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## French lyophilized plasma versus fresh frozen plasma for the initial management of trauma- induced coagulopathy: a randomized open- label trial

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### Essentials

- An immediate supply of plasma in case of trauma- induced coagulopathy is required.
- The Traucc trial compared French Lyophilised Plasma (FLyP) and Fresh Frozen Plasma (FFP).
- FLyP achieved higher fibrinogen concentrations compared with FFP.
- FLyP led to a more rapid coagulopathy improvement than FFP.

### Summary:

#### Background

Guidelines recommend beginning hemostatic resuscitation immediately in trauma patients. We aimed to investigate if French lyophilized plasma (FLyP) was more effective than fresh frozen plasma (FFP) for the initial management of trauma- induced coagulopathy.

#### Methods

In an open- label, phase 3, randomized trial (NCT02750150), we enrolled adult trauma patients requiring an emergency pack of 4 plasma units within 6 h of injury. We randomly assigned patients to receive 4- FLyP units or 4- FFP units. The primary endpoint was fibrinogen concentration at 45 min after randomization. Secondary outcomes included time to transfusion, changes in hemostatic parameters at different time- points, blood product requirements and 30- day in- hospital mortality.

#### Results

Forty- eight patients were randomized (FLyP,  $n = 24$ ; FFP,  $n = 24$ ). FLyP reduced the time from randomization to transfusion of first plasma unit compared with FFP (median[IQR],14[5–30] vs. 77[64–90] min). FLyP achieved a higher fibrinogen concentration 45 min after randomization compared with FFP (baseline- adjusted mean difference,  $0.29 \text{ g L}^{-1}$ ; 95% confidence interval [CI], 0.08–0.49) and a greater improvement in prothrombin time ratio, factor V and factor II. The between- group differences in coagulation parameters remained significant at 6 h. FLyP reduced fibrinogen concentrate requirements. Thirty- day in- hospital mortality rate was 22% with FLyP and 29% with FFP.

### **Conclusion**

FLyP led to a more rapid, pronounced and extended increase in fibrinogen concentrations and coagulopathy improvement compared with FFP in the initial management of trauma patients. FLyP represents an attractive option for trauma management, especially when facing logistical issues such as combat casualties or mass casualties related to terror attacks or disasters.

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### **Keywords**

blood transfusion  
coagulopathy  
fibrinogen  
plasma transfusion  
trauma

### **Introduction**

Traumatic injury is the leading cause of death worldwide among persons under the age of 45 years<sup>1</sup>. Currently, it accounts for 10% of all deaths and the three leading causes of death from injuries (motor vehicle collisions, homicide and suicide) are all predicted to rise compared with other causes of death<sup>1</sup>. Thus, trauma continues to represent a global public health problem<sup>2</sup> and recent terrorist attacks have brought to attention the issue of managing mass casualties.

In both trauma and mass casualties, severe hemorrhage remains a major cause of potentially preventable deaths<sup>3</sup>. Death from traumatic exsanguination usually occurs rapidly, typically within the first 6 h, and trauma- induced coagulopathy (TIC) increases both the risk and severity of bleeding.

Trauma- induced coagulopathy appears immediately following trauma, at the scene and before resuscitation<sup>4</sup>. This coagulopathy is characterized by hyperfibrinolysis, hypofibrinogenemia, activated systemic anticoagulation and endothelial dysfunction<sup>5</sup> and is associated with poor clinical outcome<sup>3</sup>.

Accordingly, trauma management has evolved towards hemostatic resuscitation as early as possible. Current guidelines recommend that monitoring and measures to support coagulation be initiated immediately upon hospital admission<sup>3</sup>. They also recommend transfusing plasma at a plasma:red blood cell (RBC) ratio of at least 1 : 2 in the initial management of patients with expected massive hemorrhage; that is, the period between arrival in the emergency department and availability of results from coagulation monitoring<sup>3</sup>.

The immediate delivery of plasma creates serious logistical challenges. Indeed, fresh frozen plasma (FFP) requires time- consuming preparation, including controlled thawing.

Lyophilized plasma is an alternative to solve this logistical issue and allows immediate plasma transfusion<sup>6</sup>. The French Military Blood Institute (Centre de Transfusion Sanguine des Armées) manufactures French lyophilized plasma (FLyP) to support overseas operations of the French armed forces<sup>7</sup>. FLyP is a universal therapeutic viro- inactivated

plasma, compatible with all blood types, which can be reconstituted in less than 6 min at the point-of-care. Thus, FLYP is an attractive, logistically superior alternative to FFP that allows quick delivery of plasma and immediate application of high plasma:RBC ratios in the trauma setting.

In this context, the Transfusion for Trauma-induced Coagulopathy and Fibrinogen Concentration (TRAUCC) trial was designed to address a simple question: in trauma patients requiring immediate delivery of plasma at a high ratio, is lyophilized plasma more effective than FFP for the initial management of trauma-induced coagulopathy?

To answer this question, we performed a prospective randomized controlled trial including trauma patients requiring immediate transfusion with high ratios. In these patients, we assessed whether initial FLYP transfusion would increase fibrinogen concentration compared with FFP transfusion.

