Efectividad del concentrado de fibrinógeno en pacientes traumáticos con hemorragia crítica

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Evaluation of the efficiency under current use of human fibrinogen concentrate in trauma patients with life-threatening hemorrhagic disorders

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The aim of the study was to assess the influence of fibrinogen concentrate on survival when it is used in trauma patients with life-threatening hemorrhagic disorders. Secondly, to evaluate when the fibrinogen concentrate administration maximizes its efficacy, and to describe what other concomitant treatment the patients received in order to control their life-threatening hemorrhage. Retrospective, observational, and multicenter study was carried out in three trauma areas between June 2012 and June 2014. The totality of trauma patients with a documented life-threatening hemorrhage who received a fibrinogen concentrate prescription was included in the study. Demographic and analytical data, admission diagnosis, treatment indication, fibrinogen concentrate dose, survival after 1 and 7 days, hospitalization time, and concomitant blood product treatment were collected. One hundred and twenty-three patients were finally included. The mean dose of fibrinogen concentrate administered was 2.87 g. The mean initial fibrinogen plasma level was 1.49 g/l, which rose to 2.26 g/l. The number of patients who survived after 24 h was 80.49%, and 69.11% after 7 days. Lower fibrinogen plasma levels are statistically associated with a higher probability of death after 7 days (\(P = 0.004\)). The most suitable threshold to recommend the fibrinogen concentrate administration has been found to be 1.5 g/dl (\(P = 0.006\), after 24 h; \(P = 0.032\), after 7 days). Finally, the most common concomitant treatment was the erythrocytes concentrate. A statistically significant relationship between lower fibrinogen plasma levels and a higher probability of death after 7 days has been found. Our data support the threshold of 1.5 g/l as the recommended level to administer fibrinogen concentrate in trauma patients. Blood Coagul Fibrinolysis 28:66–71

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Introduction

Uncontrolled post-traumatic bleeding is the leading cause of potentially preventable death among trauma patients, with 55% mortality. Approximately one-half of trauma patients with hemorrhage present with coagulopathy on hospital admission. The presence of an early coagulopathy makes trauma patients significantly more likely to die, to suffer from multiple organ failure, or to have a prolonged stay in hospital. Moreover, up to 20% of trauma-associated deaths are potentially preventable if blood loss and coagulopathy could be early controlled. Thus, when facing a critical hemorrhage a remarkable goal should be the early treatment and control of the coagulopathy [1–7].

The early treatment of the coagulopathy consists mainly of the rapid diagnosis and control of source of bleeding by surgical methods, and on the replacement therapy of defective clotting factors. According to the specific deficit, the replacement will involve the administration of fibrinogen concentrate, prothrombin complex concentrate (PCC), and/or fresh frozen plasma (FFP) [8–11]. Fibrinogen is a plasma glycoprotein synthesized solely by the liver, and it plays a key role for both platelet aggregation, and fibrin formation and stabilization. It has been described that low fibrinogen concentrations are associated with an increased risk of bleeding and a higher mortality. In addition, fibrinogen is usually the most vulnerable coagulation factor, reaching low critical levels during the course of a severe injury. A variety of causes for fibrinogen depletion in major trauma have been identified, such as blood loss or dilution, consumption, hyperfibrinolysis, hypothermia, and acidosis [12–15]. Fibrinogen concentrate is produced from pooled human plasma using the Cohn–Onkey cryoprecipitation procedure. The benefits of fibrinogen concentrate compared to FFP are that the concentration is standardized, its administration does not require blood matching, it is stored as a lyophilized powder at room temperature, and it can be easily reconstituted with sterile water, needing low infusion volumes (the lyophilized human
fibrinogen concentrate is typically reconstituted in 50 ml of sterile water to a final concentration of 20 g/l [12–16].

The current European Trauma Guidelines [8,17] and the Guidelines from the European Society of Anaesthesiology [9] recommend plasma fibrinogen levels in trauma patients not lower than 1.5–2.0 g/l (grade 1C). The fibrinogen concentrate administration is also recommended when a significant bleeding is accompanied by thrombelastometric signs of a functional fibrinogen deficit. FFP is also highly recommended with an initial dose of 10–15 ml/kg (grade 1B). Regarding the PCC use, it is only indicated for the emergency reversal of vitamin K-dependent oral anticoagulants and in hemophilic patients. Its ‘off-label’ use for the treatment of uncontrolled bleeding of a nonanticoagulated trauma patient is recommended with a grade 2C [10,17].

