Effect of Fibrinogen concentrate administration on early mortality in traumatic hemorrhagic shock: a propensity score analysis

Article *in* Journal of Trauma and Acute Care Surgery · February 2020

DOI: 10.1097/TA.0000000000002624

CITATIONS
22

READS
993

16 authors, including:

S.R Hamada
Assistance Publique – Hôpitaux de Paris
93 PUBLICATIONS **1,964** CITATIONS
SEE PROFILE

Mohammed nadjib Benlaldj
École Polytechnique
1 PUBLICATION **22** CITATIONS
SEE PROFILE

Eric Meaudre
Military Teaching Hospital Sainte Anne, Toulon
219 PUBLICATIONS **2,384** CITATIONS
SEE PROFILE

Marc Leone
Aix-Marseille University
907 PUBLICATIONS **25,531** CITATIONS
SEE PROFILE

Effect of fibrinogen concentrate administration on early mortality in traumatic hemorrhagic shock: A propensity score analysis

Sophie Rym Hamada, MD, Romain Pirracchio, MD, PhD, Jocelyn Beauchesne, Mohammed Nadjib Benlaldj, Eric Meaudre, MD, Marc Leone, MD, PhD, Julien Pottecher, MD, PhD, Paer Selim Abback, MD, Tobias Gauss, MD, Mathieu Boutonnet, MD, Fabrice Cook, MD, Delphine Garrigue, MD, Frédéric Lesache, MD, Josse Julie, Alexandra Rouquette, MD, PhD, *and* **Jacques Duranteau, MD, PhD***, Paris, France*

BACKGROUND: Fibrinogen concentrate is widely used in traumatic hemorrhagic shock despite weak evidence in the literature. The aim of the study was to evaluate the effect of fibrinogen concentrate administration within the first 6 hours on 24-hour all-cause mortality in traumatic hemorrhagic shock using a causal inference approach.

METHODS: Observational study from a French multicenter prospective trauma registry was performed. Hemorrhagic shock was defined as transfusion of four or more red blood cell units within the first 6 hours after admission. The confounding variables for the outcome (24-hour all-cause mortality) and treatment allocation (fibrinogen concentrate administration within the first 6 hours) were chosen by a Delphi method. The propensity score was specified with a data-adaptive algorithm and a doubly-robust approach with inverse proportionality of treatment weighting allowed to compute the average treatment effect. Sensitivity analyses were performed.

RESULTS: Of 14,336 patients in the registry during the study period, 1,027 in hemorrhagic shock were analyzed (758 receiving fibrinogen concentrate within 6 hours and 269 not receiving fibrinogen concentrate). The average treatment effect, expressed as a risk difference, was −0.031 (95% confidence interval, −0.084 to 0.021). All sensitivity analysis confirmed the results.

CONCLUSIONS: Fibrinogen concentrate administration within the first 6 hours of a traumatic hemorrhagic shock did not decrease 24-hour all-cause mortality. (*J Trauma Acute Care Surg.* 2020;88: 661–670. Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.)

LEVEL OF EVIDENCE: Prognostic, level III.

KEY WORDS: Trauma; hemorrhage; fibrinogen; mortality.

Fibrinogen concentrate is widely used in traumatic hemorrhagic shock[1] despite weak evidence in the literature. In vivo, fibrinogen and platelets are paramount to form a solid clot. Some experimental studies based on thromboelastometric tests[2] and a mathematical model[3] suggest that a fibrinogen level of 1.5 g/L to 2 g/L is necessary to maintain adequate hemostatic properties. A drop in plasma levels below these values is common during hemorrhagic shock, especially in case of trauma-induced coagulopathy.[4]

Trauma-induced coagulopathy reflects trauma severity and correlates with mortality. Its pathophysiology is multifactorial

Submitted: September 22, 2019, Revised: December 27, 2019, Accepted: January 19, 2020, Published online: February 14, 2020.

From the Department of Anesthesiology and Critical Care (S.R.H., J.D.), AP-HP, Bicêtre Hôpitaux Universitaires Paris-Sud, Université Paris-Sud, Le Kremlin Bicêtre; CESP (S.R.H., A.R.), INSERM, Université Paris-Sud, UVSQ, Université Paris-Saclay; CESP (S.R.H., A.R.), INSERM, Maison de Solenn; Department of Anesthesiology and Critical Care (R.M.), AP-HP, Hôpital Europeen Georges Pompidou, Universite Paris Descartes; École Polytechnique (J.B., M.N.B.), Paris; Department of Anesthesiology and Critical Care (E.M.), Military Teaching Hospital Sainte-Anne, Toulon; French Military Health Service Academy (E.M.), Ecole du Val-de-Grâce, Paris; Department of Anesthesiology and Critical Care (M.L.), AP-HM, Aix Marseille Université, Hôpital Nord, Marseille; Department of Anesthesiology and Critical Care (J.P.), Hôpitaux Universitaires de Strasbourg; Faculté de Médecine (J.P.), Fédération de Médecine Translationnelle de Strasbourg, Université de Strasbourg, Strasbourg, France; Department of Anesthesiology and Critical Care (P.S.A., T.G.), Beaujon Hospital, HUPNVS, AP-HP, Clichy; Department of Anesthesiology and Intensive Care (M.B.), Percy Military Teaching Hospital, Clamart; Department of Anesthesiology and Critical Care (F.C.), AP-HP, Hôpital Henri Mondor, Université Paris Est, Créteil; CHU Lille (D.G.), Pôle de l'Urgence, Pôle d'Anesthesie-Réanimation, Lille; Department of Anesthesiology and Critical Care (F.L.), Centre Hospitalier Universitaire Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, University Pierre et Marie Curie; CMAP (J.J.), INRIA, XPOP, École Polytechnique, Paris; Public Health and Epidemiology Department (A.R.), AP-HP, Bicêtre Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, France.

A.R. and J.D. contributed equally to this study.

Collaborators: The Traumabase Group.

Sylvain Ausset, MD (Anesthesiology and Critical Care, Hôpital Interarmées Percy, Clamart, France); Anatole Harrois, MD, PhD (Université Paris Sud and Department of Anaesthesiology and Critical Care, Hôpital Bicêtre, Groupement Hôpitaux Universitaires Paris Sud, AP-HP, Kremlin Bicêtre, France); Anne Godier, MD, PhD (Université Paris Descartes and Department of Anaesthesiology and Critical Care, Hôpital Européen Georges Pompidou, APHP, Paris, France); Thomas Geeraerts, MD, PhD (Department of Anesthesiology and Critical Care, Hospital, University Toulouse III Paul Sabatier, Toulouse, France); Jean-Luc Hanouz, MD, PhD (Hôpitaux Universitaires de Caen, Department of Anesthesiology and Critical Care, Caen, France); Catherine Paugam-Burtz, MD, PhD (Université Denis Diderot and Beaujon University Hospital, Hôpitaux Universitaires Paris Nord-Val-De-Seine, Clichy, AP-HP, France); Alain Meyer, MD (Hôpitaux Universitaires de Strasbourg, Department of Anesthesiology and Critical Care, Strasbourg, France); Jeanne Chatelon, MD (Department of Anesthesiology and Critical Care, AP-HM, Aix Marseille Université, Hôpital Nord, 13015 Marseille, France); and Mathieu Raux, MD, PhD (Sorbonne University and Department of Anesthesiology and Critical Care, AP-HP, Hôpitaux Universitaires Pitié-Salpêtrière, 47-83 Boulevard de l'Hôpital, 75013, Paris, France).

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jtrauma.com).

Address for reprints: Sophie Rym Hamada, MD, Department of Anesthesiology and Critical Care, AP-HP, Hôpitaux Universitaires Paris-Sud, Université Paris-Sud, 78 rue du Général Leclerc, 94275 Le Kremlin Bicêtre; CESP, INSERM, Université Paris-Sud; UVSQ, Université Paris-Saclay; or CESP, INSERM, Maison de Solenn, 97 Boulevard de Port-Royal, 75014 Paris, France; email: sophiehamada@hotmail.com.