## **Methods**

### **Study design and participants**

The TRAUCC trial was a monocentric phase 3, randomized, open-label, active-controlled, single-center clinical trial designed to determine the efficacy of early transfusion of FLYP vs. FFP for the initial management of trauma-induced coagulopathy.

Severely injured adult trauma patients admitted directly to the trauma center from the injury scene were eligible for the trial if the attending doctor decided on an immediate transfusion of an 'emergency pack' of 4 red blood cell units associated with 4 plasma units in a 1 : 1 ratio within 6 h of injury. Patients were ineligible if they met at least one of the following criteria: transfusion of any blood product or coagulation factor concentrate prior to randomization, admission from another healthcare facility, devastating injuries and expected imminent death, recent history of anticoagulant therapy, known pregnancy, age under 18 years, or lack of mental capacity per national legal standards prior to trauma.

Consent procedures were established by the local regulatory instances and the institutional ethics committee. Informed consent was obtained from trauma patients if physical and mental capacity allowed. If patients could not provide consent, proxy consent was obtained from a relative or representative. If a proxy was unavailable, then consent was deferred or waived. When consent was deferred or provided by a proxy, the patient was informed about the trial as soon as possible and consent sought for use of the data collected.

The trial was approved by the institutional review board (Comité de Protection des Personnes Nord-ouest IV, approval number: CPP12/18), as per French regulations. The trial was monitored by the Clinical Research Unit of the Lille University Hospital in France. This study was registered at ClinicalTrials.gov, number NCT02750150.

### **Randomization and blinding**

Participants were randomly assigned in a 1 : 1 ratio to receive either FLYP or FFP. The allocation sequence was provided by a statistician, who did not take part in assessing the patients at any point of the study. The sequence was based on a computer-generated list of random numbers that was used to assign the patients to either the FLYP or FFP group, in blocks of four participants (2:2 per block). Allocation was concealed using a sealed opaque envelope and occurred as soon as inclusion was determined. The patient was declared randomized when the envelope seal was broken.

The trial was open-label: clinicians, study staff and trial participants could not be blinded to treatment allocation because of the inherent characteristics of the studied products. However, allocation was concealed to the hemostasis department assessing biological parameters.

### **Procedures**

Patients were randomly allocated to receive 4 units of FLYP or 4 units of FFP in association with 4 packed RBC units; blood products were electronically ordered and the 4 units of

allocated plasma were prepared accordingly. The 4 units of FLYP were immediately reconstituted at the bedside in the trauma center and were immediately transfused into the patient. The 4 units of FFP were issued by the blood bank after thawing following the order, delivered after thawing to the trauma center by a pneumatic system, and transfused into the patient upon receipt.

Blood samples were drawn at different time- points: at randomization (baseline sample), and 45 min, 6, 12 and 24 h after randomization.

With the exception of the first four plasma units, medical management was identical in both groups throughout the entire follow- up period. All participants received standard care according to contemporary European and national trauma guidelines<sup>3</sup>. The follow- up period for safety events and mortality was up to day 30.

### **Outcomes**

The primary endpoint was the fibrinogen concentration (STA Liquid Fib, Diagnostica Stago, Asnières sur Seine, France) at 45 min after randomization. Secondary endpoints included: (i) the rate of patients with a fibrinogen concentration above the recommended  $1.5 \text{ g L}^{-1}$  threshold at 45 min, (ii) changes from randomization in hemostatic parameters measured at different time- points (45 min, 6, 12 and 24 h after randomization), including fibrinogen concentration, prothrombin time (PT) ratio (STA Neoplastin R15, Diagnostica Stago), activated partial thromboplastin time (APTT) ratio (Triniclot aptt HS, Diagnostica Stago), coagulation factors II and V (Plasma deficient FII, FV, Diagnostica Stago), fibrin monomer (Liatest FM, Diagnostica Stago), base excess and serum lactate (ABL800 FLEX, Radiometer, Copenhagen, Denmark); (iii) time to transfusion, including interval between randomization and transfusion of the first plasma unit and interval between randomization to end of transfusion of the fourth plasma unit, (iv) fibrinogen concentrate and blood product requirements over the first 24 h after randomization, and (v) all- cause hospital death within 30 days of injury.

### **Statistical analysis**

We calculated that a sample of 42 patients would provide 90% power to detect a mean difference between treatment groups of  $0.5 \text{ g L}^{-1}$  in fibrinogen concentration at 45 min after randomization, with a two- sided type I error of 0.05, assuming a standard deviation of  $0.5$ <sup>8</sup>. Because the sample size calculation did not take into account that the analysis of covariance adjusted for baseline values was planned to be used to compare the primary endpoint, the power was expected to be greater than 90%.

All analyses were performed on all randomized patients in their original group of randomization (intention- to- treat analysis). A per- protocol sensitivity analysis was performed for the primary endpoint after excluding patients who did not meet all the enrolment criteria (administration of coagulation factor concentrate before randomization, and patients who discontinued intervention or did not receive red blood cell transfusion).

Categorical variables were expressed as frequencies and percentages. Quantitative variables were expressed as mean (standard deviation) or median (interquartile range, IQR). Normality of distribution was assessed graphically and using the Shapiro–Wilk test.

