition, the high concentration of fibrinogen in FC (20 g/L) enables it to be replaced intravenously with a small volume (200 mL to administer 4 g of fibrinogen), whereas replacement of fibrinogen with cryoprecipitate where the concentration of fibrinogen is widely variable and lower (8–16 g/L) and FFP where the concentration of fibrinogen is much lower (2 g/L) requires a larger volume and thereby may lead to transfusion-associated circulatory overload [19]. Finally, there is growing evidence in nontrauma patients, for instance, in cardiac surgery, that the use of coagulation factor concentrates, including FC, guided by point-of-care coagulation analyses, reduces blood product requirements as well as overall treatment cost [20,21].

Although 1 systematic review compared clinical effectiveness of FFP with FC in surgical and/or massive trauma patients [22], only 1 review has summarized all the literature concerning FC in bleeding trauma patients. Published in 2011, the authors found 1 observational study and 3 case reports, with only 131 patients treated with FC [23]. Since then, interest in FC has been rising steadily because of perceived benefits of addressing TIC directly. As the prelude to a possible clinical trial in trauma patients, we aimed to review the entire current published experience of FC in early severe trauma with massive hemorrhage.

2. Methods

The review has been designed to maximize adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [24].

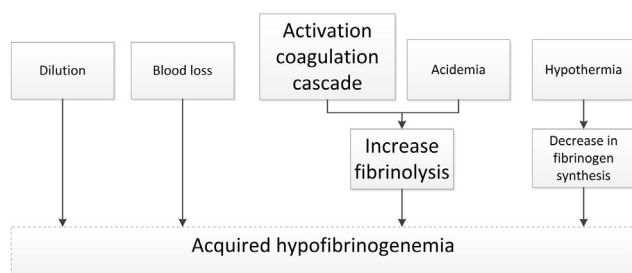


Fig. 1. Factors contributing to hypofibrinogenemia in trauma patients.

2.1. Eligibility criteria, information sources, and search strategy

We systematically searched in MEDLINE via OVID and in the Cochrane Library to identify published reports of clinical experiences of FC in adults with trauma, regardless of the study's outcome. We used the subject heading "fibrinogen" and the text words "fibrinogen concentrate." Similarly, we searched for the subject heading "wound and injuries" and "multiple trauma" and the text words "trauma." We confined our search to English language articles published between January 2000 and April 2013. Articles were eligible if they reported FC used in management of severe trauma patients. We excluded preclinical studies and pediatric studies. Additional articles were added if found in the references of the selected articles and if they fulfilled the eligibility criteria. Eligibility assessment was based on the title or abstract and on full text if required.

2.2. Data collection process and items

The following were extracted by 1 reviewer (CA): study design (for instance, case report, observational cohort, retrospective or prospective study), sample size, inclusion criteria, period, protocol (fibrinogen plasma level threshold, prehospital or hospital phase, comparative group), results (dose of FC administered, outcomes), and safety information.

3. Results

Three hundred four articles were identified. Most were excluded at the level of title or abstract based on relevance (Fig. 2). Twelve were considered eligible for this review: 4 case reports [25–28] and 8 observational case series [9,29–35]. Of these 8 case series, 7 were retrospective [9,29–31,33–35], including 3 with matched pairs analysis or propensity score matching [31,33,34] and 1 that used Trauma Injury Severity Score (TRISS) to control for patient severity [35]. One was a multicenter observational study. Of these studies, 3 were not restricted to trauma patients. There were no randomized controlled trials (RCTs).

3.1. Case reports

The 4 case reports illustrate successful resuscitation of trauma patients who had massive hemorrhage with FC in addition to other products (Table 1) [25–28]. In all cases, the administration of FC was in response to fibrinolysis as demonstrated by rotational thromboelastometry (ROTEM). Patients received between 5 and 16 g of FC in the ED or operating room (OR). Two patients also received prothrombin complex concentrate (PCC) and/or tranexamic acid [25,28]. One patient received 3 bags of FFP along with 5 g of FC [28]. These 4 cases suggest that aggressive management of coagulopathy with FC with and without antifibrinolytics and other coagulation factors is feasible and may be effective. Nonetheless, no clear conclusions, especially concerning savings in volume of blood products required, can be drawn.

