

The use of fibrinogen concentrate for the management of trauma-related bleeding: a systematic review and meta-analysis

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Abstract

Haemorrhage following injury is associated with significant morbidity and mortality. The role of fibrinogen concentrate in trauma-induced coagulopathy has been the object of intense research in the last 10 years and has been systematically analysed in this review. A systematic search of the literature identified six retrospective studies and one prospective one, involving 1,650 trauma patients. There were no randomised trials. Meta-analysis showed that fibrinogen concentrate has no effect on overall mortality (risk ratio: 1.07, 95% confidence interval: 0.83-1.38). Although the meta-analytic pooling of the current literature evidence suggests no beneficial effect of fibrinogen concentrate in the setting of severe trauma, the quality of data retrieved was poor and the final results of ongoing randomised trials will help to further elucidate the role of fibrinogen concentrate in traumatic bleeding.

Keywords: fibrinogen concentrate, trauma, bleeding, mortality.

Introduction

Severe trauma is a major cause of mortality, being responsible for more than five million deaths annually worldwide¹. Uncontrolled post-traumatic bleeding is the leading cause of death among these patients and is a major challenge for trauma care providers². Blood loss that leads to an endogenous derangement of haemostasis, as well as dilutional and consumption coagulopathy complicate the control of haemorrhage in these patients. It has been estimated that about one third of all bleeding trauma patients present with a coagulopathy upon admission to hospital³. This early trauma-induced coagulopathy, which significantly worsens the patients' prognosis⁴, is nowadays a well-recognised multifactorial condition resulting from a combination of bleeding-induced shock, tissue injury-related thrombin-thrombomodulin-complex generation and the activation of anticoagulant and fibrinolytic pathways⁵⁻⁷. In this context, it is evident that the immediate correction of the acquired coagulation

disorder is one of the primary goals of the treatment protocols of trauma centres⁸. Among the various haemostatic treatments available, supplementation of fibrinogen has received growing attention in the last years^{9,10}, considering that this is the first coagulation factor to reach a critically low concentration during activation of coagulation and bleeding and its reduction is associated with a worse outcome in injured patients^{11,12}. Fibrinogen is a plasma glycoprotein synthesised by the liver which plays a critical role in haemostasis by acting as an endogenous substrate for fibrin formation and by inducing clot formation and platelet aggregation^{13,14}. Fibrinogen supplementation can be achieved using fresh-frozen plasma, cryoprecipitate or plasma-derived, virally-inactivated, fibrinogen concentrate¹⁵⁻¹⁸, with the available therapeutic approaches differing from country to country¹⁴. Traditionally, a threshold level of 1.0 g/L was established for fibrinogen supplementation in patients with congenital fibrinogen deficiency¹⁴, whereas the threshold for patients with acquired fibrinogen deficiency, including those with trauma-related coagulopathy, is still debated. In fact, with the exception of a few guidelines that indicate trigger levels of fibrinogen less than 1.5-2 g/L¹⁹⁻²¹, the previous recommendations, including the Italian Society of Transfusion Medicine and Immunohaematology (SIMTI, *Società Italiana di Medicina Trasfusionale e Immunoematologia*) guidance document¹⁷, indicate levels less than 0.8-1 g/L. Current European guidelines recommend supplementation of fibrinogen concentrate in trauma patients if significant bleeding is accompanied by viscoelastic signs of a functional fibrinogen deficit or a plasma fibrinogen level of less than 1.5-2.0 g/L (grade 1C)¹, but this recommendation appears to reflect the opinion of the panel of experts rather than being based on evidence^{22,23}. Indeed, although a number of randomised controlled trials investigating the use of fibrinogen concentrate in severe traumatic haemorrhage are currently underway, their results have not yet been published in full²⁴⁻²⁶. Moreover, the urgently needed, well-conducted, additional prospective clinical trials in bleeding patients with acquired fibrinogen deficiency

should not only focus on dosing strategies and thresholds but should also be adequately powered to detect main and secondary selected outcomes²⁷. The aim of this review is to analyse systematically the available literature evaluating the role of fibrinogen concentrate in the management of severe trauma.

Methods

Search methods

A computer-assisted literature search of the MEDLINE, EMBASE and SCOPUS electronic databases was performed to identify reports on clinical experience of the use of fibrinogen concentrate in patients with trauma. We used the search term combination "fibrinogen concentrate" and "trauma" or "bleeding". In addition, we hand-searched the reference lists of the most relevant items (original studies and reviews) in order to identify further eligible studies not captured in the initial literature search.