Comparison of fibrinogen concentrations at 45 min after randomization between the two treatment groups was performed using analysis of covariance (ANCOVA) adjusted for baseline fibrinogen concentration. We derived the adjusted mean difference (FLyP vs. FFP) and its 95% confidence intervals (CIs) from the ANCOVA model as treatment effect size. To compare changes in hemostatic parameters between the two treatment groups, a constrained longitudinal data analysis (cLDA) model was used<sup>9, 10</sup>. In this model, both the baseline and post- baseline values are modeled as dependent variables using a linear mixed model, and the true baseline means are constrained to be the same for the two treatment groups to adjust for observed baseline difference. The between- group differences in changes from randomization

to the time of interest (45 min, 6, 12 and 24 h after) were estimated by the time- by- treatment group interaction. We visually inspected the normality of model residuals and detected no deviations from normality assumption for all hemostatic parameters. Regarding other endpoints, we used Mann–Whitney *U*- tests to compare the transfusion intervals and the cumulative levels of fibrinogen concentrate and blood product at 24 h after randomization, and we used the Fisher's exact test to compare the 30- day hospital mortality rates.

All statistical tests were two- sided and  $P < 0.05$  was considered statistically significant. No adjustment for multiple testing was applied for all secondary objectives considered as exploratory. Data were analyzed using the SAS software package, release 9.4 (SAS Institute, Cary, NC, USA).

### Role of the funding source

The funders had no role in the design, collection, analysis or interpretation of the data, in the writing of the report, or in the decision to submit the article for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

### Results

From July 2013 to March 2016, a total of 48 patients were randomized and enrolled in the TRAUC trial, with 24 patients assigned to receive 4 units of FLYP (FLyP group) and 24 assigned to receive 4 units of FFP (FFP group). Among them, one patient from the FLYP group was subsequently found to have a history of long- term anticoagulant treatment. As soon as this information was available the study was discontinued for this patient. Discontinuation occurred before assessment of the primary endpoint (fibrinogen concentration measurement); thus, this patient was excluded from the primary efficacy analysis (Fig. 1). As shown in Table 1, baseline characteristics were well balanced across the two treatment groups.

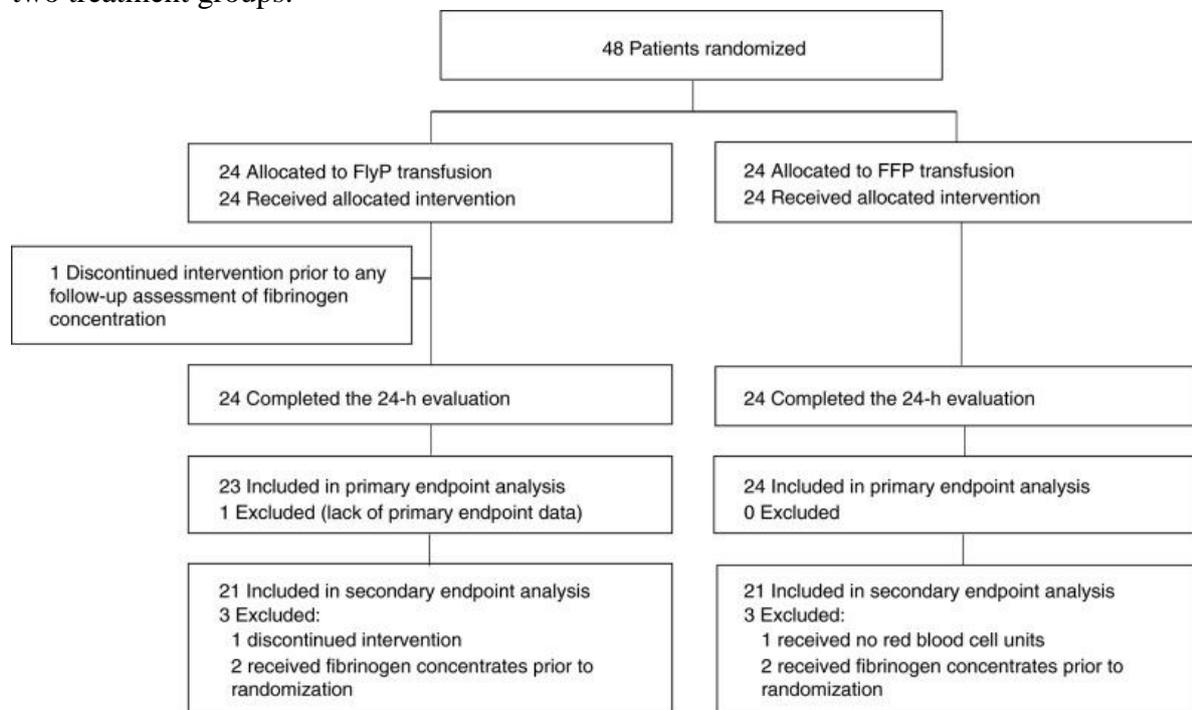


Figure 1. Study flow chart.