It is a common understanding that fibrinogen concentrate plays a key role in the treatment of critical hemorrhage, when it is not due to vitamin K-dependent oral anticoagulants. Thus, the fibrinogen concentrate consumption has kept increasing in our background. However, there is also suspicion that fibrinogen concentrate is not always used as the guidelines recommend.

The current study aims to assess the influence of fibrinogen on survival when it is used in trauma patients with life-threatening hemorrhagic disorders. The secondary objectives are to evaluate when the fibrinogen concentrate administration maximizes its efficacy, and to describe what other concomitant treatment the patients received in order to control their life-threatening hemorrhage.

Methods
Study design
Analytical, observational, retrospective, and multicenter study carried out in three trauma areas of three third-level trauma hospitals between June 2012 and June 2014. The three hospitals were: the Universitary Hospital of Vall d’Hebron (Barcelona), the Universitary Hospital of Bellvitge (Barcelona), and the Universitary Hospital of Virgen del Rocío (Sevilla). The study was favorably evaluated by each Institution’s Ethics Committee.

Patients were identified from pharmacy-dispensing records. The totality of trauma patients with a documented life-threatening hemorrhagic disorder who received a human fibrinogen concentrate (Riastap, CSL Behring, Bern, Switzerland) prescription were included in the study over a period of 24 months.

Parameters of evaluation
Clinical records were consulted and the data collected were as follows: demographic data, admission diagnosis, treatment indication, fibrinogen dose; plasma fibrinogen levels, activated partial thromboplastin time (aTTP), Quick time, hemoglobin, and hematocrit before and after treatment; survival after 1 and 7 days, hospitalization time, and concomitant blood product treatment.

To evaluate the efficacy of fibrinogen concentrate, the following parameters were analyzed: changes in blood tests before and after fibrinogen replacement, the mean plasma fibrinogen increase, the mean fibrinogen biological recovery, and the relationship between fibrinogen plasma levels and survival after 24 h and 7 days.

Fibrinogen analysis
Fibrinogen plasma levels were determined by an optical coagulometer, as daily clinical practice. Firstly, they were determined by a derived fibrinogen measurement. If levels were below 2 g/l, Clauss fibrinogen was used.

Statistical analysis
With regard to the statistical analysis, for descriptive purposes, data are expressed as frequencies, mean, and SD, or median and interquartile range, depending on the nature of the variable. As a general rule, the paired Student’s t test was used to compare means (Mann–Whitney U test, when necessary). The chi-square test (Fisher’s exact test, when necessary) was used to compare proportions.

The Student’s t test for paired data was used to evaluate plasma fibrinogen differences before and after administration of the drug. To evaluate the association between plasma fibrinogen concentration previous and after the treatment, and 24-h and 7-day patient survival, a logistic regression was performed.

Statistical analysis was performed using the SPSS version 15.0 (SPSS Inc., Chicago, Illinois, USA) software package. For single-outcome comparisons, the treatment effect was considered significant, if P values were 0.05 or less.

Results
A total of 140 trauma patients, having a prescription of fibrinogen concentrate (Riastap), and with a documented life-threatening hemorrhage episode or in high-risk of a severe bleeding, were identified and initially considered to be included in the study. Full evidence of fibrinogen concentrate administration and available analytic data about fibrinogen plasma levels, before and after the fibrinogen administration, according to their clinical records, was finally found and confirmed in 123 patients.

Patients’ mean age was 53 years (range 18–88), 35% were women, and 65% men. The most frequent backgrounds that led to the life-threatening hemorrhage or high risk of severe bleeding were polytraumatism (48.10%), sepsis (18.99%), and severe burns (7.59%). Among the patients, 76% underwent surgery, whereas 88% suffered from an active hemorrhage. The mean hospitalization period was 38 days (0–180 days). The percentage of patients that
survived after 24 h of follow-up was 80.49% (mortality 19.51%), and 69.11% (30.89%) survived after 7 days.