3.2. Retrospective case series

Seven retrospective studies have reported the use of FC in trauma patients with serious bleeding (Table 2). Two reports from single centers were not restricted to trauma and included patients with other causes for massive hemorrhage receiving FC for low fibrinogen [9,29]. The administration of FC was based on plasma fibrinogen level with a threshold of 1 and 2 g/L, respectively. The study of Fenger-Eriksen et al [9] enrolled 43 patients including 6 with trauma and reported a significant decrease in transfusion requirements and a significant improvement in laboratory coagulation indices in individual patients after fibrinogen administration. The authors

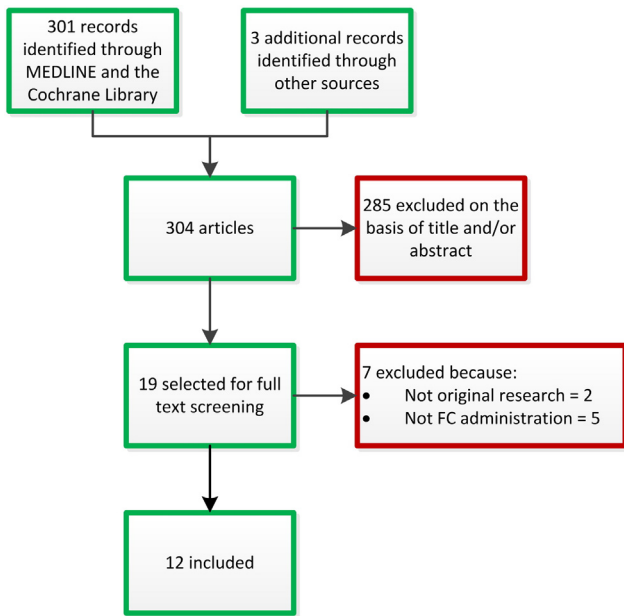


Fig. 2. Flow diagram of study selection.

did not adjust for confounding interventions, which may affect bleeding and blood product requirement. Danes et al [29] also reported outcomes of 69 patients, 11 with trauma, and showed a significant improvement from baseline laboratory coagulation parameters 24 and 72 hours after FC administration. They also found a positive association between 7-day survival and higher fibrinogen level after FC administration in patients with acute hypofibrinogenemia [29].

Four retrospective studies compared a variety of outcomes in severe trauma patients treated with different hemostatic therapies including FC without FFP, FC plus FFP, and FFP alone [30,31,33,34]. One of these studies [30] compared blood product requirements between trauma patients treated with FC and/or PCC and patients receiving only FFP, finding a significantly lower volume of blood products transfused in patients receiving concentrated factors. However, the groups were not matched, and there were significant differences in their characteristics, including blood pressure and abbreviated injury scale, which would have affected outcome. No multivariate analysis was presented.

The other 3 retrospective studies used case-controlled matched analyses. One [33] compared the blood product volume requirement in 36 bleeding trauma patients receiving either FC (±PCC) without FFP with those who received FFP alone, matching for age, Injury Severity Score (ISS), base excess (BE), and international normalized ratio. They found a significantly lower volume of RBC units transfused (mean, 3 [interquartile range {IQR}, 0-5] vs 12.5