Table 1. Baseline characteristics

Empty Cell	FLyP ( <i>n</i> = 23)	FFP ( <i>n</i> = 24)
Age, years	48.0 ± 16.5	38.0 ± 15.6
Male sex, <i>n</i> (%)	19 (82.6)	16 (66.7)
Weight, kg	77.1 ± 11.2	72.9 ± 12.4
Mechanism: blunt trauma, <i>n</i> (%)	17 (73.9)	22 (91.7)
Injury severity score	23.5 ± 9.7	27.5 ± 11.4
Score > 15, <i>n</i> (%)	18 (78.3)	21 (87.5)
Glasgow Coma Score, median [IQR]	3 [3–15]	3 [3–13.5]
Systolic blood pressure, mmHg*	92 ± 23	92 ± 19
<90 mmHg, <i>n</i> (%)	12 (54.5)	13 (54.2)
Norepinephrine use, <i>n</i> (%)	13 (56.5)	10 (41.7)
Heart rate, beats/min†	104 ± 26	104 ± 20
> 120 beats/min, <i>n</i> (%)	8 (36.4)	4 (17.4)
Respiratory rate, cycles/min, median [IQR]	15 [15–20]	15 [15–20]
Hemoglobin, g dL <sup>-1</sup>	8.8 ± 2.0	7.9 ± 1.6
< 10 g dL <sup>-1</sup> , <i>n</i> (%)	18 (78.3)	21 (87.5)
Platelet count, × 10 <sup>3</sup> /microliter	174 ± 64	170 ± 70
< 100 × 10 <sup>3</sup> /microliter, <i>n</i> (%)	1 (4.35)	3 (12.5)
pH, median [IQR]	7.2 [7.2–7.3]	7.2 [7.2–7.3]
Tranexamic acid, <i>n</i> (%)	19 (82.6)	22 (91.7)
Time from trauma to randomization, min, median [IQR]	122 [88–205]	117 [80–147]

FFP, fresh frozen plasma; FLyP, French lyophilised plasma; IQR, interquartile range; SD, standard deviation. Values are mean ± SD unless otherwise indicated.

\*

One missing value for group FLyP.

†

One missing value in each group.

### Primary endpoint

After adjustment for baseline differences in fibrinogen concentration, the mean fibrinogen concentration 45 min after randomization was significantly higher in the FLyP group than in the FFP group (Table 2). Compared with FFP, the use of FLyP was associated with a mean difference in fibrinogen at 45 min, adjusted on baseline values, of 0.29 g L<sup>-1</sup> (95% CI, 0.08 to 0.49; *P* = 0.006). As a result, 48% (*n* = 11) of patients in the FLyP group and 25% (*n* = 6) in the FFP group had fibrinogen concentrations at 45 min above the recommended

1.5 g L<sup>-1</sup> threshold ( $P = 0.10$ ). A similar mean difference in fibrinogen concentration at 45 min between FLYP and FFP was found in the per- protocol sensitivity analysis (Table 2).  
Table 2. Primary outcome: fibrinogen level (g L<sup>-1</sup>) at 45 min after randomization

Empty Cell	FLyP		FFP		Difference in fibrinogen at T45 adjusted on baseline value, mean (95% CI)*	P- value*
	No.	Mean ± SD	No.	Mean ± SD		
ITT analysis						
T0	23	1.44 ± 0.90	24	1.14 ± 0.51		
T45	23	1.57 ± 0.78	24	1.05 ± 0.51	0.29 (0.08 to 0.49)	0.006
PP analysis						
T0	21	1.41 ± 0.94	21	1.12 ± 0.49		
T45	21	1.56 ± 0.81	21	0.93 ± 0.40	0.40 (0.23 to 0.57)	<0.001

CI, confidence interval; FFP, fresh frozen plasma; FLYP, French lyophilised plasma; ITT, intention to treat; PP, per protocol; SD, standard deviation. T0 indicates fibrinogen level at randomization (baseline) and T45 fibrinogen level 45 minutes after randomization.

\*

Calculated using analysis of covariance adjusted for baseline value.

## Secondary Endpoints

### Hemostatic parameters

The changes in coagulation parameters within 45 minutes of randomization differed significantly between the two treatment groups, except for APTT ratio and fibrin monomers (Table 3). FlyP transfusion was associated with an improvement in all coagulation parameters (PT ratio, factor II and factor V) within 45 min, whereas these parameters worsened or remained unchanged in the FFP group. The beneficial effect of FLYP on fibrinogen concentration remained significant 6 h after randomization (Fig. 2). At 6 h, the estimated mean change from randomization was 1.18 g L<sup>-1</sup> (95% CI, 0.87–1.49) in the FlyP group and 0.68 g L<sup>-1</sup> (95% CI, 0.37 to 0.98) in the FFP group (mean between- treatment difference, 0.51 g L<sup>-1</sup>; 95% CI, 0.14 to 0.88;  $P = 0.008$ ). Moreover, similarly to 45 min after randomization, changes 6 h after randomization in PT ratio, factor II and factor V also remained greater in the FLYP group. After 6 h, the beneficial effects of FLYP on coagulation parameters diminished progressively and changes from baseline were no longer different between the two groups.