Study selection

Studies were selected independently by two reviewers (MF and CM), with disagreements resolved through discussion and on the basis of the opinion of a third reviewer (GML). Assessment of potential eligibility was based on the title or abstract and on the full text if required. Articles were eligible if they reported the fibrinogen concentrate used in the management of severe trauma patients. Only studies published in full in English between January 2000 and February 2017 and enrolling at least ten patients were included in this systematic review. For each study included in the systematic review, the following data were extracted by two reviewers (MF and GM) independently: study design, sample size, protocol (fibrinogen plasma level threshold, comparative group) and results (dose of fibrinogen administered, outcomes), adverse events.

Outcomes

According to the study design of the different trials, the following outcomes were considered: mortality (overall in-hospital mortality, mortality at 6 hours, mortality at 24 hours, mortality at 72 hours, mortality at 7 days, mortality at 30 days and time to death), transfusion requirements (red blood cells and platelets), laboratory coagulation parameters and clinical outcomes (sepsis, multi-organ failure, days of ventilation, duration of hospitalisation and thromboembolic events).

Statistical evaluation and meta-analysis

The study designs were reviewed and the quality of the evidence at study level was evaluated. Each study was defined as prospective or retrospective, the presence of a control arm was confirmed, and the randomisation

of the treatment allocation was determined. The control group was assessed if assigned by the experimenter, or simply observed *a posteriori* as exposure, as in cohort/observational studies. Uncontrolled studies were excluded from meta-analytical evaluation, as studies failing to set up an investigational arm treated with fibrinogen concentrate, and a control group treated otherwise. In order to proceed to meta-analytical pooling, all outcomes were reviewed and, if observed in at least three of the included studies, used as a measure of the effect of fibrinogen concentrate in a therapeutic efficacy evaluation. Any relevant binary event (e.g., death) was comparatively pooled as risk incidence (e.g., overall in-hospital mortality) in a cross-sectional way. The protective effect of fibrinogen concentrate was measured as a risk ratio with Mantel-Haenszel weighting. Heterogeneity was reported as the I-squared index.

Results

Literature search

In total, 319 articles were found after the initial electronic and manual search (Figure 1). Of these, 264 were excluded as focusing on other topics. Thus, 55 potentially relevant articles were identified and the next screening led to the exclusion of another 48 studies (case reports, case series with less than ten patients included, reviews, protocols of randomised controlled trials, studies not containing informative data). The remaining seven studies (6 retrospective and 1 prospective)²⁸⁻³⁴ were included in this systematic review (see Table I

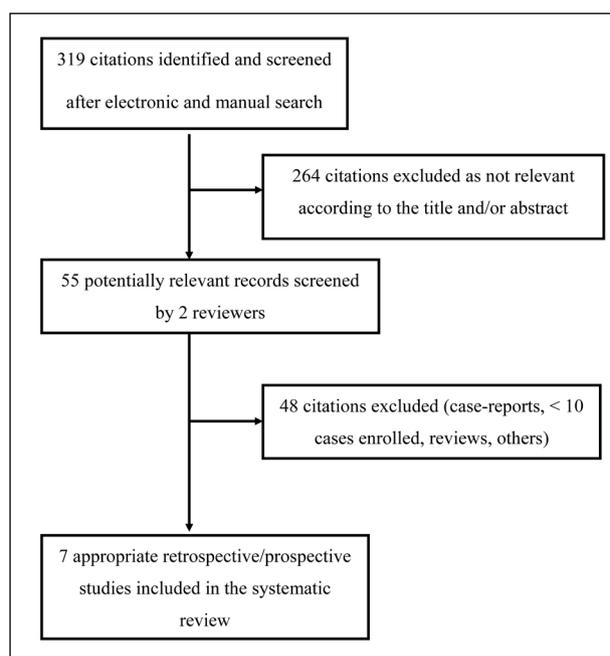


Figure 1 - Flow chart of the inclusion of the studies.

for the main characteristics and results of the studies included and the online supplementary content for a more detailed description). Overall, 1,650 trauma patients were enrolled in the seven studies evaluated²⁸⁻³⁴.