The mean dose of fibrinogen concentrate administered was 2.87 g (SD 1.69 g). Initially, fibrinogen plasma level was 1.49 g/l (SD 1.05 g/l), which rose after fibrinogen concentrate administration, to 2.26 g/l (SD 1.05 g/l). The mean absolute increase in plasma fibrinogen level was 0.61 g/l (SD 1.02 g/l), which represents an 82.86% of relative increase. The biological recovery was 106%.

Before the fibrinogen concentrate administration, hemoglobin and hematocrit were 9.79 g/dl and 29.23%, respectively. Regarding the coagulation parameters, the Quick time and aTTP were 57.55% and 50.44 s. After the fibrinogen concentrate administration, hemoglobin and hematocrit increased to 10.06 g/dl and 29.44%, without statistical significance. After 3 days, the values were maintained at 9.73 g/dl and 28.76%. Quick time and TTPA, both significantly improved to 66.72% (P = 0.006) and 42.98 s (P = 0.032). A trend to the stabilization is generally observed after 3 and 7 days (85.17% and 32.36 s after 7 days). When assessing the results, it will have to be taken into account that other blood derivate were concomitantly administered and somehow influence the hemostatic recovery.

The mean fibrinogen plasma levels before the fibrinogen concentrate administration of those who survived after 24 h was 1.59 g/dl, and 1.09 g/dl for those who died (P = 0.018). If fibrinogen plasma levels before the fibrinogen concentrate administration are compared between those who were alive after 7 days, and those who died, the difference is even greater: 1.65 and 1.13 g/dl (P = 0.003). When a logistic regression is performed, it is observed that lower fibrinogen plasma levels before the fibrinogen concentrate administration are associated with a higher risk of death at 7 days (P = 0.004).

Moreover, the logistical regression shows a statistically significant relationship between fibrinogen plasma levels after the fibrinogen concentrate administration and survival at 24 h (P = 0.024), and 7 days (P = 0.008). If fibrinogen plasma levels after the fibrinogen concentrate administration are compared between those who survived and those who died, the difference is only statistically significant after 7 days – 2.42 and 1.84 g/dl (P = 0.008), respectively.

In order to look for the most suitable threshold to recommend the fibrinogen concentrate administration, patients were classified, depending on their initial fibrinogen plasma level (< or >1 g/dl; < or >1.5 g/dl; and < or >2 g/dl). It turned out that the difference in survival between groups below and above 2 g/dl was not statistically significant (P = 0.727, after 24 h; P = 0.070, after 7 days). However, the difference was statistically significant for the threshold established at 1.5 g/dl (P = 0.006, after 24 h; P = 0.032, after 7 days). Logically, the difference between groups when the threshold is established at 1 g/dl was also statistically significant (P = 0.002, after 24 h; P = 0.097, after 7 days).

Similarly, stratification was carried out to set up a therapeutic goal for the fibrinogen concentrate administration. Patients were this time classified depending on their fibrinogen plasma level after the fibrinogen concentrate administration, and group’s survival was compared. Reaching a fibrinogen plasma level of 2.5 g/l made a statistically significant difference (P = 0.008).

The most common concomitant treatment was the erythrocytes concentrate (78.67%), followed by the administration of FFP (45%). Platelet concentrates and tranexamic acid were administered to 30.67% of the patients. PCC (29.33%) and vitamin K (9.33%) were found in fourth and fifth place, respectively. Other less frequent treatment in the critical hemorrhage was calcium chloride (8%). Fluid therapy, either crystalloids or colloids, has been considered to be under-reported as records were only found for 17.33% of the patients.

Although safety outcomes were not a specifically defined endpoint, any adverse drug reaction or thromboembolic events were recorded during the first 24 h after the fibrinogen administration.

**Discussion**

Fibrinogen is a key protein in the new ‘cell-based’ model of hemostasis that involves four consecutive overlapping stages (initiation, amplification, propagation, and stabilization), in which the conversion of fibrinogen to a covalently linked fibrin network is the final stage [18,19]. It has been observed that fibrinogen is the first coagulation factor to fall to a suboptimal level early during bleeding and dilutional coagulopathy. Thus, fibrinogen monitoring and supplementation, if necessary, is recommended in patients with massive bleeding to maintain plasma fibrinogen levels above 1.5–2.0 g/l [8–11].