Table 3. Hemostatic parameters from randomization to 24 h according to treatment group

Hemostatic parameter	FLyP group		FFP group		Difference in change from baseline, mean (95% CI)*	P- value*
	No.	Mean ± SD	No.	Mean ± SD		
Fibrinogen						
T0	23	1.44 ± 0.9	24	1.14 ± 0.5	–	–
45 min	23	1.57 ± 0.8	24	1.05 ± 0.5	0.29 (0.09 to 0.48)	0.006
6 h	22	2.50 ± 0.6	23	1.93 ± 0.6	0.51 (0.14 to 0.88)	0.008
12 h	22	2.69 ± 0.7	23	2.44 ± 0.4	0.20 (–0.17 to 0.57)	0.29
24 h	20	3.61 ± 0.7	17	3.45 ± 0.6	0.16 (–0.26 to 0.58)	0.45

Hemostatic parameter	FlyP group		FFP group		Difference in change from baseline, mean (95% CI)*	P- value*
	No.	Mean $\pm$ SD	No.	Mean $\pm$ SD		
PT ratio						
T0	23	1.54 $\pm$ 0.6	24	1.53 $\pm$ 0.3	–	–
45 min	23	1.46 $\pm$ 0.4	24	1.74 $\pm$ 0.5	–0.28 (–0.43 to –0.13)	<0.001
6 h	22	1.19 $\pm$ 0.2	23	1.34 $\pm$ 0.3	–0.16 (–0.31 to –0.02)	0.027
12 h	22	1.18 $\pm$ 0.1	23	1.18 $\pm$ 0.2	0.00 (–0.08 to 0.07)	0.90
24 h	20	1.22 $\pm$ 0.1	19	1.20 $\pm$ 0.1	0.02 (–0.06 to 0.10)	0.62
APTT ratio						
T0	23	1.42 $\pm$ 1.0	24	1.76 $\pm$ 1.0	–	–
45 min	23	1.43 $\pm$ 1.0	24	2.26 $\pm$ 1.9	–0.38 (–0.78 to 0.02)	0.063
6 h	22	1.06 $\pm$ 0.2	23	1.44 $\pm$ 0.9	–0.34 (–0.71 to 0.04)	0.077
12 h	22	1.06 $\pm$ 0.2	23	1.20 $\pm$ 0.5	–0.12 (–0.32 to 0.08)	0.23
24 h	21	1.14 $\pm$ 0.2	19	1.16 $\pm$ 0.2	–0.11 (–0.31 to 0.10)	0.28
Factor II						
T0	23	56.87 $\pm$ 21	24	51.17 $\pm$ 18	–	–
45 min	23	59.35 $\pm$ 21	24	43.83 $\pm$ 16	10.5 (5.55 to 15.44)	<0.001
6 h	22	67.27 $\pm$ 17	23	53.83 $\pm$ 15	9.33 (2.82 to 15.83)	0.006
12 h	22	62.36 $\pm$ 16	23	58.57 $\pm$ 13	0.76 (–6.29 to 7.82)	0.83
24 h	18	61.50 $\pm$ 17	17	59.94 $\pm$ 12	–2.94 (–9.31 to 3.44)	0.36
Factor V						
T0	23	52.61 $\pm$ 32	24	41.33 $\pm$ 26	–	–
45 min	23	53.17 $\pm$ 28	24	32.83 $\pm$ 23	11.05 (5.89 to 16.21)	<0.001
6 h	22	65.68 $\pm$ 24	23	49.04 $\pm$ 23	9.62 (0.58 to 18.66)	0.038
12 h	22	69.64 $\pm$ 26	23	58.35 $\pm$ 21	4.31 (–4.80 to 13.42)	0.35
24 h	18	75.94 $\pm$ 29	17	72.00 $\pm$ 15	–1.06 (–12.25 to 10.13)	0.85
Fibrin monomers						
T0	23	106.8 $\pm$ 56	24	117.2 $\pm$ 48	–	–
45 min	23	105.8 $\pm$ 57	23	123.9 $\pm$ 48	–7.69 (–29.52 to 14.15)	0.48
6 h	21	111.4 $\pm$ 50	23	126.0 $\pm$ 34	–11.38 (–34.42 to 11.67)	0.33
12 h	22	93.6 $\pm$ 46	23	122.0 $\pm$ 42	–27.63 (–54.34 to –0.93)	0.043
24 h	17	52.2 $\pm$ 55	16	64.9 $\pm$ 43	–14.06 (–50.04 to 21.91)	0.43

