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# Fibrinogen Based Resuscitation in Trauma Induced Coagulopathy Decreases Blood-Derived Products Consumption: A Retrospective Study

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## Abstract

**Introduction:** Trauma-Induced Coagulopathy (TIC) is associated with increased early transfusion requirements, organ failure and high mortality. Fibrinogen or Fresh Frozen Plasma (FFP) based strategies are both used for its treatment. This retrospective study compares initial resuscitation strategies and its implication in consumption of (BDP) in trauma patients.

**Methods:** Observational cohort retrospective study of patients with major trauma, admitted in a tertiary Intensive Care Unit (ICU) between 2013 and 2017 that received any BDP in the first 24 hour after admission. Primary outcome was the difference of RBC and total BDP administration at 24h between groups. Secondary outcomes were the impact of each strategy on ICU mortality, ICU length of stay and acute kidney injury. Non-parametric statistical tests were applied.

**Results:** We included 104 trauma patients, 89% submitted to bleeding control surgery, with a median age of 46 (IQ: 31-62) and SAPSII of 39 (IQ: 26-51). Over the years of the study there was an increase in the use of fibrinogen use. Patients were subdivided into FFP (n=34) or fibrinogen group (n=70) according to the predominant use of each. The consumption of total BDP at 24h and RBC at 6h were lower in the fibrinogen group ($p<0.01$, $p=0.05$, respectively). There was a statistically difference in urea values at 24h ($p=0.002$), which may indicate less organ dysfunction in fibrinogen group. There was no difference in ICU mortality, although we observed an increased in ICU length in the FFP group ($p=0.01$).

**Conclusion:** Compared with FFP-based treatment, the initial management with fibrinogen concentrate may decrease the consumption of total BDP at 24h after ICU admission.

**Keywords:** Trauma-Induced Coagulopathy; Blood transfusion; Fibrinogen; Fresh Frozen Plasma

## Introduction

Severe bleeding, the leading cause of preventable death in trauma patients, has its management based on coagulopathy control and surgery. Trauma-Induced Coagulopathy (TIC) is a multifactorial entity, occurring almost universally in severe trauma [1]. TIC is associated with increased early transfusion requirements, the development of organ failure and high mortality [1]. It results from direct blood loss, hemo-dilution and increased fibrinolytic activity and is enhanced by trauma-associated mechanisms, namely, acidosis, hypothermia and hypocalcemia [2,3].

Effective and early treatment of TIC is important and affects early mortality as well as other relevant clinical endpoints. Classical treatment of TIC was anchored on massive fixed-ratios




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transfusion therapy, based on Fresh Frozen Plasma (FFP) and Red-Blood Cells (RBC) replacement [4]. Increased understanding on the role of hypofibrinogenemia in major trauma has led to the hypothesis that fibrinogen supplementation, inappropriately achieved through plasma, would be beneficial [5]. Coupled to these hypotheses, the use of goal-directed therapy based on viscoelastic methods increasingly suggested a strategy based on fibrinogen, the first coagulation factor to be affected in TIC [6]. Although plasma contains all coagulation factors, administration of plasma to bleeding patients brings no consistent correction of clot function and may dilute fibrinogen levels [7].

Thus, current treatment of TIC might be changing towards a more tailored approach, based on coagulation factors replacement. Despite these recent advances, concentrate-based recommendations for TIC management are currently supported on expert consensus and require further validation. According to some authors, such tailored concentrate-based treatment may be associated with decreased transfusion of red blood cells amongst other blood products (REF). On that behalf, we designed a real-life retrospective study to evaluate the possible overall blood derived products consumption associated with a fibrinogen-based approach.

## Methods

### Study Design

We performed an observational cohort retrospective study, using a pragmatic evaluation of real-life practice, comparing treatment strategies concerning administration of blood products in patients with major trauma between 2013 and 2017 admitted in a tertiary Intensive Care Unit (ICU) of a university teaching hospital. Trauma management in our hospital does not follow any institutional protocol and the transfusion strategy is led by the anesthesiologist, critical care physician or surgeon that receives the patient in collaboration with the Blood bank.

**Patients:** The inclusion criteria were: 1) age above 17 years old; 2) at least one blood-derived product administered; 3) admittion in the ICU due to trauma. Patients with no fibrinogen concentrate or FFP transfusion were excluded.