The main objective of this retrospective study was to assess the influence of fibrinogen on survival when it is used in trauma patients with life-threatening hemorrhagic disorders. It has been found a significant positive correlation between survival and higher fibrinogen plasma levels after the fibrinogen concentrate administration, both after 24 h (P = 0.024), and after 7 days (P = 0.008). Moreover, lower initial fibrinogen plasma levels are statistically associated with a higher probability of death after 7 days (P = 0.004). This fact seems to support the early administration of the fibrinogen concentrate when fibrinogen plasma levels are low, in order to improve the probability of survival.

Previous studies have also established a relationship between plasma fibrinogen levels and survival in acquired fibrinogen deficiency [13,20]. Farriols-Danés et al. [13] carried out a study including all forms of
acquired severe hypofibrinogenaemia, not only trauma patients. Sixty-nine patients were included, and 62% corresponded to consumptive hypofibrinogenaemia. After a median dose of 4 g, the mean fibrinogen biological recovery was 109.1% (in the current study: 106%). When focusing on the 11 trauma patients, the initial fibrinogen plasma levels were 0.91 ± 1.35 g/l (in the current study: 1.49 ± 0.61 g/l).

According to some recent reviews [21–23], there is no universally accepted critical fibrinogen concentration in trauma patients, although the key role of fibrinogen in the control of life-threatening hemorrhages is widely accepted. British [24,25] and American [26] guidelines recommend administering fibrinogen if the concentration falls below 1 g/l. Meanwhile, the current European Trauma Guidelines [8,17], the ones from the European Society of Anaesthesiology [9], the Canadian National Advisory Committee on Blood and Blood Products [27], and Hemomas [11] recommend a plasma fibrinogen concentration in trauma patients not lower than 1.5–2.0 g/l.

In the current study a threshold for the fibrinogen concentrate administration has been pointed out to be 1.5 g/dl. This fact would support the threshold (1.5 g/l) recommended by the current European Trauma Guidelines [8,17], the ones from the European Society of Anaesthesiology [9], the Canadian National Advisory Committee on Blood and Blood Products [27], and the recently published Spanish Hemomas [11]. Apart from this, a therapeutic goal for the fibrinogen administration to reach has been suggested: 2.5 g/l.

The most common concomitant treatment was the erythrocytes concentrate (78.67%) as they need to be replaced after the critical hemorrhage. When it comes to the red line, target hemoglobin of 7–9 g/dl has been recommended (grade 1C), but the effects of the hematocrit on blood coagulation have not been fully elucidated [8–11].

The FFP (45%) is found as the second more often concomitant treatment. Typically, standard preparation FFP contains 2.0 g/l (range 0.9–3.2 g/l) of fibrinogen, as well as other pro and anticoagulant factors found in plasma, acute-phase proteins (cytokines), electrolytes, immunoglobulin, and albumin. Thus, the increase in the fibrinogen plasma levels and the improvement in the coagulation parameters should not be exclusively attributed to the fibrinogen concentrate administration.

Interestingly, FFP was more often concomitantly used with fibrinogen concentrate than PCC (45 vs. 29.33%). However, clinical guidelines for the management of critical hemorrhage are increasingly recommending the PCC off-license use as the advantages of PCC over FFP are manifold. PCCs are concentrated and have minimal effect on fluid balance (large volumes of FFP increase blood volume, dilute platelets, and red blood cells, and may overload a fragile cardiac and renal system); they are easily stored (temperatures <25 °C), and, unlike FFP, do not require special conditions (FFP requires thawing). Finally, PCCs can be administered independently of blood type (FFP requires blood-type matching) and can be administered within a short time. But the most critical benefit of PCCs is the rapid onset of effect and speed in which anticoagulation can be reversed [8–11].