[IQR, 8-20], $P < .005$) and platelets transfused (mean, 0 vs 2 bags [IQR, 1-3]) in the group of patients receiving concentrated factors compared with the patients receiving only FFP. This study suggested that FC may more effectively decrease traumatic bleeding than FFP alone. The incidence of multiorgan failure (MOF) was also significantly lower in patients receiving FC in this study. Innerhofer et al [34] compared patients who received FC without FFP ($n = 66$) vs FC with FFP ($n = 78$), reporting a lower volume of blood products transfused, including RBC and platelets, in patients receiving only FC. There was no difference in clinical outcomes. This retrospective study increased the robustness of its findings by adjusting for patient severity using propensity scores. This propensity score-matched analysis conducted in 28 patient pairs confirmed the results. Finally, the largest retrospective study analyzed 294 pairs of trauma patients who required at least 1 RBC unit and had high risk of bleeding and who did or did not receive FC in the hospital. This study matched for demographics, injury severity including the ISS and the Trauma Associated Severe Hemorrhage (TASH) score, and transfusion characteristics (massive transfusion, FFP/RBC ratio, and PCC administration) [31]. There was no difference in the volume of blood products transfused, including RBC, FFP, and platelets in patients receiving FC vs patients without FC. The 6-hour mortality was lower in the FC group (10.5% vs 16.7%; $P = .03$) but not the overall hospital mortality [31]. In this study, both groups received the same volume of FFP, and the FC dose was not reported and may have been small. Patients resuscitated with FC were more likely to develop MOF than the others (73.8 vs 61.9; $P = .03$) possibly because the survivors in this group were sicker than surviving control patients. This study increases equipoise hinting at additional benefits of FC compared with current blood product therapies. It may be that FC does not add benefit in a hospital setting, or it may simply be that all patients in both groups received sufficient factor replacement independent of their FC. Finally and importantly, interpretation of these results is subject to debate because matching criteria included posttreatment parameters (massive transfusion requirement, FFP/RBC unit ratio, and requirement for PCC).

Of the 5 retrospective case series restricted to trauma patients, 1 analyzed the outcome of 131 severe trauma patients after ROTEM-guided hemostatic therapy with FC ($n = 128$) and PCC ($n = 98$) and compared their mortality with that predicted using injury severity scores. The authors found a significant decrease in the observed mortality when compared with the TRISS-predicted mortality (24.4% vs 33.7%; $P = .032$) but not compared with mortality that was predicted by the Revised Injury Severity Classification (RISC) score (24.4% vs 28.7%; $P > .05$) [35]. When the analysis was restricted to patients without brain injury ($n = 114$), observed mortality was significantly lower than predicted mortality using both scores [35]. This comparison of observed vs predicted mortality has limitations and is not strong support for FC, but it improves upon previous uncontrolled case reports and case series.

Table 1
Case reports about clinical use of FC in severe trauma patients with bleeding

Reference	Presenting condition	Timing of administration	Fibrinolysis monitoring/threshold level	FC (Haemocomplettan P, CSL) dose	Other blood products, coagulation factors, or antifibrinolytics	Outcome
Brenni et al [25]	1, severe blunt abdominal trauma	Hospital phase (ED and OR)	ROTEM-guided administration	16 g	RBC 7 U, tranexamic acid 1 g	Alive
Schochl et al [26]	1, high-velocity severe trauma receiving aspirin and clopidogrel	Hospital phase (ED and OR)	ROTEM-guided administration	14 g	RBC 4 U, platelets 2 bags	Alive
Schochl et al [27]	1, severely injured multiple trauma	Hospital phase (ED and OR)	ROTEM-guided administration, for FIBTEM MCF ≥ 10 mm	13 g	RBC 12 U, PCC 4000 IU	Alive
Grassetto et al [28]	1, massive hemorrhage from facial fractures	Hospital phase (ED and OR)	ROTEM-guided administration	5 g	PCC 1000 IU, platelets 2 bags, tranexamic acid 2 g, RBC 11 U, FFP 3	Alive

MCF indicates maximum clot firmness; PCC, prothrombin complex concentrate (factors II, VII, IX, and X); ED, emergency department; OR, operating room.