We collected from the electronic health record demographic variables (age, sex, height, weight), type of trauma, surgery, chronic anticoagulant therapy, critical care scores (Sequential Organ Failure Assessment [SOFA] at admission and Simplified Acute Physiology Score II [SAPS II]), consumption of blood derived products in the first 24 hours (in the first 6 hours, and in the remaining 18 hours) and laboratory variables in first 24 hours. Total blood products included red blood cells, platelets, fresh frozen plasma, fibrinogen concentrate, prothrombinic concentrate and Factor Eight Inhibitor Bypass Activity (FEIBA).

**Primary and secondary outcomes:** The primary outcome was the reduction of RBC and total Blood Products (BDP) administration according to the primary strategy of coagulation control, in the first 24 h. Secondary outcomes were the impact on mortality, ICU length of stay and acute kidney injury.

### Ethical Statement

Our study was approved by the Ethical Board of Centro Académico Médico de Lisboa, and given its retrospective nature informed consent was waived.

### Statistical Analysis

Because the hypothesis of normal distribution was not reasonable, continuous data are presented as medians with 25$^{th}$ and 75$^{th}$ Interquartile Ranges (IQRs), with comparisons between the groups performed by non-parametric tests – Kolmogrov-Smirnov. Categorical data are reported as frequencies (%) and analyzed using proportion test. Stata/SE v15.1 was used for statistical analysis. P≤0.05 was set as the statistical significance level.

## Results

A total of 224 trauma patients were admitted to the ICU during the study period, of whom 104 were included (Figure 1).

Patients included had a median age of 46 (IQ: 31-62), were mostly male (75%) and featured a median SAPSII of 39 (IQ: 26-51). 72.1% had head trauma, 53% had abdominal trauma, 41% pelvic trauma and 71% thoracic trauma, and 89% of the patients were submitted to bleeding control surgery. From the patients included 10 patients did not receive fibrinogen, 46 patients did not receive FFP and 10 did not receive red blood cell concentrate, although all patients included received at least one blood derived product. The patients included received in median 2 (IQ: 0-4) g of fibrinogen and 2 (0-4) units of FFP in the first 6 hours after hospital admission.

For each patient we divided the total number of fibrinogen units by FFP units administered in the first 6 hours and we use a cut-off of 1.0 to divide into fibrinogen (more than 1.0 in the ratio, or only fibrinogen) of FFP (less than 1.0 in the ratio or only FFP) groups. Consequently, patients were separated into predominant FFP (n= 34) or fibrinogen (n= 70) based blood product transfusion (Table 1). Interestingly, there was a bias towards a steady increase in patients included in the fibrinogen group during the five-year period of inclusion in this study [Odds ratio 2.1 (1.5-2.9) p<0.001; Figure 2]. Apart from a predominance of pelvic trauma, FFP patients' characteristics did not differ from the patients in the fibrinogen group. There was also no difference between groups regarding baseline hemoglobin level (10.0 vs 10.8 g/dL, p= 0.57), platelet level (177 vs 171 x $10^3$/L, p= 0.21) or INR (1.27 vs 1.16, p=0.09). There was however a tendency for higher baseline fibrinogen level in the fibrinogen group [130 (85-156) vs 177 (142-233) mg/dL, p= 0.06].

The consumption of blood products was studied at 6 h and 24 h (Table 2 and Figure 3). Patients in fibrinogen group received overall less total units of blood derived products (12 vs 4, P < 0.001), particularly less red blood cells (4.5 vs 2.5 units, p= 0.05) in the first 24 hours.

We then asked if either strategy could influence laboratorial values at 24 h or in fluid therapy or support with vasoactive drugs (Table 3). We found only a higher value in platelet level in the fibrinogen group [111 (95-158) vs 159 (123-211), p= 0.007] and a higher urea in the FFP group [47.5(33-52) vs 35(26-44) mg/dL, p=0.002]. Of note, there were no differences regarding maximum noradrenaline dose [0.31 (0.0-1.16) in FFP vs 0.27 (0.0-1.2) ucg/kg/min in fibrinogen group, p=0.73], lactate at 24 hours [32 (15-44) vs 22 (14-34), p= 0.12] or need for re-surgery for bleeding control (3 vs 7%, p=0.36). Although our sample size was small there was a tendency for increase in incidence of acute kidney injury (52 vs 39%, p= 0.16) and moderate to severe ARDS (14 vs 7%, p= 0.22) in FFP group.