Quality assessment and outcome analysis

The quality of evidence of the seven studies evaluated was poor, according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria³⁵. All studies were retrospective, except that by Weiss *et al.*³¹. All were cohort studies, in which the treatment allocation was an observed (post-hoc) exposure, instead of a randomised controlled trial or quasi-experimental studies with predetermined eligibility criteria and prior allocation. No study was

randomised. Three studies were uncontrolled (Danes *et al.*²⁸, Schoechl *et al.*²⁹, Weiss *et al.*³¹), and were, therefore, excluded from the meta-analytic approach. The study by Innerhofer *et al.*³³ was also excluded because all patients received fibrinogen concentrate, and the investigational group received fibrinogen concentrate plus fresh-frozen plasma (so, the topic was the effect of fresh-frozen plasma). All the remaining retrospective studies (Schoechl *et al.*³⁰, Nienaber *et al.*³², Wafaisade *et al.*³⁴) depended on the German Trauma Register of *Deutschen Gesellschaft für Unfallchirurgie* (TR-DGU) and were evaluated for a possible meta-analytic approach.

The outcomes were defined in several ways (Table II). However, overall mortality was recorded in all three

Table I - Main characteristic of the studies included in the systematic review evaluating fibrinogen concentrate in trauma patients.

First author, year [ref.]	Study design	N. of patients	Trigger for administering fibrinogen concentrate	Fibrinogen dose	Outcomes	Main results
Danes, 2008 [28]	Retrospective	11	Fibrinogen level <1 g/L	Median 4 g	Mortality at 24 hours and 7 days after FC	Association between plasma fibrinogen levels and 7-day survival. No adverse effects.
Schochl, 2010 [29]	Retrospective	128	ROTEM MCF <10 mm	Median 7 g	Comparison of the observed mortality with the predicted mortality by TRISS and RISC	The observed mortality was 24.4%, lower than the TRISS-predicted mortality of 33.7% (p=0.032) and the RISC score-predicted mortality of 28.7% (p>0.05).
Schochl, 2011 [30]	Retrospective	681 (80 FC ± PCC vs 601 FFP)	ROTEM MCF <10 mm	Median 6 g	Requirements of platelets and RBC units; mortality	RBC: 71% of patients in the FC group vs 97% in the FFP group (p<0.001). Platelets: 9% of patients in the FC group vs 44% in the FFP group (p<0.001). No mortality difference.
Weiss, 2011 [31]	Prospective observational	62	Fibrinogen level <1.45 g/L, blood loss >2.0 L	4 g	Hospital mortality	Significant correlation between plasma fibrinogen level at the end of surgery and at 24 h post-FC; 3% thromboembolic complications.
Nienaber, 2011 [32]	Retrospective	36 (18 FC vs 18 FFP)	ROTEM guided	Median 4 g	Morbidity, mortality and transfusion requirements	Fewer RBC transfusions in the FC group (3 U vs 12.5 U, p<0.005). No difference in overall mortality. No FC-related thromboembolic events.
Innerhofer, 2013 [33]	Retrospective	144 (66 FC vs 78 FC + FFP)	ROTEM MCF <7 mm; fibrinogen level <1.5-2 g/L	2 g FC only; 4 g FC + FFP	Coagulation parameters before and after treatment; blood products for the first 24 hours; clinical outcomes	Fewer blood products transfused in the FC group (RBC: 2 U vs 7 U, p<0.001; platelets: 0 U vs 1 U, p<0.001). No difference in clinical outcomes.
Wafaisade, 2013 [34]	Retrospective	588 (294 with FC and 294 without FC)	NA	NA	6-hour, 24-hour, 30-day and in-hospital mortality; MOF incidence	6-hour mortality: 10.5% (FC+) vs 16.7% (p=0.03). No difference in 24-hour, 30-day, and in-hospital mortality. MOF 61.2% in the FC vs 49% in the non-FC group (p=0.003); 6.8% of thromboembolic events in FC vs 3.4% in the non-FC group (p=0.06).

ROTEM: thromboelastometry; MCF: maximum clot firmness; TRISS: Trauma Injury Severity Score; RISC: Revised Injury Severity Classification; FC: fibrinogen concentrate; FFP: fresh-frozen plasma; PCC: prothrombin complex concentrate; MOF: multi-organ failure; NA: not available; RBC: red blood cell.

Table II - Overview and outcomes evaluated in the studies included in the systematic review.

Author	Year	Target	Prospective	Controlled	Randomised	Outcomes													
						Mortality					Coag.			Requirements		Clinical			
						6 h	24 h	72 h	7 d	30 d	All	TTD	RBC	Plts	Sepsis	MOF	Vent. days	LOS	TE
Danes ²⁸	2008	FC	No	No	No	*	*	*	*	*									*
Schoechl ²⁹	2010	FC	No	No	No				*										
Schoechl ³⁰	2011	FC	No	Yes	No			*	*				*						
Weiss ³¹	2011	FC	Yes	No	No			*	*					*					*
Nienaber ³²	2011	FC	No	Yes	No			*	*				*		*	*	*	*	*
Innerhofer ³³	2013	FFP	No	Yes	No			*	*				*		*	*	*	*	*
Wafaisade ³⁴	2013	FC	No	Yes	No	*	*	*	*				*		*	*	*	*	*