Table 2
Clinical studies reported and evaluating FC in trauma patients

n	Reference	n, population, study period	Study design	Fibrinolysis monitoring threshold level	FC (Haemocomplettan P, CSL) dose	Other blood products given	Outcomes	Main results	Adverse effects
1	Fenger-Eriksen et al [9]	43 patients with massive hemorrhage who received FC for hypofibrinogenemia Only 6 trauma patients	Single-center retrospective Hospital phase	Fibrinogen plasma level <2 g/L	2 g (1-5)	FFP RBC Platelets	Transfusion requirement changes in laboratory coagulation indices and blood lost 24 h before and after FC	Transfusion of RBC, FFP, and platelets were significantly reduced in the 12 h after FC compared with the 12 h before ($P < .0001$) Blood loss before FC, 4000 mL/12 h (1500-7750) vs 50 mL/12 h (0-425) after FC ($P < .05$)	3 events (including 1 unexplained death) not be entirely excluded transitory
2	Farriols Danes et al [29]	69 patients + severe plasma fibrinogen <1 g/L + life-threatening hemorrhagic disorders Only 11 trauma 2002-2005	Single-center retrospective Hospital phase	Fibrinogen plasma level <1 g/L	3.52 g (0.5-8)		Plasma fibrinogen, APTT, and PT 24 h and 72 h after FC, mortality 24 h and 7 d after FC	Effective to correct plasma fibrinogen level, APTT, and PT ($P < .001$) Association between plasma fibrinogen after FC administration and 7-d mortality in patients with acute hypofibrinogenemia	No adverse effects
3	Schochl et al [30]	80 patients in FC group vs 601 patients in FFP group ISS ≥ 16 and BE -2 mmol/L or less AIS abdomen, thorax, extremities ≥ 3 2006-2009	Single-center retrospective, not matched Comparison FC \pm PCC no FFP vs FFP only Hospital phase	TEM prolonged clotting time >1.5 times normal	6 g (3-9)	PCC 1200 (0-2400)	Platelets and RBC units requirement Mortality	RBC: 71% of patients in the FC group vs 97% in the FFP group ($P < .001$) Platelets: 9% of patients in the FC group vs 44% in the FFP group ($P < .001$) No difference in mortality	NA
4	Schochl et al [35]	131 trauma + ≥ 5 RBC units in the first 24 h, 128 received FC and 98 of them received PCC 2005-2009	Single-center retrospective Hospital phase (ED and first 24 h)	ROTEM MCF <10 mm by FibTEM	6 g (4-9) before ICU admission 7 g (5-11) in the first 24 h	Platelets, volume unknown (n = 7) FFP volume unknown (n = 12) Factor VIIa, dose unknown (n = 8) Tranexamic acid or aprotinin, dose unknown (n = 7)	Comparison of the observed mortality with the predicted mortality by TRISS and RISC	Observed mortality, 24.4% vs 33.7% for the predicted mortality by TRISS ($P = .032$), no difference when the RISC was used Subgroup without TBI (n = 114) observed mortality, 14% vs 27.8% when predicted by TRISS ($P = .0018$) and 14% vs 24.3% when predicted by RISC ($P = .014$)	NA
5	Weiss et al [32]	223 acute bleeding including 154 surgical bleed, 7 spontaneous bleed, 62 trauma bleed, 223 received FC 2008-2009	Prospective multicenter observational Hospital phase	Fibrinogen plasma level <1.45 g/L (1.10-1.87) + blood lost 2.0 L (1.4-3.0) ROTEM if available	4 g (2-4)	FFP (n = 92): 12 U (8-18) RBC (n = 93): 8 U (4-12) PCC (n = 43): 2 g (1-2.5) Tranexamic acid (n = 34): 0.5 g (1-1)	Hospital mortality	Significant correlation between plasma fibrinogen level at the end of surgery and at 24 h post-FC	3% thromboembolic complications
6	Nienaber et al [33]	36 trauma ISS ≥ 16 and BE -2 mmol/L or less upon ED admission and AIS abdomen, thorax, extremities ≥ 3 2005-2007	Retrospective double-center matched pair analysis 18 cases, FC and/or PCC without FFP; 18 controls, only FFP Matched criteria: age,	NA	FC 4 g (2-4)	RBC, platelets, and FFP in the controlled group Same plus FC and PCC 1200 IU (800-1200) in the FC/PCC group	Incidence of sepsis, MV days in ICU, ICU and hospital LOS, MOF incidence, hospital mortality, transfusion requirements of platelets, FFP, RBC	MOF in 11/18 in the FFP group vs 3/18 in the FC/PCC group ($P = .015$) Transfusion in the first 24 h: RBC units: 3 (0-5) in the FC/PCC group vs 12.5 (8-20) ($P < .005$)	No