DOI: 10.1097/TA.0000000000002624

combining consumption of clotting factors, dilution, activation of the fibrinolytic system, hypothermia, acidosis, platelet dysfunction, and glycocalyx alteration. All of these factors directly and primarily affect fibrinogen polymerization, leading to an early decrease in fibrinogen levels. Low plasma fibrinogen levels are predictive of bleeding risk, need for transfusion, and mortality.[5] Nevertheless, the benefit on mortality of fibrinogen administration is not established, and observational studies with low evidence grade have been conducted with conflicting results.[6] Four randomized clinical trials evaluated the feasibility of fibrinogen concentrate administration in trauma patients and its efficacy on coagulopathy, but none has formally demonstrated whether fibrinogen administration can improve the outcome.[7–10]

French[11] and European guidelines[12] have nonetheless recommended to administer fibrinogen concentrate or cryoprecipitate when plasma fibrinogen level drops below 1.5 g/L to 2 g/L (grade 2+ and 1C recommendations, respectively). These recommendations are confessed being based on weak evidence and expert opinions. Therapeutic plasma is known to have a low aptitude to increase fibrinogen levels (average of 2 g/L).[13–15] In contrast, fibrinogen concentrate has the advantage of (1) being immediately available, (2) rapidly reconstituted with no group compatibility matching needed, (3) bringing little volume avoiding further dilution, and (4) quickly restoring targeted fibrinogen concentrations (in average, 3 g is supposed to increase fibrinogen concentration of 1 g/L).[9] Nevertheless, fibrinogen concentrate remains an expensive hemostatic medication raising some ethical and pragmatic concerns, as it is not proven yet to have any impact on outcome.

Our hypothesis, strongly supported by existing literature, was that fibrinogen administration decreased the mortality of trauma patients in hemorrhagic shock. Thus, the aim of the present study was to evaluate the impact of fibrinogen concentrate administration within the first 6 hours of hospital admission on 24-hour all-cause mortality in traumatic hemorrhagic shock. Secondary objectives concerned its effect if given earlier (within the first hour) and its effect on transfusion requirements at 6 hours, multiple organ failure, intensive care unit mortality, and length of stay.

PATIENTS AND METHODS

Trauma Centers and Registry

This multicenter observational study used the data collected prospectively from a trauma registry (Traumabase, www.traumabase.eu) growingly shared between trauma centers in France. The 11 participating centers progressively joined the registry since 2011. The Traumabase obtained approval from the Advisory Committee for Information Processing in Health Research (Comite Consultatif sur le Traitement de l'Information en Recherche en Santé [CCTIRS], 11.305bis) and from the National Commission on Data Protection (Comission Nationale Informatique et Liberté [CNIL], 911461) and met the requirement of local and national ethics committee (Comité de Protection des Personnes, Paris VI). The structure of the database integrates algorithms for consistency and coherence and the data monitoring is performed by a central administrator. Sociodemographic, clinical, biological, and therapeutic data (from the prehospital phase to the discharge of intensive care unit) are systematically collected for all admitted trauma patients (200 core data and 51 data from specific modules, e.g., hemorrhagic shock). A description of the emergency medical system in France can be found in Hamada et al.[16,17]: patients transferred to the trauma rooms of trauma centers are suspected to be major trauma by the physician-staffed prehospital team. All patients transported to the trauma bays of the participating centers are included in the registry (Traumabase).

Study Population

In the registry, hemorrhagic shock was defined as transfusion of at least four red blood cell (RBC) concentrates within the first 6 hours after admission. Because no consensual definition exists in the literature, the scientific board of the registry chose this threshold to account for both intensity and volume of bleeding. This 6-hour time frame has been chosen because the patient is considered to have undergone hemostasis maneuvers and because ongoing multiple organ failure database indicates that this is the critical period that analyzes life-threatening coagulopathy and its direct effects on mortality.[18] Considering the amount of 4 RBCs, this is a compromise of Sperry et al.'s[19] 8 RBCs in 12 hours, Godier et al.'s[20] 6 RBCs in 24 hours, and massive transfusion definition (10 RBCs per 24 hours or 5 RBCs per 4 hours).[21] Thus, the validation of the registry threshold triggers a special module including 35 variables covering bleeding source, transfusion strategies, therapeutic interventions, and the worst physiological parameters over the first 24 hours, which were populated. All patients admitted into the participating trauma centers between January 2012 and March 2018 and fulfilling criteria for hemorrhagic shock were included. Patients were not included if they were younger than 16 years or if they had missing data on fibrinogen administration or mortality.

Fibrinogen Concentrate Administration and Outcome

All participating centers are invited to comply to the same guideline, published by French and European societies, recommending to give fibrinogen concentrate when plasma levels drop below 1.5 g/L to 2 g/L. Nevertheless, along trauma care, the clinical management was left to the discretion of the physician in charge. In all the centers, fibrinogen concentrate (FC) could also be given empirically, before laboratory results, according to the severity of the patient and consequent suspected coagulopathy. In France, only FC is available, while cryoprecipitate is not. A vial contains 1.5 g fibrinogen. French guidelines recommend giving a first dose of 3 g.[11] The doses of FC administration were collected during initial resuscitation in the trauma bay, then at 6 hours, and at 24 hours. For the main objective, the *treatment* was defined as any administration of fibrinogen concentrate within the first 6 hours (FC H6; binary variable) after hospital admission. *Early FC* administration (i.e., any administration of FC during the first hour of initial resuscitation) was also studied in secondary objective. Viscoelastic tests were available in three of the participating centers, and their use depended on the physician in charge and local conditions.

Outcomes

The main outcome measure was 24-hour all-cause mortality. The causal quantity targeted in this study as the primary endpoint was the average treatment effect (ATE).[22] The ATE evaluates the average effect of a treatment in a selected population

where all individuals have the same probability of receiving the treatment. It compares the effect on the chosen outcome of the treated versus the untreated patients. Secondary outcomes included the impact of early FC administration on all-cause 24-hour mortality and the impact of FC H6 on transfusion requirements at 6 hours, multiple organ failure (24-hour sequential organ failure assessment [SOFA]), intensive care unit mortality, and length of stay.

Statistical Analysis

According to the Hsieh formula[23] and supported by prior data,[24] a sample size of 1,024 (ratio treated/untreated, 2.8) was needed to detect an 8% difference in 24-hour mortality (25% vs. 17%) with an 80% power (post hoc analysis).

Continuous data were described as mean (SD) or median (quartiles 1–3) as appropriate, and categorical variables as count (percentage). To handle with missing data, we performed imputation using the factorial analysis multivariate data method (R package FactoMineR, version 1.41).

To account for confounding by indication, the ATE was estimated using the double-robust augmented inverse probability of treatment weighting estimation. The propensity score (PS) was estimated by a logistic regression model.[25] As recommended, all available confounding variables (related to treatment and outcome) and all prognostic variables (related to outcome) were selected to be introduced in the PS model.[26,27] A Delphi approach gathering 13 European experts from 6 different countries was used to identify these variables[28] (Supplemental Digital Content 1, Supplementary Table A1, http://links.lww.com/TA/B572). The retained variables were used as covariates for the PS estimation.