The administration of platelet concentrates (30.67%) and tranexamic acid (30.67%) was found in the third place. The recommendation is generally to administer platelet concentrate to maintain the platelet count above 50 × 10⁶/platelets/l, as platelet function decreases exponentially below this point [1]. When it comes to tranexamic acid, its pros and cons have to be taken into account. On one hand, recent randomized controlled studies have shown its cost-effectiveness, whereas, on the other hand, it has been associated with hypercoagulability states and an increased tromboembolic risk in determined patients [8–11].

Although none of the patients was currently anticoagulated with oral vitamin K-dependent anticoagulant, PCC (29.33%) and vitamin K (9.33%) were found in fourth and fifth places, respectively.

In massive hemorrhage, fluid therapy also plays an essential role in restoring intravascular volume. Nevertheless, the optimal fluid resuscitation strategy has not yet been determined. The main side effect of volume resuscitation using crystalloids is dilutional coagulopathy, whereas artificial colloids such as starches and gelatins additionally impair fibrin polymerization. The controversial studies about hydroxyethyl starch that had shown a major necessity of renal replacement and a major mortality in septic, critical, or burnt patients has led some health agencies to warn about its side effects [28–32]. However, fluid therapy, either crystalloids or colloids, has been considered to be under-reported in the current study as clinical records were only found for 17.33% of the patients.

In another report, Schlimp et al. [33] studied the impact of fibrinogen concentrate alone or with PCC (±FFC) on plasma fibrinogen level and fibrin-based clot strength (FIBTEM) in major trauma. Standard coagulation tests reflected the more severe was the coagulopathy, the more complex was the haemostatic therapy administered. Total 24-h fibrinogen concentrate dose also increased with complexity of hemostatic therapy. As it has also been observed in our study, coagulation therapy based on fibrinogen concentrate was largely effective for maintaining plasma fibrinogen levels. Supranormal levels were not observed, either on single-dose or repeated dose. This might be due to the hemostatic monitorization and to the ongoing consumption at the site of injury and surgery.
Similarly to the current study, Schöchl et al. [34] investigated administration of fibrinogen concentrate as first-line hemostatic therapy in trauma patients with severe bleeding: additional PCC therapy was administered if recent coumarin intake or prolonged clotting time was observed. These treatments were guided by thromboelastometry, which is claimed to be a huge improvement in the coagulopathy diagnosis as it precisely tells what coagulation factors are missing. The observed mortality (24.4%) was compared with the theoretical mortality calculated by the Trauma Injury Severity Score (TRISS) mortality (33.7%; \( P = 0.032 \)) and the Revised Injury Severity Classification (RISC) score of 26.7% \(( P > 0.05 \)). The overall mortality of the current study was 30.89% (69.11% patients survived after 7 days).

The study was a retrospective observational one, and potential errors are inherent in this type of analysis. As a retrospective chart review was used, the data set was limited and could be subjected to bias. Moreover, patients were concomitantly transfused and received other therapies (platelets and erythrocytes concentrates, PCC, FFP, vitamin K, tranexamic acid, etc.) in addition to the fibrinogen replacement, and the exact contribution of each one cannot be determined. Finally, for future studies, it would be interesting to have a control group to compare with, as well as to collect some additional data as lactate (indirect marker of oxygen deficiency), base deficit values (indirect estimation of global tissue acidity due to the impaired perfusion), body temperature (direct marker of hypothermia), SBP (direct marker of oxygen perfusion), and fibrinogen degradation products (direct marker of fibrinogen consumption and hyperfibrinolysis).

In conclusion, a statistically significant association has been established between the lower fibrinogen plasma levels (<1.5 g/l) before the fibrinogen concentrate administration and a higher risk of death. Apart from this, reaching the therapeutic goal of 2.5 g/l after the fibrinogen concentrate administration made a statistically significant difference. Thus, the current study has supported the recommendation made by the current European Trauma Guidelines [8,17], the ones from the European Society of Anaesthesiology [9], Hemomas [11], and the Canadian National Advisory Committee on Blood and Blood Products [27], about a plasma fibrinogen concentration in trauma patients not lower than 1.5 g/l.

**Acknowledgements**

**Conflicts of interest**

C.G.-G. and J.B.M.-R. are currently doing some research on fibrinogen, and CSL Behring has economically contributed to the research project.

**References**


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