*Reported. FC: fibrinogen concentrate; FFP: fresh-frozen plasma; Mortality: at 6 hours, 24 hours, 72 hours, 7 days, 30 days; All: overall mortality in hospital; TTD: time to death; RBC: red blood cell; Plts: platelets; Coag: laboratory coagulation parameters; MOF: multi-organ failure; Vent. days: ventilation days; LOS: length of stay; Adverse: adverse effects; TE: thromboembolic events.

of these studies^{30,32,34}, and meta-analytic pooling could be performed. The pooled effect of fibrinogen concentrate on overall mortality, measured as a risk ratio (RR) with Mantel-Haenszel weighting and fixed effects method, was not significant (RR 1.07, 95% confidence intervals 0.83-1.38) (Figure 2). No heterogeneity was detected by the I-squared index (0%, p=0.604). However, the range of mortality rates in control groups was broad (9.9% to 25.5%). With regards to the other outcomes of interest, it was not possible to perform meta-analytic pooling of red blood cell transfusion requirements as the three studies with this type of information (Schoechl *et al.*³⁰, Nienaber *et al.*³², Innerhofer *et al.*³³) were not comparable since Schoechl *et al.*³⁰ reported data in a binary form (i.e., the percentage of patients who avoided red blood cell transfusion), Nienaber *et al.*³² presented their data in a continuous form (i.e., the median number of red blood cell units transfused within the first 6 and 24 hours after admission), and Innerhofer *et al.*³³ evaluated fresh-frozen plasma, and not fibrinogen concentrate, as their end-point. Finally, multi-organ failure was reported by Nienaber *et al.*³² and Wafaisade *et al.*³⁴. Whereas the incidence was lower in the fibrinogen concentrate-treated group in the former study (16.7 vs 83.3%), the opposite was observed in the latter one (61.2 vs 49.0%).

Discussion

Trauma-related coagulopathy, which results from the rapid depletion of circulating coagulation factors because of consumption and blood loss, is a leading cause of mortality, being responsible for up to 40% of trauma-related deaths^{36,37}. In cases of massive traumatic bleeding, the updated European guidelines recommend first restoration of circulating volume and secondarily haemostatic measures via transfusion of blood products or pharmaceutical agents¹. In this context, the role of fibrinogen concentrate administered as immediate treatment in trauma has been investigated recently^{38,39}. In a study conducted by Schochl *et al.*²⁹ including 128 bleeding trauma patients, goal-directed coagulation management using thromboelastometry-guided administration of fibrinogen concentrate together with prothrombin complex concentrate was evaluated retrospectively. The observed mortality rate was lower in these patients than that predicted by the Trauma Injury Severity Score (TRISS) and the Revised Injury Severity Classification (RISC) score²⁹. In a subsequent retrospective study conducted by the same group, comparing blood product requirements between trauma patients treated with fibrinogen concentrate and/or prothrombin complex concentrate, but no fresh-frozen plasma, and patients receiving only fresh-frozen plasma, it was found that a significantly smaller volume of blood products was transfused in patients receiving coagulation factor