To verify the identifiability of the target parameter, the region of common support (PS score overlap between the treated and the untreated) was checked using Kernel density plots. The inverse probability of treatment weights (IPTW) were defined at the individual level as 1/PS in the treated and 1/(1 − PS) in the untreated. Imbalance in the covariate distribution was assessed before and after weighting using the mean standardized difference. A successful balance is inferred if residual imbalance is small for all confounders. An absolute value of 10% has been empirically considered as acceptable.[29] The double-robust augmented inverse probability of treatment weighting estimator allowed to compute ATE (expressed as risk difference) and its standard error with cross-fitting (R package grf, version 0.10.0). The doubly robust estimation combines intrinsically a regression on the outcome with a model for the exposure (the PS) to estimate the causal effect of an exposure (the treatment, FC administration) on an outcome (24-hour all-cause mortality). The same methodology was applied to assess the secondary endpoint on the effect of early FC administration. Sensitivity analyses were performed using the following methods to compute the ATE: ATE targeted PS matching, double robust methods using PS computed by nonparametric data-adaptive algorithms (random forest), and PS-adjusted logistic regression (Supplemental Digital Content 2, Supplementary Material B, http://links.lww.com/TA/B573). To evaluate the robustness of our results in relation to our definition of hemorrhagic shock, we performed sensitivity analyses for *massive transfusion* subpopulation, defined by three packed RBCs within 1 hour.[30] We also accounted for the hospital clustering effect by including the variable center in the computation of the ATE even if some hospitals included a small number of patients (Supplemental Digital Content 3, Supplementary Material C, http://links.lww.com/TA/B574) and sensitivity analyses. We performed multivariate linear regression analyses to address the effect of FC administration (H6) on transfusion requirement (adjusted on Trauma Associated Severe Hemorrhage [TASH] and Assessment of Blood Consumption [ABC] score,[31,32] tranexamic acid administration, and RBC/fresh frozen plasma [FFP] ratio), 24-hour SOFA and intensive care unit length of stay (adjusted on age, sex, head abbreviated injury severity, injury severity score, cardiac arrest, transfusion, and coagulopathy), and a multivariate logistic regression for intensive care unit mortality (adjusted on Revised Injury Severity Classification (RSC) score,[33] tranexamic acid administration, and RBC/FFP ratio). The following assumptions of linear regression were graphically checked: linearity of the relationship between the independent and the dependent variables, normality of the residuals, and homoscedasticity, and we assessed numerically the absence of multicollinearity of the variables ($r < 0.8$).

All tests were two-sided and the $p \leq 0.05$ was considered significant. The R 3.5.1 software (R Foundation for Statistical Computing, Vienna, Austria) was used for analysis.

RESULTS

Study Population

Among the 14,336 patients admitted in the participating trauma centers during the study period, 1,088 (8%) were in hemorrhagic shock and 1,027 were included for analysis (Fig. 1). Overall patients' characteristics are presented in Table 1.

Among the 1,027 patients analyzed, 758 (74%) received FC within the first 6 hours and 269 did not. Differences in patients' characteristics between the two groups are detailed in Tables 2 and 3. Imbalances in the original sample showed that patients who received FC were more severely injured, more severely bleeding, and presented with more severe hemodynamic instability and coagulopathy than the control group (Table 2). However, patients not receiving FC were older, had more comorbidities, and were receiving more coagulation targeted therapies (Tables 2 and 3). Mortality within the first 24-hour accounted for 64% (230 of 359 deaths) of the observed deaths, but they represented 90% (106 of 118 deaths) of the deaths secondary to exsanguination (Table 2).

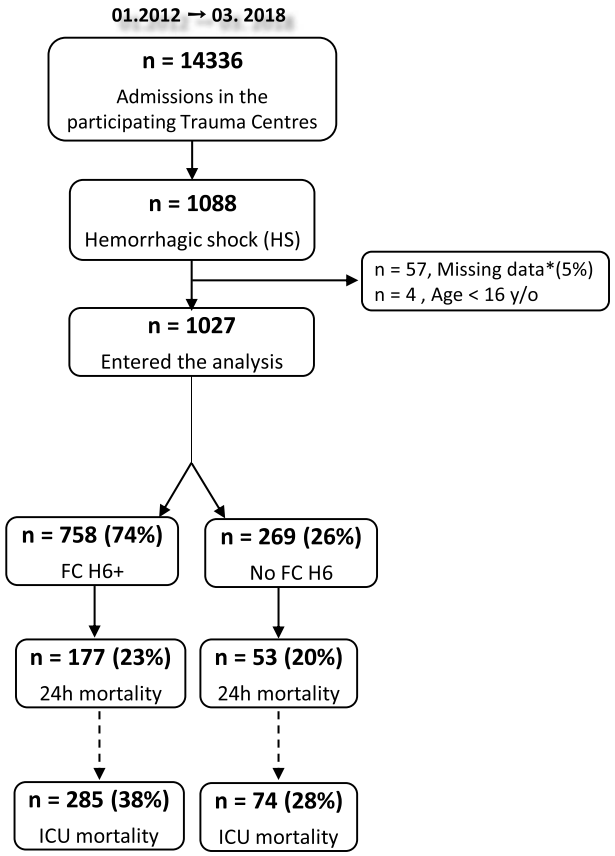
PS Weighting and Balance Measures

The Delphi process identified a total of 34 variables, and an agreement was obtained for 20 variables. These 20 variables were used to calculate the PS. Details on the Delphi process are presented in Supplemental Digital Content 1, Supplementary Table A1, http://links.lww.com/TA/B572.

Inverse probability of treatment weighting adequately balanced the major differences between the two groups (Fig. 2). After weighting, absolute mean standardized differences (MSDs) were less than 10% for all confounders (Table 3).

Primary Objective

In the original cohort, the univariate analysis showed no difference in the 24-hour mortality between patients receiving or not receiving FC within the first 6 hours (177 [23%] vs. 53 [20%] death, respectively; $p = 0.25$). After inverse probability of treatment weighting, the 24-hour mortality difference remained



* Missing on exposure (n=49), outcome (n=6) or both (n=2)

Figure 1. Flow chart of the study. *Data missing on exposure (n = 49), outcome (n = 6), or both (n = 2). No significant difference between the excluded sample with missing data (n = 57) and the analyzed sample (n = 1,027) on variables of interest except for injury severity score 27 vs. 33 ($p = 0.013$) and penetrating mechanism 25% vs. 14% ($p = 0.04$) respectively.

nonsignificant with an ATE expressed as a risk difference in day 1 mortality of −0.031 (95% CI, −0.084 to 0.021]). All sensitivity analyses used to compute the ATE showed consistent results as displayed in Table 4.

Secondary Objectives

When considering early FC administration within 1 hour of admission, 350 patients (35%) received FC, within a median delay of 40 minutes (30–54 minutes) after admission. No difference was found between the patients receiving or not early FC (ATE, −0.030; 95% CI, −0.072 to 0.012). Sensitivity analyses showed consistent results (Table 4).

Transfusion requirements are presented in Table 2. The assumptions were verified for the computed multiple linear regression models. After adjusting on potential confounders, FC administration was not associated with RBC and FFP transfusion requirements at 6 hours ($p = 0.2$ and $p = 0.16$), intensive care unit length of stay ($p = 0.97$), 24-hour SOFA ($p = 0.96$), and intensive care unit mortality ($p = 0.77$).

DISCUSSION

Fibrinogen concentrate administration is recommended by French and European societies for traumatic hemorrhagic shock resuscitation, although its impact on outcome is still unclear. This study is the first one to attempt a causal inference approach to address this question. Using a large multicenter French trauma registry, FC administration was found not to be associated with a decrease in 24-hour mortality after controlling for potential confounders.