Hemostatic parameter	FlyP group		FFP group		Difference in change from baseline, mean (95% CI)*	P- value*
	No.	Mean $\pm$ SD	No.	Mean $\pm$ SD		
Base excess						
T0	22	-7.3 $\pm$ 6.2	21	-10.2 $\pm$ 4.2	–	–
45 min	20	-7.7 $\pm$ 3.5	21	-11.5 $\pm$ 5.9	2.35 (-0.66 to 5.36)	0.12
6 h	22	-5.3 $\pm$ 2.8	22	-7.8 $\pm$ 4.5	1.80 (-0.38 to 3.97)	0.10
12 h	22	-4.5 $\pm$ 3.0	21	-6.2 $\pm$ 4.0	1.46 (-1.02 to 3.93)	0.24
24 h	20	-2.6 $\pm$ 3.4	20	-3.8 $\pm$ 2.5	1.77 (-0.70 to 4.23)	0.15
Serum lactate						
T0	22	4.55 $\pm$ 1.9	22	5.25 $\pm$ 3.7	–	–
45 min	20	3.95 $\pm$ 1.7	21	5.74 $\pm$ 5.2	-0.74 (-1.99 to 0.52)	0.24
6 h	22	2.66 $\pm$ 1.6	22	3.50 $\pm$ 2.8	-0.52 (-1.48 to 0.44)	0.28
12 h	22	2.25 $\pm$ 1.3	19	2.69 $\pm$ 2.4	-0.54 (-1.73 to 0.65)	0.36
24 h	17	1.92 $\pm$ 1.1	19	1.70 $\pm$ 0.8	0.28 (-0.39 to 0.95)	0.39

T0 indicates values at randomization (baseline). APPT, activated partial thromboplastin time; CI, confidence interval; FFP, fresh frozen plasma; FLYP, French lyophilised plasma; PT, prothrombin time; SD, standard deviation.

\*

Estimated using a constrained longitudinal data analysis model to adjust on baseline values (T0).