ISS, BE, and INR	Retrospective matched-pairs analysis	NA	NA	6 h mortality, 24 h, 30-d, and hospital mortality	Platelets unit: 0 in the FC/PCC group vs 2 (1–3) ($P < .005$) No other difference
7	Wafaisade et al [31] 294 pairs (total 588 patients) Trauma + ISS ≥ 16 + at least 1 RBC + TASH score ≥ 9 2005–2010	Retrospective matched-pairs analysis 294 patients with FC and 294 without FC, matched criteria: demographics, injury, massive transfusion, FFP/RBC ratio, PCC administration	NA	RBC units: 12.8 ± 14.3 (FC ⁺) vs 11.3 ± 10.0 (FC) ($P = .2$) FFP bags: 10.6 ± 11.4 vs 8.7 ± 8.2 ($P = .07$) Platelets units: 1.2 ± 1.6 vs 1.0 ± 1.3 ($P = .3$) No difference for PCC, factor VIIa, tranexamic acid	6 h mortality 10.5% (FC ⁺) vs 16.7% ($P = .03$) No thromboembolic events in FC ⁺ group vs 3.4% ($P = .06$)
8	Innerhofer et al [34] Trauma ISS ≥ 15 , multiple blunt injury, survival for at least 24 h, and need for haemostatic agents 2005–2008	Single-center retrospective n = 66 in hemostatic agents (FC \pm PCC) group, n = 78 in FFP group (FFP \pm FC \pm PCC) Propensity score matching analysis (n = 28 pairs) Hospital phase (first 24 h)	ROTEM FIBTEM MCF <7 mm Plasma fibrinogen level <1.5–2 g/L	Coagulation parameters before and after treatment Blood products volume for the first 24 h Clinical outcomes	4 h, 6 h FIBTEM MCF, PT, platelets were higher in the FC group ($P < .05$) Less blood products transfused in the FC group (RBC: 2 U [0–6] vs 7 U [4–11], $P < .001$; and platelets 0 U [0, 0] vs 1 [0, 2], $P < .001$) No difference in clinical outcomes

ISS, Injury Severity Score; LOS, length of stay; INR, international normalized ratio; FC, fibrinogen concentrate; BE, Base excess; TASH, trauma associated severe hemorrhage; APTT, activated partial thromboplastin time; PT, prothrombin time; ROTEM, thromboelastometry; MCF, maximum clot firmness; TRISS, Trauma injury severity score; RISC, revised injury severity classification; PCC, prothrombin complex concentrate (factors II, VII, IX and X); TASH, trauma associated severe hemorrhage; NA, not available; AIS, Abbreviated injury scale; ED, emergency department; OR, operating room; FC, fibrinogen concentrate; BE, Base excess; TASH, trauma associated severe hemorrhage; APTT, activated partial thromboplastin time; PT, prothrombin time; ROTEM, thromboelastometry; MCF, maximum clot firmness; TRISS, Trauma injury severity score; RISC, revised injury severity classification; PCC, prothrombin complex concentrate (factors II, VII, IX and X); TASH, trauma associated severe hemorrhage; NA, not available; AIS, Abbreviated injury scale; ED, emergency department; OR, operating room.

3.3. Prospective observational study

The only published prospective observational study of FC to treat bleeding associated with hypofibrinogenemia and including trauma patients was performed in 28 German and Austrian hospitals over 12 months. A total of 223 patients were included, of whom 62 (28%) had trauma diagnoses. Patients had a median plasma level before FC administration of less than 1.45 g/L (IQR, 1.1–1.87) and a median blood loss of 2.0 L (IQR, 1.4–3.0). The median dose of FC administered was 4 g (IQR, 2–4), whereas a median of 37 mL/kg body weight (25–58 mL/kg) of FFP with a fibrinogen concentration of 2.7 g/L of plasma [36] was also administered. The overall hospital mortality was 27%. The authors found that plasma fibrinogen at the end of surgery and 24 hours after FC administration was significantly higher in the survivors compared with the nonsurvivors [32]. No conclusions about efficacy of FC could be generated.