TABLE 1. Patients Characteristics

Characteristics	All Patients (n = 1,027)	Missing Data, n (%)
Age, y	41 (19)	0 (0%)
Sex (female)	303 (30%)	0 (0%)
Mechanism: blunt trauma	884 (86%)	0 (0%)
Mechanism: penetrating	143 (14%)	0 (0%)
ASA status (≥2)	347 (37%)	93 (9.1%)
Anticoagulant or antiplatelet therapy	59 (5.7%)	0 (0%)
Prehospital management		
Lowest SAP, mm Hg	64 (34)	3 (0.3%)
Highest HR, beat/min	115 (32)	5 (0.5%)
Lowest SpO_2 (%)	95 [80–99]	12 (1.2%)
Initial Glasgow Coma Scale	14 [5–15]	15 (1.5%)
Cardiac arrest during resuscitation	240 (23%)	0 (0%)
Prehospital fluid expansion, mL	1,416 (802)	49 (4.8%)
Total prehospital time, min	81 (38)	165 (16.1%)
Trauma center with viscoelastic test	223 (22%)	0 (0%)
Initial hospital management and biology		
Body temperature, °C	34.4 (1.5)	164 (16%)
RBC transfusion in trauma bay	2 [1–4]	6 (0.6%)
FFP transfusion in trauma bay	0 [0–3]	6 (0.6%)
Noradrenaline administration	958 (94%)	2 (0.2%)
Hemoglobin, g/dL	8.7 (2.3)	4 (0.4%)
Prothrombin time ratio, %	48 (20)	57 (5.6%)
Platelets count, $10^3/mm^3$	177 (84)	41 (4%)
Blood lactate, mmol/L	6.7 (5.0)	45 (4.4%)
Fibrinogenemia, g/L	1.4 (0.8)	53 (5.2%)
Severity and scores		
Hemoperitoneum at FAST assessment	306 (33%)	105 (10.2%)
Unstable pelvic fracture	287 (28%)	9 (0.9%)
AIS head	2 [0–4]	3 (0.3%)
ISS	33 [21–43]	2 (0.2%)
RBC transfusion in the first 6 h	6 [4–9]	6 (0.6%)
FFP transfusion in the first 6 h	4 [3–8]	6 (0.6%)
Ratio FFP/RBC ≥ 1:1.5 (at 6 h)	648 (63%)	6 (0.6%)
Tranexamic acid administration	878 (87%)	18 (1.8%)
FC in the first 6 h, g	3 [0–3]	0 (0%)
Death within 24 h	230 (22%)	0 (0%)
Death during hospital stay	359 (35%)	0 (0%)

Data are expressed in mean (SD), median [quartiles 1–3] according to the variables distribution, or counts (%).

MSD, mean standardized difference; ASA, American society of anesthesiologists; SAP, systolic arterial blood pressure; HR, heart rate; SpO2, peripheral saturation in oxygen; FAST: focused assessment with sonography for trauma; AIS, Abbreviated Injury Severity; ISS, Injury Severity Score.

TABLE 2. Twenty-four Hours Transfusion Requirement, Severity Scores, and Outcome Between Patient Receiving or Not FC Within the First 6 Hours

Variables	FC H6 (n = 758)	No FC H6 (n = 269)	*p*
Within the first 6 h			
FibAT score ≥5	5.1	4.5	<0.001
RBC H6	7 [5–10]	5 [4–6]	<0.001
FFP H6	6 [4–8]	3 [2–4]	<0.001
Ratio FFP/RBC ≥ 1:1.5	513 (68%)	135 (50%)	<0.001
Ratio FFP/RBC ≥ 1:2	670 (89%)	202 (75%)	<0.001
PCU H6	1 [0–1]	0 [0–0]	<0.001
FC H6, g/L	3 [3–4.5]	—	<0.001
Ratio fibrinogen (g/L)/RBC	0.86 [0.70–1.1]	0.33 [0.25–0.50]	<0.001
Within the first 24 h			
Crystalloid infusion H24, mL	4,000 [2,500–6,500]	3,000 [1,500–5,250]	<0.001
Colloid infusion H24, mL	500 [0–1,500]	250 [0–1,000]	<0.001
RBC H24	8 [6–13]	5 [4–7]	<0.001
FFP H24	7 [4–11]	4 [2–6]	<0.001
PCU H24	1 [0–2]	0 [0–1]	<0.001
Fibrinogen H24	3 [3–6]	0 [0–0]	<0.001
rFVIIa received	22 (3%)	0 (0%)	0.01
Tranexamic acid received	680 (91%)	198 (75%)	<0.001
Lowest hemoglobin, g/dL	7.7 [6.5–8.8]	8.5 [7.4–9.7]	<0.001
Highest lactate, mmol/L	6 [4–10]	4 [3–7]	<0.001
Lowest fibrinogen, g/L	1.1 [0.7–1.5]	1.5 [1.2–1.9]	<0.001
Lowest prothrombin ratio, %	20 [27–52]	51 [42–62]	<0.001
Operative therapy	592 (78%)	195 (73%)	0.07
SOFA H24	11 [8–13]	8 [5–11]	<0.001
SAPS II	55 [40–70]	44 [34–66]	<0.001
Outcomes			
ICU LOS	7 [1–20]	5 [1–16]	0.04
Hospital LOS	19 [2–50]	19 [4–41]	0.69
24-h mortality, n (%)	177 (23%)	53 (20%)	0.21
– CNS	40 (23%)	13 (25%)	0.06
– Exsanguination	79 (45%)	27 (51%)	
– MOF	51 (29%)	7 (13%)	
– Miscellaneous	5 (3%)	6 (11%)	
After 24-h mortality, n (%)	108 (15%)	21 (8%)	<0.01
– CNS	62 (57%)	16 (76%)	<0.01
– Exsanguination	11 (10%)	1 (5%)	
– MOF	31 (29%)	1 (5%)	
– Miscellaneous	4 (4%)	3 (14%)	
Total ICU mortality, n (%)	285 (38%)	74 (28%)	<0.01

The prevalence of thromboembolic complications (deep vein thrombosis and pulmonary embolism) and acute respiratory distress syndrome was not collected in the registry.

FibAT score was from Gauss et al.[34]

Ratio fibrinogen (g/L)/RBC indicates ratio between the total amount of fibrinogen received (adding 0.5 g of fibrinogen in an FFP to the amount of fibrinogen given by FCs) divided by the number of RBC.

PCU, platelets concentrate unit; rFVIIa, recombinant activated factor VII; SAPS II, simplified acute physiologic score; ICU, intensive care unit; LOS, length of stay; CNS, central nervous system; MOF, multiple organ failure; H6, within 6 hours; H24, within 24 hours.

Previous studies have reported an association between fibrinogen levels and mortality,[5,34,35] others have shown that early fibrinogen supplementation allows maintaining higher levels of fibrinogen,[7,8] and a recent meta-analysis on the efficacy and safety of FC in surgical patients with bleeding showed a reduction in all-cause mortality in the treated group.[36] Nevertheless, the results of the present study failed to confirm a potential beneficial impact on mortality in bleeding trauma patients. The delay of FC administration may be one of the key point for a successful treatment. Indeed, the fibrinogen is among the earliest coagulation protein to drop in case of major bleeding,[37] and the fibrin strands that form in a low fibrinogen environment are more prone to fibrinolysis.[38] An existing score (the FibAT score[39]) is able to accurately predict plasma fibrinogen levels below 1.5 g/L on admission in trauma patients (combining age, heart rate, arterial pressure, lactate, capillary hemoglobin, and free fluid on ultrasound examination). This score is intended to trigger early fibrinogen administration in the centers where no viscoelastic test device (VET) is available. It might have helped physicians to administer FC before laboratory results were obtained. Nevertheless, in our cohort, the patients receiving early FC in the initial resuscitation phase, that is, within the first 40 minutes, did not demonstrate improved outcome. Another hypothesis to explain the absence of statistically significant impact of FC on mortality in our study could be the lack of power to detect a difference (confidence interval of the ATE unbalanced toward negative values). A risk difference of −0.031 means that 1 death could be avoided every 32 patients treated by FC.