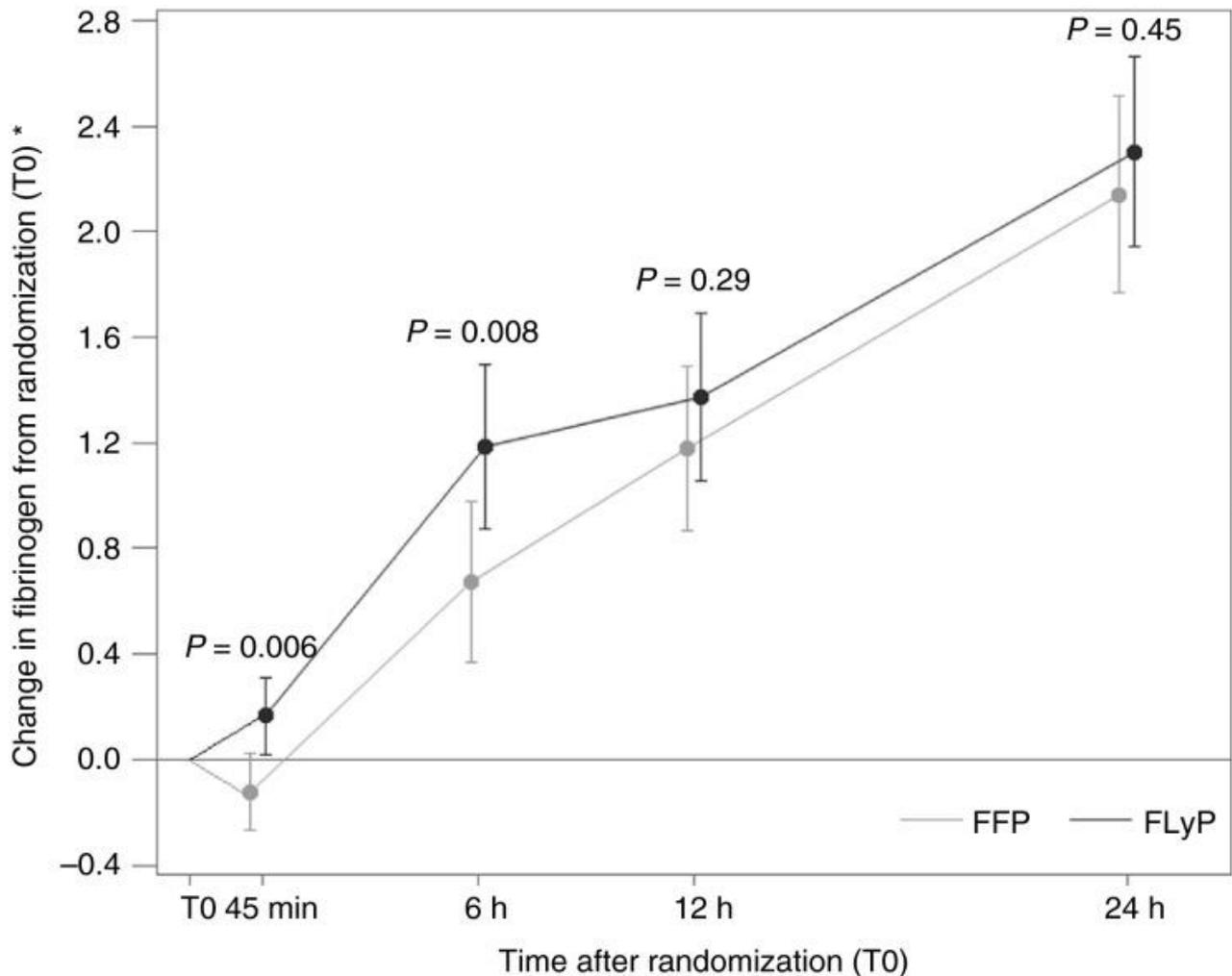


Figure 2. Change from randomization (T0) to 45 min, 6, 12 and 24 h in coagulation parameters in fibrinogen concentration. Mean changes (and their 95% confidence interval) from randomization were estimated using a constrained longitudinal data analysis model to adjust on baseline values (T0). *P*- values for comparison of mean changes at each time- point were reported. After adjustment for baseline values, the estimated mean change (95% CI) at 45 min after randomization was  $0.17 \text{ g L}^{-1}$  (95% CI, 0.02 to 0.31) in the FlyP group and  $-0.12 \text{ g L}^{-1}$  (95% CI,  $-0.27$  to 0.02) in the FFP group (mean between- treatment group difference,  $0.29 \text{ g L}^{-1}$ ; 95% CI, 0.09 to 0.48; *P* = 0.006). APPT, activated partial thromboplastin time; FFP, fresh frozen plasma; FLYP, French lyophilised plasma; PT, prothrombin time; T0, randomization.

We found no difference in changes in base excess and serum lactate at any time- point. In both study groups, base excess increased over time, whereas serum lactate decreased.

#### Transfusion intervals

In comparison to FFP, the use of FLYP reduced the transfusion intervals. From randomization, the median [IQR] time to transfusion of the first plasma unit was shorter in the FLYP group (14 [5–30] min) than the FFP group (77 [64–90] min, *P* < 0.0001). As a result, the interval between randomization and end of transfusion of the 4 units was also reduced with FLYP compared with FFP (median [IQR], 45 [45–70] vs. 112 [91–125]; *P* < 0.0001).

#### Blood product and fluid requirements and all- cause mortality

The need for fibrinogen concentrates was reduced in the FLYP group compared with the FFP group over the first 24 h after randomization, albeit at the threshold for statistical significance

( $P = 0.052$ ). No difference was observed regarding RBC transfusion requirements or fluid therapy using either crystalloid or colloid solutions (Table 4).

Table 4. Median cumulative requirement of fibrinogen concentrates, transfusion and fluid therapy at 24 h after randomization

Empty Cell	FLyP		FFP		<i>P</i> - value
	No.	Median [IQR]	No.	Median [IQR]	
Fibrinogen concentrates, 1.5- g doses	23	2 [0–3]	24	3 [2–4]	0.052
Crystalloids, 500- mL doses	21	3 [2–4]	22	4 [3–5]	0.28
Colloids, 500- mL doses	22	1.5 [1–2]	23	2 [1–4]	0.12
Platelet concentrate, units	23	0 [0–1]	24	1 [0–2]	0.14
Red blood cell, units	23	6 [4–10]	24	7 [6–11.5]	0.12
Plasma, units	23	4 [4–8]	24	5.5 [4–9]	0.27

IQR, interquartile range; FFP, fresh frozen plasma; FLyP, French lyophilised plasma.

All- cause in- hospital mortality within 30 days after randomization occurred in 12 (26%) patients overall without difference between the two treatment groups; five (22%) deaths occurred in the FlyP group and seven (29%) in the FFP group ( $P = 0.56$ ). All deaths occurred after completion of the randomized treatment and all except one in each group occurred after the first 24 h.

### Discussion

Our randomized trial shows that FLyP allows a more rapid, pronounced and extended increase in fibrinogen concentration than FFP, and is more effective in achieving one major endpoint of the initial management of trauma- induced coagulopathy. To our knowledge, the TRAUC trial is the first randomized trial of lyophilized plasma in severe trauma patients, and its successful outcome conveys several important messages.

First, the TRAUC trial confirms, in a civilian ‘real- life’ clinical setting, that lyophilized plasma is superior to frozen plasma for the rapid delivery of plasma. This is crucial, because (i) hemorrhage remains the leading cause of preventable death in trauma patients, (ii) most early deaths due to hemorrhage occur within 2–3 h 11., 12., and (iii) TIC development increases mortality<sup>13</sup>. As a result, plasma transfusion should begin immediately to prevent and treat TIC and improve survival. However, immediate plasma transfusion faces logistical challenges. Fresh frozen plasma must be thawed, making it difficult to transfuse the first plasma concomitantly with the first packed RBC. In our trial, median time to first FFP transfusion was 77 [64–90] min, which was close to times previously reported in both US and English trauma centers 14., 15. A prospective study including trauma patients with activation of the massive hemorrhage protocol in 22 English trauma centers reported that the median time to first FFP transfusion was 87 (43–229) min after arrival<sup>15</sup>. As a result, less than 15% of patients reached an FFP:RBC ratio of 1 : 2 or higher within the first hour of admission, demonstrating that FFP is not suitable for initial hemostatic resuscitation.