Finally, we observed no difference in ICU mortality between groups, but we did find a significant decrease in ICU length of stay [11 (6-21) vs 5(2-14), p=0.01] in the fibrinogen group.

**Table 1**: Baseline characteristics of study population.

| | Total (n= 104) | FFP group (n= 34) | Fibrinogen group (n=70) | P |
|---|---|---|---|---|
| **Male sex, n(%)** | (74.0) | (76.5) | (72.9) | 0.69 |
| **Age (years), median (75% IQ range)** | 46 (32-62) | 50 (33-69) | 42 (30-59) | 0.19 |
| **BMI (Kg/m2), median (75% IQ range)** | 22 (21-25) | 27 (23-29) | 21 (20-23) | 0.65 |
| **Surgery, n(%)** | 93 (89.4) | 30 (88.2) | 63 (90.0) | 0.78 |
| **Re-surgery, n(%)** | 6 (6.4) | 1 (3.3) | 5 (7.9) | 0.36 |
| **Head trauma, n(%)** | 75 (72.1) | 22 (64.7) | 53 (75.7) | 0.24 |
| **Thoracic trauma, n(%)** | 74 (71.0) | 25 (73.5) | 49 (70.0) | 0.71 |
| **Abdominal trauma, n(%)** | 56 (53.8) | 20 (58.8) | 36 (51.4) | 0.48 |
| **Pelvic trauma, n(%)** | 43 (41.3) | 20 (58.8) | 32 (32.9) | 0.01 |
| **Limb trauma, n(%)** | 73 (70.2) | 25 (73.5) | 48 (68.6) | 0.60 |
| **Previous OAC, n(%)** | 2 (1.9) | 1 (3.0) | 1 (1.4) | 0.60 |
| **SOFA admission,median (75% IQ range)** | 7 (4-11) | 8 (6-11) | 6 (3-10) | 0.36 |
| **SAPSII,median (75% IQ range)** | 39 (26-51) | 39 (28-47) | 40 (24-54) | 0.43 |

FFP=fresh frozen plasma. BMI=body-mass index. OAC= Oral Anticoagulant; SAPSII =Simplified Acute Physiology Score; SOFA= Sequential Organ Failure Assessment; *Re-surgery in first 24h after the first one. ¥ missing data for 5 patients (2 in FFP and 3 in fibrinogen group)

**Table 2:** Blood products transfusions by type and total.

| Blood products/ units | FFP group (n = 34) | Fibrinogen group (n = 70) | p value |
|---|---|---|---|
| **RBC 6h** | 3 (1.75 to 6) | 2 (1 to 3) | 0.05 |
| **RBC 24h** | 1 (0 to 2) | 0 (0 to 1) | 0.127 |
| **Total RBC** | 4.5 (2 to 7.25) | 2.5 (1.75 to 4) | 0.048 |
| **Platelet** | 2 (1 to 3) | 1 (0 to 2) | 0.127 |
| **FFP 6h** | 4 (2.75 to 6) | 0 (0 to 2) | < 0.01 |
| **Fibrinogen 6h** | 4 (0 to 5.25) | 4 (3 to 5) | 0.06 |
| **Fibrinogen 24h** | 0 | 0 | 1.00 |
| **Total BDP** | 12 (7 to 19) | 4 (2 to 8.25) | < 0.01 |

Median and 25-75 % IQR are presented for each parameter. FFP=fresh frozen plasma. RBC 6h= Red blood cell transfusion in first 6 hours. RBC 24h = Red blood cell transfusion in the first 24 hours, except for the first 6 hours. Total RBC= RBC 6h + RBC 24 h; a FFP 6h= Fresh frozen plasma in first 6 hours; FFP 24h= Fresh frozen plasma, in the first 24 hours, except for the first 6 hours; Total BDP = total blood products transfusion in the first 24 hours.