It is noteworthy that, in the present cohort, FC was not administered in lieu of fresh frozen plasma (Tables 1 and 2) as in some other studies.[9] Indeed, even if the manufacturing process of therapeutic plasma leads to a decrease in the concentrations of procoagulant and anticoagulant substances (especially fibrinogen[40]), those remain balanced and plasma behaves as the physiological buffer of fibrinolysis and clotting via a whole range of proteins. Moreover, plasma has been suggested to have a protective effect on the glycocalyx, the impairment of which is associated with an increase in vascular permeability and the release of heparin-like substances, acting as anticoagulants.[41]

In the original sample, patients receiving early FC were more critically ill and presented a higher risk of death according to the Trauma Related Injury Severity Score (TRISS)-predicted mortality. Choosing the appropriate endpoint for a trauma hemorrhage study is of paramount importance. The analysis of recent high-quality prospective studies on severely bleeding trauma patients provides new evidence to support early endpoints:[42] among 1,245 patients enrolled in the Prospective, Observational, Multicenter, Major Trauma Transfusion (PROMMTT)[43] and 680 enrolled in the Pragmatic Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial,[24] 94% (89 of 95 deaths and 81 of 86 deaths, respectively) of hemorrhagic deaths occurred within 24 hours of hospital admission. In our study, 90% (106 of 118 deaths) of hemorrhagic deaths also occurred within the first 24 hours. Fibrinogen is a drug targeting some processes of trauma-induced coagulopathy, so its main impact is expected in those patients, translating into a decrease in early mortality. We chose to study *all-cause* mortality because treating coagulopathy can also benefit to patients with severe traumatic brain injury and early hemorrhage control may reduce the risk of delayed organ failure.[44]

TABLE 3. Imbalance in Patients' Characteristics Before and After Weighting by the PS

Patients' Characteristics	FC H6 (n = 758)	No FC H6 (n = 269)	Unadjusted MSD	Postweighting MSD
*Age, y	40 (18)	44 (20)	−23.7	1.2
Sex (female)	225 (29%)	78 (29%)	−0.7	2.1
*Blunt trauma	659 (87%)	225 (84%)	3.3	1.3
*ASA status (≥ 2)	241 (35%)	106 (43%)	8.5	−0.9
Anticoagulant or antiplatelet therapy	32 (4.2%)	27 (10%)	5.8	0.8
Prehospital management				
*Lowest SAP, mm Hg	62 (34)	70 (34)	54.0	3.6
Highest HR, beat/min	117 (31)	109 (33)	24.8	−15.1
Lowest SpO_2, %	94 [79–99]	96 [88–99]	−19.6	−2.7
Initial Glasgow Coma Scale	12 [4–15]	15 [8–15]	−30.5	−4.2
*Cardiac arrest during resuscitation	188 (25%)	52 (19%)	−5.4	3.1
*Prehospital fluid expansion, mL	1,467 (807)	1,275 (773)	24.8	0.0
Total prehospital time, min	82 (38)	79 (38)	12.1	−0.8
*Trauma center with viscoelastic test	180 (24%)	43 (16%)	−7.8	0.6
Initial hospital management and biology				
*Body temperature, °C	34.3 (1.6)	34.9 (1.3)	−29.6	3.3
*RBC transfusion in trauma room	3 [2–4]	2 [0–4]	24.1	2.2
*FFP transfusion in trauma room	0 [0–3]	0 [0–3]	86.0	4.3
Noradrenalin administration	725 (96%)	233 (87%)	−9.3	−3.8
*Hemoglobin, g/dL	8.4 (2.3)	9.3 (2.2)	−39.6	0.2
*Prothrombin time ratio, %	46 (20)	56 (20)	−47.7	−2.2
Platelets count, $10^3/mm^3$	170 (82)	200 (86)	−32.1	−12.1
*Blood lactate, mmol/L	7.1 (5.1)	5.3 (4.4)	32.4	−6.4
*Fibrinogenemia, g/L	1.3 (0.7)	1.7 (0.8)	−47.1	−2.0
Severity and score				
*Hemoperitoneum at FAST assessment	241 (35%)	65 (27%)	−8.5	−2.3
*Unstable pelvic fracture	233 (31%)	54 (20%)	−10.2	−3.7
*AIS head	2 [0–4]	0 [0–3]	28.2	−1.8
*ISS	34 [24–45]	25 [16–36]	46.3	−2.4
RBC transfusion in the first 6 h	7 [5–10]	5 [4–6]	75.5	−2.9
FFP transfusion in the first 6 h	6 [4–8]	3 [2–4]	86.0	1.5
*Ratio FFP/RBC ≥ 0.7 (at 6 h), %	513 (68%)	135 (50%)	−18.0	−1.7
*Tranexamic acid administration, %	680 (91%)	198 (75%)	−16.4	−0.0
Death within 24 h	177 (23%)	53 (20%)	−3.6	−5.7
Death in ICU	285 (38%)	74 (28%)		
TRISS predicted mortality	41%	28%		

*Variables used for the computation of the PS (reaching 30% agreement among Delphi experts).

Data are expressed in mean (SD), median [quartile 1–3] according to the variables distribution, or counts (%).

Noradrenalin administration follows the recommendation 14 of European guidelines on management of major bleeding and coagulopathy after trauma (fifth edition).[12]

MSD, mean standardized difference; ASA, American Society of Anesthesiologists; SAP, systolic arterial blood pressure; HR, heart rate; SpO2: peripheral saturation in oxygen; FAST, focused assessment with sonography for trauma; AIS, Abbreviated Injury Severity; ISS, Injury Severity Score; ICU, intensive care unit.

The study presents some limitations inherent to its observational design. First, the use of double-robust causal estimator allowed to control for allocation bias, but we cannot definitively rule out the existence of residual bias because of unmeasured confounders. Indeed, the PS-derived statistical approach used in this study to account for confounding by indication due to nonrandom treatment is based on a set of assumptions, the stronger being the absence of significant unmeasured confounders. This statistical approach carries several potential pitfalls at each step of the process: accurate identification of the confounders, consistent PS and treatment effect estimation.[45] In our study, we meticulously chose each step to minimize the risk of bias and model misspecification: a rigorously conducted Delphi process to identify confounders, adequate balance of the major differences between the two groups using IPTW and a PS estimated using logistic regression, and the use of a doubly robust IPTW estimator to reduce the impact of potential PS model misspecification.[46,47] Moreover, all the sensitivity analyses performed found similar results. To note, in the Delphi process, *viscoelastic test results* was the only variable reaching a 30% agreement that could not be integrated in the PS model. Indeed, only three participating centers were equipped and marginally used VET. This is consistent with what is described in the literature: between 7% and 35% of center equipped.[1,48,49] The variable *VET available* was introduced as a surrogate for VET results. A conservative approach, using every single potential