Taken together, these studies provide moderate clinical evidence that FC is safe and weak evidence of possible benefit. Given its storage stability and ease of administration, FC may be especially beneficial in the early prehospital setting, but this has never been formally tested. The studies are inconclusive, heterogeneous, and insufficient to enable a meaningful meta-analysis of results to be conducted.

4. Discussion

4.1. Principal findings

This review describes the clinical studies, which have reported the use of FC in trauma patients with acute bleeding and confirmed that the current literature is limited with respect to the number and quality of the studies. The conclusions that can be drawn are similarly limited. However, 4 studies suggest that FC administration may be associated with a significant decrease in blood product requirement [9,30,33,34], and 2, with a decrease of either early mortality [31] or hospital mortality [35]. Fibrinogen concentrate administration in this population appears to be safe, as none of the studies report a significant increase in adverse events. No studies have evaluated the administration of FC in a prehospital setting. This review emphasizes the need and equipoise for randomized clinical trials evaluating the impact on patient-centered outcomes of early FC administration in trauma patients with high risk of acute coagulopathy.

4.2. Limits of available literature

Studies conducted in nontraumatic massive bleeding (including perioperative and pericardiac surgery) have suggested a potential benefit of FC [37–40]. Randomized controlled trials demonstrated that transfusion requirement was significantly reduced when FC was used as prevention or therapy of coagulopathy in cardiac surgery [37,40] or urologic surgery [39]. Fibrinogen concentrate appeared to be safe with rare immune system disorders. It is very rarely associated with thromboembolic episodes (<0.4 events per 10000 treatment episodes) [16,41,42].

In contrast to the nontrauma literature, clinical evidence for FC use in trauma patients is limited. Since the publication of the review performed by Meyer et al [23], the literature has expanded, but it has many methodological deficiencies. These include (i) only 1 study is prospective; (ii) the sample sizes are small, with only 2 studies involving more than 100 trauma patients; (iii) a high degree of heterogeneity of the comparative treatment; and (iv) heterogeneity in the measures of effect, which include clinical outcomes (6 hours, 24 hours, and hospital mortality and MOF), transfusion outcomes (volume of blood products transfused), and biological outcomes (ability to correct the coagulopathy, coagulation results). Furthermore, the available studies lack rigorous analyses, with only 4 including matched-control analysis or controlling for severity of

injury. Furthermore, no studies adjust for confounders impacting on bleeding and resuscitation volume outcomes. Methods to diagnose hypofibrinogenemia, when they were documented, varied between studies; in some cases, FC administration was based on fibrinogen plasma level with variation in the threshold [9,29,32] and, in some cases, on thromboelastography results [30,35].

4.3. Implications of this review

Fibrinogen increases clot firmness and improves survival of severely injured massively bleeding patients [43–46] and fibrinogen administration (FC, cryoprecipitate, or FFP) in the early stage of trauma bleeding control is recommended [43,45,47]. In addition, recent data suggest that early high-dose fibrinogen supplementation may benefit bleeding trauma patients [48]. Nevertheless, use of FC in trauma patients is not clearly supported by any studies. Randomized controlled trials of FC in bleeding trauma patients are required before considering implementation of unproven changes in transfusion practice. This need is urgent because some clinical practice guidelines already support FC administration in bleeding trauma patients with fibrinogen deficit [14], and FC is already routinely administered in trauma patients in some countries [49]. Randomized controlled trials are difficult to conduct after a clinical therapy has already been introduced. There are currently 2 small RCTs in progress in Austria, neither of which will definitively establish whether early administration of FC will impact on trauma patient outcome. The Reversal of Trauma Induced Coagulopathy Using Coagulation Factor Concentrates or Fresh Frozen Plasma trial (NCT01545635) compares coagulation factor concentrates (FC and/or PCC and/or factor XIII) with FFP in early hospital management of severely traumatized patients (ISS > 15) with obvious bleeding and risk of hemorrhage screened by ROTEM. This single-center phase II study, which plans to enroll 200 patients by 2014, uses Sequential Organ Failure Assessment score at 24 hours as the primary outcome. This outcome is not patient centered but has presumably been chosen because this RCT is likely to be underpowered to detect differences in 30- or 90-day mortality. The Fibrinogen Concentrate in Trauma Patients Presumed to Bleed trial (NCT01475344) is a double-blind placebo-controlled, randomized pilot study, which assesses the efficacy of prehospital administration of FC in 60 severely traumatized patients with visible significant bleeding and/or with clinical signs of internal significant bleeding. Thirty patients will receive 50 mg/kg of FC, whereas 30 will receive placebo. The primary end points will be the change in the fibrinogen polymerization measured with thromboelastometric maximum clot firmness, and a 30-day follow-up is planned. This phase 2 RCT will be underpowered to detect differences in clinical outcomes. Furthermore, neither of these RCTs includes a health-economic analysis, which is essential in understanding the cost and benefit of such an expensive therapy.