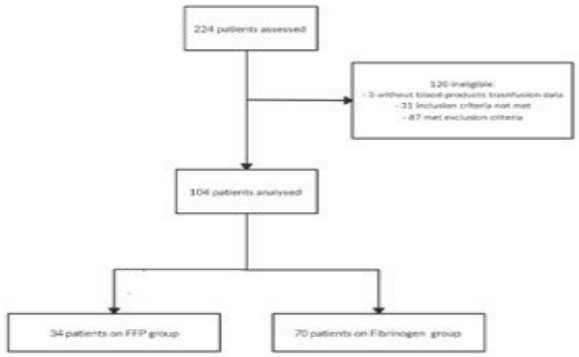


**Figure 1:** Patient inclusion fluxograma.

**Table 3:** Laboratorial values 24 hours after ICU admission.

| | Total | FFP group | Fibrinogen group | p value |
|---|---|---|---|---|
| **Lactate** | 87 | 30 | 57 | 0.118 |
| **Patients** | 22 (14.5 to 36) | 32 (14.75 to 44.25) | 22 (14 to 34) | |
| **Median (mg/dL)** | | | | |
| **APTT** | 82 | 30 | 52 | 0.092 |
| **Patients** | 29.3 (26.9 to 32.03) | 30.35 (28.4 to 32.8) | 28.75 (25.8 to 31.55) | |
| **Median (sec)** | | | | |
| **INR** | 80 | 30 | 50 | 0.18 |
| **Patients** | 1.22 (1.22 to 1.4) | 1.24 (1.14 to 1.43) | 1.22 (1.12 to 1.32) | |
| **Median** | | | | |
| **Hemoglobin** | 99 | 34 | 65 | 0.905 |
| **Patients** | 8.7 (7.8 to 9.8) | 8.5 (7.55 to 9.63) | 8.8 (8,0 to 10.1) | |
| **Median (g/dL)** | | | | |
| **Platelets** | 98 | 33 | 65 | 0.007 |
| **Patients** | 144.5 (108.75 to 192.5) | 111 (94.5 to 163) | 159 (122 to 211.5) | |
| **Median (x $10^9$/L)** | | | | |
| **Fibrinogen** | 56 | 20 | 36 | 0.095 |
| **Patients** | 251.5 (187.25 to 841) | 227.5 (148.5 to 287.5) | 279 (195.3 to 355.8) | |
| **Median (mg/dL)** | | | | |
| **Creatinine** | 89 | 30 | 59 | 0.35 |
| **Patients** | 1.10 (0.8 to 1.59) | 1.30 (0.9 to 1.725) | 1.00 (0.80 to 1.50) | |
| **Median (mg/dL)** | | | | |
| **Urea** | 96 | 34 | 62 | 0.002 |
| **Patients** | 37 (29.25 to 50.75) | 47.5 (32.75 to 52.5) | 35 (25.75 to 44) | |
| **Median (mg/dL)** | | | | |

For each variable n, median and 25-75% IQR are presented. FFP=fresh frozen plasma; APPT=activated partial thromboplastin time; INR=international normalised ratio. *Control group was 29 seconds for all patients