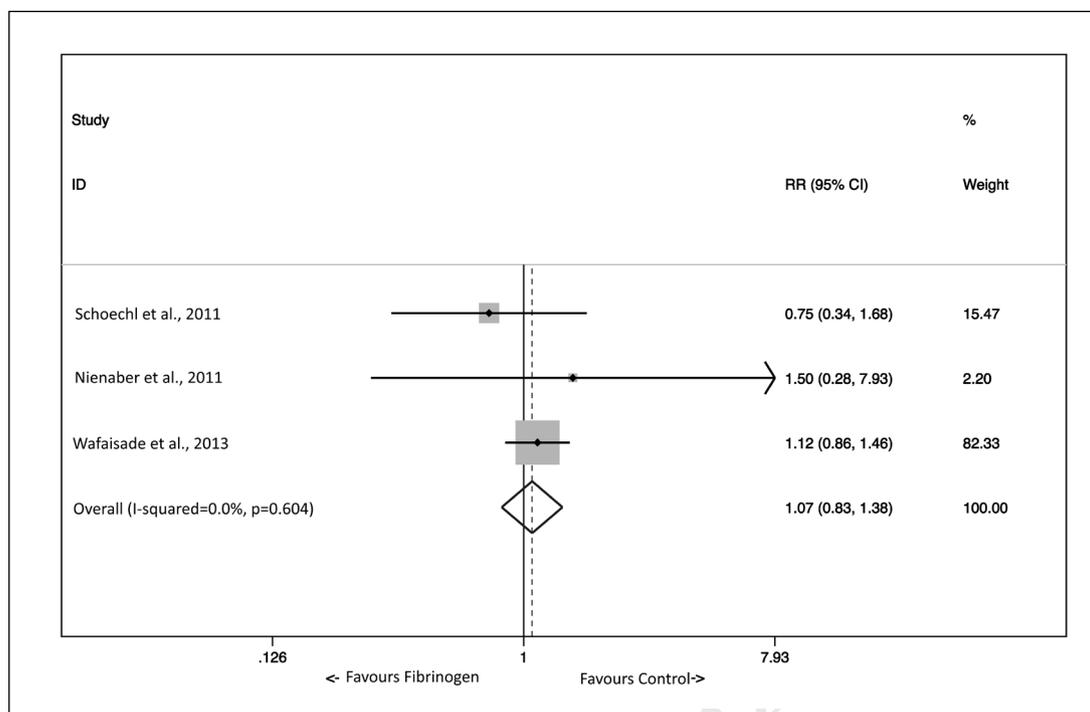


Figure 2 - Effect of fibrinogen concentrate on overall in-hospital mortality.

The effect was measured comparatively as the risk ratio (RR) in three studies amenable to meta-analytical pooling. Squares denote RR, with size proportional to the weight assigned to the study. Horizontal bars indicate 95% confidence intervals (CI) for each study. The diamond represents the aggregate effect, with the width representing the 95% confidence interval of the total effect.

concentrates³⁰. Innerhofer *et al.*³³ compared patients who received fibrinogen concentrate without fresh-frozen plasma (n=66) or fibrinogen concentrate with fresh-frozen plasma (n=78), reporting smaller volumes of blood products transfused, including red blood cells and platelets, in patients receiving only the fibrinogen concentrate. There was no difference in clinical outcomes. Propensity score-matching confirmed that additional fresh-frozen plasma administration was associated with more red blood cell and platelet transfusions without additional benefit in restoring haemostasis. A retrospective study of 294 trauma patients conducted by Wafaisade *et al.*³⁴ further evaluated whether administration of fibrinogen concentrate is associated with improved outcomes. Although 6-hour mortality was significantly reduced in the fibrinogen concentrate group, overall mortality was not significantly different between groups. In contrast to other studies, red blood cell requirement was not reduced in the fibrinogen concentrate group. The only published prospective observational study in this clinical setting is that by Weiss *et al.*³¹ in which a total of 223 patients were included, of whom 62 (28%) were trauma patients and received fibrinogen concentrate in association with fresh-frozen plasma. Interestingly, the authors found that plasma fibrinogen levels at the end of surgery and 24 hours after administration of fibrinogen concentrate

were significantly higher in the survivors than in the non-survivors.

The current evidence on the use of fibrinogen concentrate in massive bleeding associated with severe trauma is mostly restricted to retrospective analyses. Indeed, of the seven studies identified in this systematic review (Table I), only one was prospective. In addition, although a wide array of outcomes were assessed by the different studies, rendering a comparative analysis very difficult, we were able to perform a meta-analysis of three retrospective studies that evaluated the main outcome, overall mortality.

In general, although a number of studies have reported on the use of fibrinogen concentrate for the treatment and prevention of acquired bleeding, its beneficial effect is still debated, mainly because of the low quality of the published clinical evidence and the data collected seem weak and insufficient as a basis for therapeutic or prophylactic guidelines⁴⁰.

The results of our meta-analysis do not support a benefit in terms of survival from the use of fibrinogen concentrate in the setting of severe trauma. We are, however, aware of the methodological flaws of this research, mainly due to the limited amount and poor quality of the data retrieved⁴¹. Nevertheless, this is the first attempt to perform meta-analytic pooling of studies

focused on the use of fibrinogen concentrate in traumatic haemorrhage. The final results of ongoing randomised controlled trials are required to overcome the biases present in the current literature and fully elucidate the effects of fibrinogen concentrate on allogeneic blood transfusion requirements and on survival in severely injured patients. We would like to highlight, however, that the early use of the relatively inexpensive and widely available haemostatic agent, tranexamic acid, has already shown a survival benefit in this clinical context in the frame of the Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) trial^{42,43}.

Disclosure of conflicts of interest

GML is the Editor-in-Chief of Blood Transfusion and this manuscript has undergone additional external review as a result. The other Authors declare no conflicts of interest.

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