4.4. Future research

The 2 following key questions now require careful study using multisite randomized trials: (i) is FC administration superior than another source of fibrinogen (ie, cryoprecipitate) in hospital patients? and (ii) is very early FC administration at the trauma scene associated with better outcomes? Fibrinogen concentrate infusion in hospital should be based on point-of-care transfusion and coagulation management algorithms guided by viscoelastic tests, as it has been shown to be associated with a reduction of blood products requirement in nontrauma bleeding patients [21] and it is emerging as the standard to manage massively bleeding trauma patients [50]. Two commercial point-of-care devices, ROTEM and thromboelastography, rapidly detect systemic changes in *in vivo* coagulation and subsequent lysis [51]. They give complete information about the kinetics of coagulation initiation and clot growth, clot strength, and

breakdown [52]. A prospective trial comparing FC and cryoprecipitate in early hospital management of severe traumatized patients with obvious bleeding or at risk for hemorrhage screened by thromboelastography would identify which of the 2 strategies is superior. A placebo-controlled prehospital trial of FC comparing early administration of FC out of hospital to placebo would determine if early administration of fibrinogen improves trauma patient outcomes. Trial design issues that would need to be addressed include the requirement for venous access, blinding, and a simple method to identify patients at risk for coagulopathy and bleeding.

Cost-effectiveness analyses are warranted to consider health economy advantages or disadvantages of each comparator. For instance, in Australia, the cost to user of 1 g of FC is 719 Australian dollars (AUD) with a mean dose of 4 g often required (total cost of 2876 AUD), and those of 1 U of cryoprecipitate (mean volume of 40 mL per unit and concentration of fibrinogen comprised between 8 and 16 g/L) is 51 AUD for whole blood cryoprecipitate and 274 AUD for apheresis cryoprecipitate (total cost comprised between 301 and 3288 AUD) [53].

4.5. Strengths and limitations

This review is the largest systematic review focused on FC use specifically in trauma patients. The literature search has been performed to maximize its adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [24]. Randomized trials that are in progress are also presented and discussed. Nonetheless, this review has limitations. First, it focuses only on clinical studies and did not report preclinical works. It also includes 3 studies that were not restricted to trauma patients; however, we consider their inclusion as an advantage because it allows us to report the entire published evidence for FC in trauma patients.

5. Conclusions

Trauma-induced coagulopathy has been identified as an independent risk of death, and its management is an early goal of trauma therapy. Although the pathophysiology of TIC supports early replacement of fibrinogen in severely shocked trauma patients and although FC is the only product potentially available for prehospital administration, its use out of hospital has not been evaluated. The use of FC compared with other methods of fibrinogen replacement may decrease blood product requirement, hemorrhagic shock, and MOF when administered early in severe trauma patients with hypofibrinogenemia. It also appears safe. However, current clinical evidence about FC is poor and insufficient to change clinical practice in either hospital or prehospital settings. Randomized clinical trials are required.

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