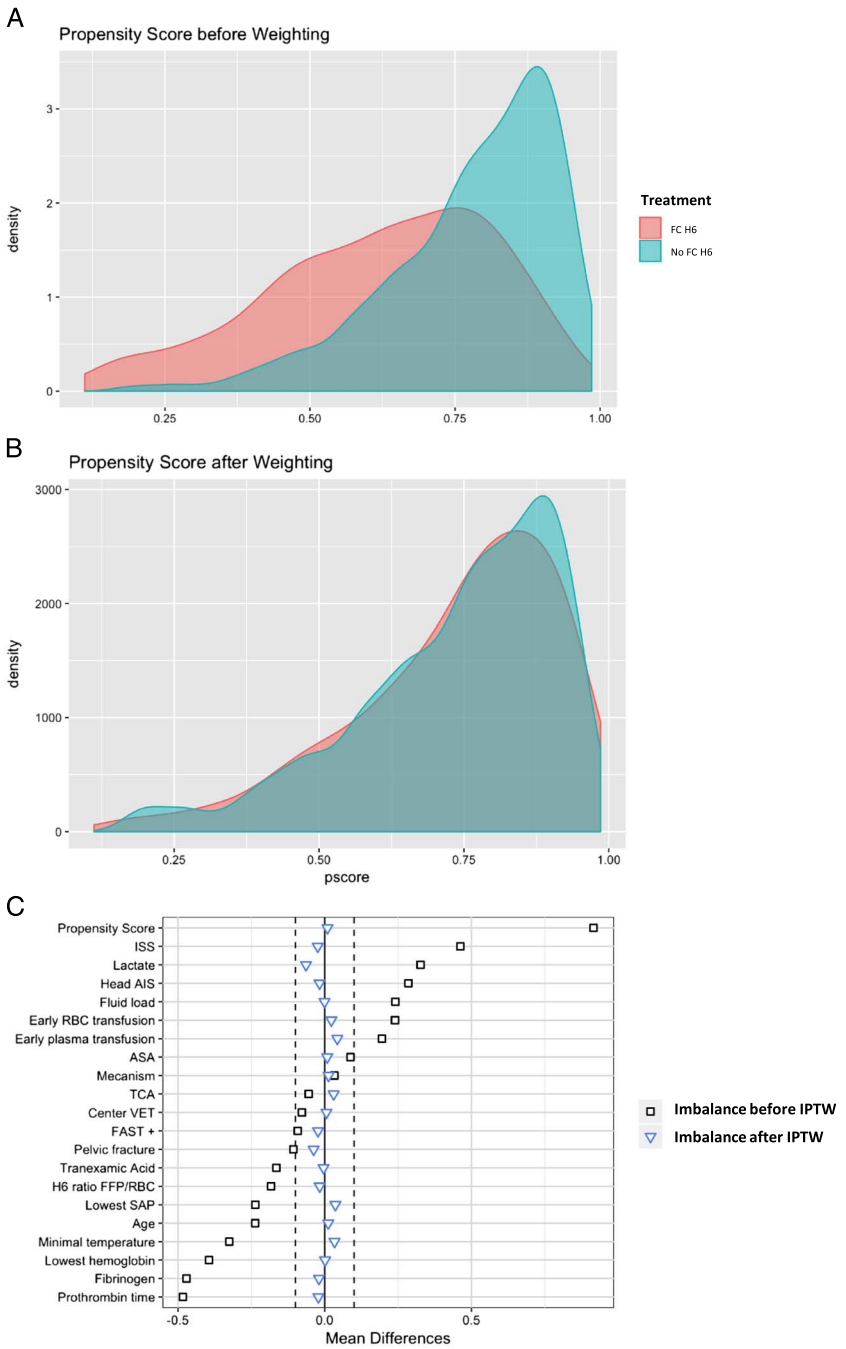


Figure 2. Propensity score common support and balancing covariates. (*A* and *B*) Propensity score common support (Kernel plots) before and after weighting by the inverse probability of treatment (IPTW). (*C*) Imbalance in patient characteristics before and after IPTW. Black squares represent imbalance before IPTW, and blue triangles represent imbalance after IPTW.

confounder listed by the experts (n = 34), even without any agreement, led to similar results (data not shown).

Second, some degree of survival bias cannot be ruled out when considering FC administration within 6 hours of hospital admission. The precise time of death within the first 24 hours was not available in the registry. Nevertheless, patients were included in the study if they had the time to receive at least four RBCs (inclusion criteria), a way to partly address the survival bias, assuming that the administration of FC would have been possible. Moreover, as a sensitivity analysis, we also estimated the impact of FC administration within the first hour and found similar results.

Third, the administration of FC was at the discretion of the physician in charge of the patient, even if based on the guidelines (Table 3). However, the design of the study is unable to prove that fibrinogen reached the targeted concentration, as the registry

TABLE 4. Sensitivity Analysis: ATE and PS Computation Using Different Methods

Statistical Method	PS	Odds Ratio	ATE	Mean SE
FC ADMINISTRATION WITHIN 6 H (PRIMARY ENDPOINT)				
n = 1,027				
Double robust AIPW	LR	—	−0.031 (−0.084 to 0.021)	0.027
Double robust AIPW	Random forest	—	−0.021 (−0.058 to 0.013)	0.020
Double robust TMLE	Random forest		−0.022 (−0.066 to 0.026)	0.023
ATE targeted matching (n = 231) Nearest neighbor, caliper 0.15	LR	—	−0.024 (−0.076 to 0.027)	0.026
Adjustment on PS	LR	0.84 (0.58–1.23)	−0.032 (−0.045 to −0.020)	0.006
FC ADMINISTRATION WITHIN 6 H (PRIMARY ENDPOINT) N = 1,027 INTERGRATING THE VARIABLE CENTER TO ACCOUNT FOR CLUSTERING EFFECT				
Double robust AIPW	Random forest	—	−0.037 (−0.078 to 0.003)	0.021
FC ADMINISTRATION WITHIN 6 H (PRIMARY ENDPOINT) MASSIVE TRANSFUSION SUBPOPULATION N = 489 (379 FC AND 110 NO FC)				
Double robust AIPW	LR	—	−0.032 (−0.120 to 0.054)	0.044
EARLY FC ADMINISTRATION* (SECONDARY ENDPOINT) N = 1,009 (359 FC AND 650 NO FC)				
Double robust AIPW	LR		−0.030 (−0.072 to 0.012)	0.021
Double robust AIPW	Random forest		−0.025 (−0.063 to 0.013)	0.020
Double robust TMLE	Random forest		−0.027 (−0.068 to 0.014)	0.021
ATE targeted matching (n = 339) Nearest neighbor, caliper 0.15	LR		−0.035 (−0.085 to 0.006)	0.023
Adjustment on PS	LR	0.88 (0.63–1.22)	−0.023 (−0.045 to −0.020)	0.005

*FC administration within the first hour of admission; imputation with Factor Analysis of Mixed Data (FAMD) (Patients and Methods section). The boxed area is our method of reference. Other specified subpopulations.

– Arrival fibrinogen of less than 1.5 g/L: 509 patients (431 FC [85%], 78 no FC [15%])

No statistical analysis of the ATE because these population are too disproportionate and some patients are fixed to a probability of 100% of receiving FC (not respecting the conditional independence and the common support validity conditions).

– First 24 h lowest fibrinogen of less than 1.5 g/L: 620 patients (510 FC [82%], 110 no FC [18%])

The calculated ATE was −0.032 (−0.118 to 0.054) with SE of 0.043.

LR, logistic regression; AIPW, augmented inverse propensity weighting; TMLE, targeted maximum likelihood estimates.

only recorded initial fibrinogen concentration and lowest concentration during the first 24 hours (Tables 2 and 3).

Finally, the study took place in French trauma centers, where patients are initially transported by physician-manned emergency medical system and hospital resuscitation is performed by anesthesiologists. These results might not be transposable to a different system. Nevertheless, the 11 participating centers are located all over the national territory, with different local case mix and practices. Unfortunately, the data on venous thromboembolism and acute respiratory distress syndrome were not included in the registry to allow the corresponding analysis.

Finally, we do believe that there is an urgent need for a prospective clinical trial on the administration of FC in trauma-related hemorrhagic shock. We would recommend performing a randomized controlled trial on a selected population of trauma patients with hemorrhagic shock and trauma-induced coagulopathy, presenting already with fibrinogen concentration of less than 1.5 g/L. This population could be targeted by a score (e.g., FibAT score), viscoelastic testing, or immediately available laboratory fibrinogen concentration measurements (or a combination of these criteria). The dose of fibrinogen administered should be higher than the previous study to be able to correct immediately and, over time, the patients' fibrinogen concentration.

CONCLUSION

The present study showed that FC administration within the first 6 hours of a traumatic hemorrhagic shock did not detect any decrease in all-cause 24-hour mortality.

The conflicting body of evidence in the literature raises questions on the proper way to use FCs. Since it is an expensive drug, certainly associated with a strong physiological rationale, but so far lacking of robust scientific evidence, this study is again advocating the urgent need for a prospective clinical trial on the administration of fibrinogen in trauma-related hemorrhagic shock.

AUTHORSHIP

S.R.H. contributed in the study design, data collection, data analysis and interpretation, literature search, and writing. R.P. contributed in the data collection, data analysis, interpretation, writing, and critical revision. T.G. contributed in the study design, data collection, literature search, and writing. J.B. and M.N.B. contributed in the statistical analysis and interpretation.

D.G., P.S.A., M.B., F.C., F.L., E.M., J.P., and M.L. contributed in the data collection, study design, and critical revision. A.R. contributed in the data analysis and interpretation, critical revision, and writing. J.D. contributed in the study design, literature search, writing, and critical revision. Traumabase Group contributed in the data collection and critical revision. The Traumabase registry has provided all the data used. All the authors and the Traumabase Group are responsible for the scientific content. The final version of the article has been validated by all the authors and the Traumabase Group.