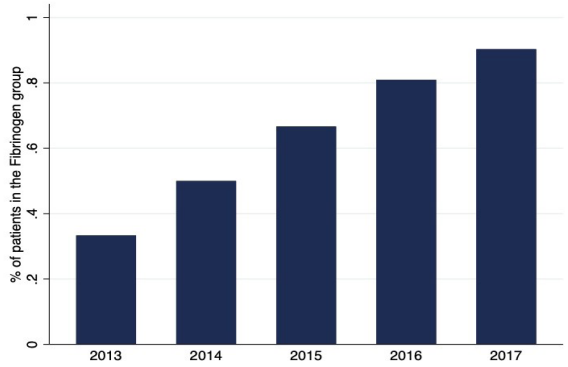


**Figure 2:** Distribution of patients by group during the 5-year study duration.

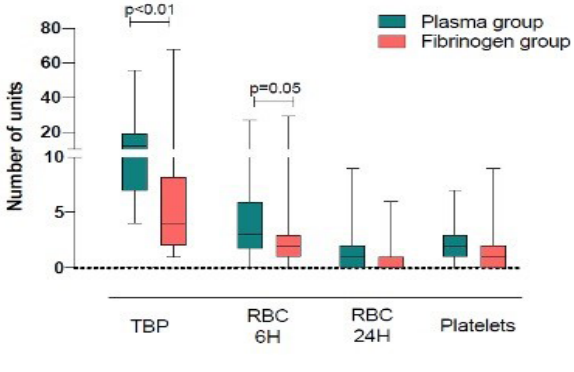


**Figure 3:** Blood products administered in the fibrinogen and FFP groups.

## Discussion

Our study was a pragmatic evaluation of daily clinical practice scenario, in which patients treated with more fibrinogen than FFP had a lower consumption of total BDP and of RBC at 6 h. Current guidelines on TIC state that in the initial management of the patients with massive hemorrhage is grounded in two strategies: FFP in a fixed FFP- RBC ratio or fibrinogen concentrate and RBC as needed [3]. Fibrinogen based strategy has its grounds on previous demonstration of fibrinogen levels lower than 1.5 g/L in as many as 73% of trauma patients with significant bleeding [8] and its independently association with higher in-hospital mortality [9], as well as on studies suggesting an increased survival associated with fibrinogen administration [10].

Despite historical understanding that early and aggressive plasma transfusion reduces mortality [11], growing evidence has highlighted the role of fibrinogen and fibrinogen-based strategies in severe traumatic bleeding. Innerhofer et al, on pivotal single-centre RCT comparing FFP to factor concentrate-based resuscitation, revealed potential harm to patients randomized to the plasma arm [12]. First-line transfusion of FFP was ineffective for early correction of bleeding and hypofibrinogenemia, leading to increased transfusion requirements. Akbari study also demonstrated that fibrinogen led to significantly less packed cells consumption [13] in a quasi-experimental randomized controlled study, in which blood products consumption between three groups (FFP, fibrinogen concentrate and control group) was studied. This has been also supported by other retrospective studies [14,15]. In a systematic review which summarized the current evidence for fibrinogen concentrate use in traumatic bleeding, fibrinogen concentrate was also associated with reduced transfusion requirements, although the quality of trails was low and with high risk of bias [16]. Nevertheless, a recent blinded, randomized, placebo-controlled trial by Curry et al. study showed no difference in transfusion requirements between arms (fibrinogen arm and placebo arm) in the first 24h [17]. There was also less platelet transfusion requirements in the fibrinogen group, without statistical significance.

Although the TIC current guidelines highlight that either previously mentioned strategy can be applied, given this uncertainty most clinicians combine both when facing a seriously ill trauma patient. Interestingly, we found a relevant change of practice over the years reflecting adaptation of still controversial evidence into clinical practice between 2013 and 2017. Although there was less blood products transfused in our study, there was no difference between groups in lactate, coagulation tests, hemoglobin, or fibrinogen levels at 24 hours. It would be perhaps more informative to compare the difference between these values and values at admission. Nonetheless, and although there is no statistically significant difference in relation to creatinine values, there a reduction in urea values in the fibrinogen group, which may suggest decreased organ dysfunction.

As in other reports, our study did not show a difference in overall mortality. Although there are some studies where decreased mortality with fibrinogen use is suggested [18], it is our belief that this outcome can hardly be considered in patients with such a complex approach (namely, type and timing of surgical interventions or different settings of pre-hospital medical rescue). Moreover, as suggested in a Cochrane systematic review the required sample size to show benefit of fibrinogen group on mortality may be as high as 10 000 [19].

Our study has several limitations. It is a single-centric study, with a small sample, a retrospective observational cohort with selection bias and missing data in laboratorial variables, with possible severe bias for some sub-group analysis. Although our study mimics what is done in real clinical practice, it is important to note both FFP and fibrinogen concentrate were mainly used in combination, which prevents us from drawing conclusions with greater relevance. Further prospective studies are needed to certain the role of fibrinogen as initial approach of TIC in severe traumatic bleeding.

## Conclusion

In conclusion, our study suggests that the use of fibrinogen over that of FFP leads to a lower consumption of total blood products, particularly RBC at 24h after ICU admission for severe trauma. It also suggests a reduction in urea at 24h and decrease ICU length of stay, possibly attesting a decrease in organ dysfunction.

## Conflict of Interest

The authors have no conflict of interest to declare.

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## Authors Contribution

GJ and SMF designed the study, analyzed data and wrote the manuscript. LC, SC and JG collected data and revised the manuscript. All authors revised and approved the final version of the manuscript.

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