ACKNOWLEDGMENTS

We thank Stefan Wager, PhD, assistant professor of Operations, Information, and Technology at the Stanford Graduate School of Business (San Francisco, CA), for his mathematical and statistical input in dealing with causal inference and Simon Quantin, economist in Institut National des Statistiques et des Etudes Economiques (Montrouge, France), for his expertise in applied statistics.

We also thank the following Delphi experts: Sylvain Ausset, MD (Anesthesiology and Critical Care, Hôpital Interarmées Percy, Clamart, France); Maria Gracia Bocci, MD (Fondazione Policlinico Universitario A. Gemelli, IRCCS, Unità di Rianimazione, Terapia Intensiva e Tossicologia—Dipartimento di Emergenza, Roma Italia); Mathieu Boutonnet, MD (Department of Anesthesiology and Intensive Care, Percy Military Teaching Hospital, Clamart, France); Emiliano Cingolani, MD (UOSD Shock Trauma, Azienda Ospedaliera San Camillo Forlanini, Rome, Italy); Ross Davenport, MD, PhD (consultant trauma and vascular surgeon at the Royal London Major Trauma Centre, Bart's Health NHS Trust, London, United Kingdom); Jean-Stephane David, MD, PhD (Département d'anesthesie reanimation, Hospices civils de Lyon, Hôpital Edouard Heriot, Lyon, France); Martin Duenser MD, PhD (Department of Anesthesiology and Intensive Care Medicine, Kepler University Hospital, Linz, Austria); Samy Figueiredo, MD, PhD (Université Paris Sud and Department of Anaesthesiology and Critical Care, Hôpital Bicêtre, Groupement Hôpitaux Universitaires Paris Sud, AP-HP, Kremlin Bicêtre, France); Christina Gaarder, MD (Department of Traumatology, Oslo University Hospital, University of Oslo, Ulleval, Norway); Delphine Garrigue, MD (CHU Lille, Pôle de l'Urgence, Pôle d'Anesthesie-Réanimation, F-59000 Lille, France); Frederic Lesache, MD (Department of Anesthesiology and Critical Care, Centre Hospitalier Universitaire Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, University Pierre et Marie Curie, Paris, France); Marc Maegele (Department of Orthopedic Surgery, Trauma Surgery, and Sports Medicine, Cologne Merheim Medical Center, Witten/Herdecke University, Cologne, Germany); and Nils Oddovar Skaga (Division of Emergencies and Critical Care, Department of Anaesthesiology, Oslo University Hospital Ullevål, Oslo, Norway).

DISCLOSURE

S.R.H. reports grants and personal fees from Laboratoire Francais du Biomedicament and Octapharma, outside the submitted work (lecture on trauma leader). J.P. reports grants from Laboratoire Francais du Biomedicament, Baxter, Getinge, and Haemonetics, during the conduct of the study, and grants from Baxter, outside the submitted work. T.G. reports personal fees from Laboratoire Francais du Biomedicament, outside the submitted work. F.L. reports personal fees from Laboratoire Francais du Biomedicament, outside the submitted work. E.M. reports other from Laboratoire Francais du Biomedicament, outside the submitted work. M.L. reports personal fees from Aguettant, Octapharma, MSD, Amomed, and Pfizer, outside the submitted work. D.G. reports grants and personal fees from Laboratoire Francais du Biomedicament and Octapharma, outside the submitted work. J.D. reports other from Laboratoire Francais du Biomédicament and Fresenius, outside the submitted work. All authors stated that the fees they received from Octapharma and Laboratoire Français du Biomédicament, both corporations that manufacture FC, were for lectures and conferences. The Traumabase has been sponsored by the Regional Health Agency of Ile de France for the years 2014 to 2018.

REFERENCES

1. Hamada SR, Gauss T, Pann J, Dünser M, Leone M, Duranteau J. European trauma guideline compliance assessment: the ETRAUSS study. *Crit Care*. 2015;19(1):423.
2. Bolliger D, Szlam F, Molinaro RJ, Rahe-Meyer N, Levy JH, Tanaka KA. Finding the optimal concentration range for fibrinogen replacement after severe haemodilution: an in vitro model. *Br J Anaesth*. 2009;102(6):793–799.
3. Bouzat P, Ageron FX, Charbit J, Bobbia X, Deras P, Nugues JBD, Escudier E, Marcotte G, Leone M, David JS. Modelling the association between fibrinogen concentration on admission and mortality in patients with massive transfusion after severe trauma: an analysis of a large regional database. *Scand J Trauma Resusc Emerg Med*. 2018;26:55.
4. McQuilten ZK, Wood EM, Bailey M, Cameron PA, Cooper DJ. Fibrinogen is an independent predictor of mortality in major trauma patients: a five-year statewide cohort study. *Injury*. 2017;48(5):1074–1081.
5. Rourke C, Curry N, Khan S, Taylor R, Raza I, Davenport R, Stanworth S, Brohi K. Fibrinogen levels during trauma hemorrhage, response to replacement therapy, and association with patient outcomes: fibrinogen levels during trauma hemorrhage. *J Thromb Haemost*. 2012;10(7):1342–1351.
6. Mengoli C, Franchini M, Marano G, Pupella S, Vaglio S, Marietta M, Liumbruno GM. The use of fibrinogen concentrate for the management of trauma-related bleeding: a systematic review and meta-analysis. *Blood Transfus*. 2017;15(4):318–324.
7. Curry N, Rourke C, Davenport R, et al. Early cryoprecipitate for major haemorrhage in trauma: a randomised controlled feasibility trial. *Br J Anaesth*. 2015;115(1):76–83.
8. Nascimento B, Callum J, Tien H, et al. Fibrinogen in the initial resuscitation of severe trauma (FiiRST): a randomized feasibility trial. *Br J Anaesth*. 2016;117(6):775–782.
9. Innerhofer P, Fries D, Mittermayr M, et al. Reversal of trauma-induced coagulopathy using first-line coagulation factor concentrates or fresh frozen plasma (RETIC): a single-centre, parallel-group, open-label, randomised trial. *Lancet Haemat*. 2017;4(6):e258–e271.
10. Curry N, Foley C, Wong H, et al. Early fibrinogen concentrate therapy for major haemorrhage in trauma (E-FIT 1): results from a UK multi-centre, randomised, double blind, placebo-controlled pilot trial. *Crit Care*. 2018;22(1):164.
11. Duranteau J, Asehnoune K, Pierre S, Ozier Y, Leone M, Lefrant J-Y. Recommandations sur la réanimation du choc hémorragique. *Anesthésie & Réanimation*. 2015;1(1):62–74.
12. Spahn DR, Bouillon B, Cerny V, et al. The European guideline on management of major bleeding and coagulopathy following trauma: fifth edition. *Crit Care*. 2019;23(1):98.
13. Ponschab M, Schöchl H, Gabriel C, Süssner S, Cadamuro J, Haschke-Becher E, Gratz J, Zipperle J, Redl H, Schlimp CJ. Haemostatic profile of reconstituted blood in a proposed 1:1:1 ratio of packed red blood cells, platelet concentrate and four different plasma preparations. *Anaesthesia*. 2015;70(5):528–536.
14. Kozek-Langenecker S, Sørensen B, Hess JR, Spahn DR. Clinical effectiveness of fresh frozen plasma compared with fibrinogen concentrate: a systematic review. *Crit Care*. 2011;15(5):R239.
15. Schöchl H, Nienaber U, Hofer G, Voelckel W, Jambor C, Scharbert G, Kozek-Langenecker S, Solomon C. Goal-directed coagulation management of major trauma patients using thromboelastometry (ROTEM)-guided administration of fibrinogen concentrate and prothrombin complex concentrate. *Crit Care*. 2010;14(2):R55.
16. Hamada SR, Gauss T, Duchateau F-X, Truchot J, Harrois A, Raux M, Duranteau J, Mantz J, Paugam-Burtz C. Evaluation of the performance of French physician-staffed emergency medical service in the triage of major trauma patients. *J Trauma Acute Care Surg*. 2014;76(6):1476–1483.
17. the Traumabase® Group, Hamada SR, Rosa A, Gauss T, et al. Development and validation of a pre-hospital "Red Flag" alert for activation of intra-hospital haemorrhage control response in blunt trauma. *Crit Care*. 2018;22(1):113.
18. Kashuk JL, Moore EE, Johnson JL, Haenel J, Wilson M, Moore JB, Cothren CC, Biffl WL, Banerjee A, Sauaia A. Postinjury life threatening coagulopathy: is 1:1 fresh frozen plasma:packed red blood cells the answer? *J Trauma Injury, Infect Crit Care*. 2008;65(2):261–271.
19. Sperry JL, Ochoa JB, Gunn SR, et al, Inflammation the host response to injury investigators. An FFP:PRBC transfusion ratio >/=1:1.5 is associated with a lower risk of mortality after massive transfusion. *J Trauma*. 2008;65(5):986–993.

20. Godier A, Bacus M, Kipnis E, Tavernier B, Guidat A, Rauch A, Drumez E, Susen S, Garrigue-Huet D. Compliance with evidence-based clinical management guidelines in bleeding trauma patients. *Br J Anaesth*. 2016; 117(5):592–600.
21. Mitra B, Cameron PA, Gruen RL, Mori A, Fitzgerald M, Street A. The definition of massive transfusion in trauma: a critical variable in examining evidence for resuscitation. *Eur J Emerg Med*. 2011;18(3):137–142.
22. Pirracchio R, Carone M, Rigon MR, Caruana E, Mebazaa A, Chevret S. Propensity score estimators for the average treatment effect and the average treatment effect on the treated may yield very different estimates. *Stat Methods Med Res*. 2016;25(5):1938–1954.
23. Hsieh FY, Bloch DA, Larsen MD. A simple method of sample size calculation for linear and logistic regression. *Stat Med*. 1998;17(14):1623–1634.
24. Holcomb JB, Tilley BC, Baraniuk S, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. *JAMA*. 2015;313(5): 471–482.
25. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70(1):41–55.
26. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer T. Variable selection for propensity score models. *Am J Epidemiol*. 2006; 163(12):1149–1156.
27. Caruana E, Chevret S, Resche-Rigon M, Pirracchio R. A new weighted balance measure helped to select the variables to be included in a propensity score model. *J Clin Epidemiol*. 2015;68(12):1415–1422.e2.
28. Hsu C-C, Sandford BA. The Delphi technique: making sense of consensus. *Pract Assess Res Eval*. 2007;12(10):1–8.
29. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. *Stat Med*. 2015; 34(28):3661–3679.
30. Savage SA, Zarzaur BL, Croce MA, Fabian TC. Redefining massive transfusion when every second counts. *J Trauma Acute Care Surg*. 2013;74(2): 396–400 -402, 402.
31. Yücel N, Lefering R, Maegele M, et al. Trauma Associated Severe Hemorrhage (TASH)-Score: probability of mass transfusion as surrogate for life threatening hemorrhage after multiple trauma. *J Trauma*. 2006;60(6): 1228–1236, 1237, 1237.
32. Nunez TC, Voskresensky IV, Dossett LA, Shinall R, Dutton WD, Cotton BA. Early prediction of massive transfusion in trauma: simple as ABC (assessment of blood consumption)? *J Trauma*. 2009;66(2):346–352.
33. Lefering R, Huber-Wagner S, Nienaber U, Maegele M, Bouillon B. Update of the trauma risk adjustment model of the TraumaRegister DGU™: the Revised Injury Severity Classification, version II. *Crit Care*. 2014;18(5):476.
34. Inaba K, Karamanos E, Lustenberger T, Schöchl H, Shulman I, Nelson J, Rhee P, Talving P, Lam L, Demetriades D. Impact of fibrinogen levels on outcomes after acute injury in patients requiring a massive transfusion. *J Am Coll Surg*. 2013;216(2):290–297.
35. Schöchl H, Forster L, Woidke R, Solomon C, Voelckel W. Use of rotation thromboelastometry (ROTEM) to achieve successful treatment of polytrauma with fibrinogen concentrate and prothrombin complex concentrate. *Anaesthesia*. 2010;65(2):199–203.
36. Fominskiy E, Nepomniashchikh VA, Lomivorotov VV, Monaco F, Vitiello C, Zangrillo A, Landoni G. Efficacy and safety of fibrinogen concentrate in surgical patients: a meta-analysis of randomized controlled trials. *J Cardiothorac Vasc Anesth*. 2016;30(5):1196–1204.
37. Chambers LA, Chow SJ, Shaffer LET. Frequency and characteristics of coagulopathy in trauma patients treated with a low- or high-plasma-content massive transfusion protocol. *Am J Clin Pathol*. 2011;136(3):364–370.
38. Raza I, Davenport R, Rourke C, et al. The incidence and magnitude of fibrinolytic activation in trauma patients. *J Thromb Haemost*. 2013;11(2):307–314.
39. Gauss T, Campion S, Kerever S, Eurin M, Raux M, Harrois A, Paugam-Burtz C, Hamada S. Fibrinogen on Admission in Trauma score: early prediction of low plasma fibrinogen concentrations in trauma patients. *Eur J Anaesthesiol*. 2018;35(1):25–32.
40. Hiippala ST, Myllylä GJ, Vahtera EM. Hemostatic factors and replacement of major blood loss with plasma-poor red cell concentrates. *Anesth Analg*. 1995;81(2):360–365.
41. Ostrowski SR, Johansson PI. Endothelial glycocalyx degradation induces endogenous heparinization in patients with severe injury and early traumatic coagulopathy. *J Trauma Acute Care Surg*. 2012;73(1):60–66.
42. Fox EE, Holcomb JB, Wade CE, Bulger EM, Tilley BC. Earlier endpoints are required for hemorrhagic shock trials among severely injured patients. *Shock*. 2017;47(5):567–573.
43. Holcomb JB, del Junco DJ, Fox EE, et al. The Prospective, observational, multicenter, major trauma transfusion (PROMMTT) study: comparative effectiveness of a time-varying treatment with competing risks. *JAMA Surg*. 2013;148(2):127–136.
44. Dutton RP, Stansbury LG, Leone S, Kramer E, Hess JR, Scalea TM. Trauma mortality in mature trauma systems: are we doing better? An analysis of trauma mortality patterns, 1997-2008. *J Trauma*. 2010;69(3):620–626.
45. Lederer DJ, Bell SC, Branson RD, et al. Control of confounding and reporting of results in causal inference studies. Guidance for authors from editors of respiratory, sleep, and critical care journals. *Ann Am Thorac Soc*. 2019;16(1):22–28.
46. Robins JM, Rotnitzky A, Zhao LP. Estimation of regression coefficients when some regressors are not always observed. *J Am Stat Assoc*. 1994; 89(427):846–866.
47. Wager S, Athey S. Estimation and inference of heterogeneous treatment effects using random forests. *J Am Stat Assoc*. 2018;113(523):1228–1242.
48. Etchill E, Sperry J, Zuckerbraun B, Alarcon L, Brown J, Schuster K, Kaplan L, Piper G, Peitzman A, Neal MD. The confusion continues: results from an American Association for the Surgery of Trauma survey on massive transfusion practices among United States trauma centers. *Transfusion*. 2016;56(10):2478–2486.
49. Camazine MN, Hemmila MR, Leonard JC, Jacobs RA, Horst JA, Kozar RA, Bochicchio GV, Nathens AB, Cryer HM, Spinella PC. Massive transfusion policies at trauma centers participating in the American College of Surgeons Trauma Quality Improvement Program. *J Trauma Acute Care Surg*. 2015; 78(6 Suppl 1):S48–S53.