To deal with this issue, several centers use thawed plasma prepared from FFP that can be maintained at 1–6 °C for up to 5 days. This extended- thawed FFP was used in the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPPR) trial, which demonstrated that early administration, within minutes of arrival, of plasma, platelets and red blood cells in a 1 : 1 : 1 ratio decreased the rate of death from exsanguination<sup>12</sup>. This immediately available plasma allowed 11 of the 12 centers of the trial to meet the goal of delivering a first pack of 6 plasma units 10 min after they were ordered<sup>16</sup>. However, the use of extended- thawed FFP is a suboptimal workaround because it exposes to a potential reduction in potency as coagulation

factor activity and a theoretical risk of bacterial contamination and increased levels of phthalate exposure<sup>17</sup>. Finally, the increasing use of extended- thawed plasma has two logistical drawbacks: potential excessive wastage if plasma is routinely thawed in advance but not always transfused, especially in small centers where demand is unpredictable, and above all, immediate delivery of extended- thawed FFP before the patient's blood group can be determined leads to AB plasma overuse while AB blood donors are scarce, further decreasing AB plasma availability.

In this context, FLYP has several advantages. FLYP is stored at room temperature and is reconstituted in approximately 6 min in 200 mL of sterile water<sup>18</sup>. Moreover, FLYP has universal ABO compatibility and lyophilization induces little change in coagulation factors<sup>7</sup>. Safety is provided by pathogen inactivation based on an amotosalen- ultraviolet illumination process. The French hemovigilance system has recorded more than 2700 transfusions of French lyophilized plasma with no report of any significant adverse effect<sup>19</sup>. FLYP is used routinely by the French military but is also available to the US military under an agreement between the US and French Governments.

Second, the TRAUMCC trial shows that an early 1 : 1 plasma:RBC ratio transfusion strategy with FLYP is more effective than with FFP for correcting TIC, as improvements of fibrinogen concentration but also PT ratio, factors II and factor V were greater in the FLYP group. Observational studies previously reported a benefit of high plasma:RBC ratios when achieved early, within the first 6 h of admission<sup>11, 20</sup>. Especially, De Biasi and colleagues showed that plasma deficit was associated with mortality in the first hour of resuscitation of trauma patients requiring urgent transfusion; afterwards this relationship diminished and disappeared<sup>21</sup>. Interestingly, although therapeutic management of FLYP and FFP groups only differed for the administration of the four first plasma products, the beneficial effect of FLYP was sustained up to 6 h after randomization (i.e. at least 4 h after the 4 plasma units were transfused in both groups). These data illustrate that the 'golden hour' management impacts the course of TIC.

Third, our data show that FLYP represents a substantial fibrinogen supply. Although plasma is usually not considered as an ideal source of fibrinogen repletion, the plasma transfusion strategy based on FLYP was associated with a reduction in fibrinogen administration<sup>7</sup>. Moreover, early administration of FLYP might not only correct the fibrinogen deficit itself but also partly reverse TIC and the mechanisms involved in fibrinogen deficit, including consumption, fibrinogenolysis, fibrinogen breakdown due to acidosis and decreased fibrinogen synthesis due to hypothermia<sup>22</sup>. This hypothesis is supported by the significant improvement in fibrin monomers observed with FLYP, 12 h after randomization. These effects may result from plasma's ability to globally promote systemic vascular stability, which mitigates the endotheliopathy of trauma; however, our study was not planned to explore plasma mechanisms of action.

Our study has several limitations. The sample size is small, calculated according to our biological endpoint and not powered to assess mortality. We used biological endpoints as surrogate markers because hemostatic resuscitation is considered as an interim standard- of- care in trauma management<sup>3</sup>. As the potential benefit of FLYP is related to the reduction of time to administration of the product, we have planned to investigate the fibrinogen concentration as early as possible at a fixed time- point (i.e. 45 min), allowing theoretically transfusion of either FLYP (reconstituted in less than 6 min) or FFP (thawed in 20 min). However, given the observed median time to administration of FFP in our study, we must acknowledge that fibrinogen concentration at 45 min after randomization does not really reflect superiority of FLYP over FFP as FFP was not transfused yet in the FFP group. Nevertheless, the beneficial effect on fibrinogen levels persisted after 6 hours. As none of the patients died before the assessment of the primary endpoint, the results were not exposed to

the immortal time bias. Despite randomization, we observed a baseline imbalance between groups in the primary outcome of fibrinogen concentration, probably due to the small sample size. However, this difference was taken into account in the primary endpoint (fibrinogen at 45 min after randomization) comparison using an analysis of covariance adjusted for baseline fibrinogen concentrations. Another limitation inherent to the study design was the open label use of the studied products. This was unavoidable because point-of-care preparation of FLYP vs. the blood bank thawing and delivering FFP contributed to the studied inherent advantages and disadvantages of each.

In conclusion, these data show that FLYP is superior to FFP for faster plasma transfusion. FLYP induces a faster and greater fibrinogen increase and TIC improvement. FLYP is an attractive option for trauma management, especially when facing logistical issues such as combat casualties or civilian mass casualties related to terrorism or natural disasters.

### **Addendum**

D. Garrigue and A. Godier obtained funding for the trial, co-coordinated the trial, and drafted the manuscript. A. Glacet obtained funding for the trial, collected the data, and supervised the inclusions. P. Goldstein supervised the collection of the data, critically reviewed the endpoints, and was consulted for interpretation of clinical data. A. Sailliol, E. Resch, C. Paris, and P. Renom coordinated the availability of the products and were consulted for the interpretation of all the transfusion-related data. A. Bauters supervised all the biological analysis and critically reviewed the manuscript. E. Kipnis and B. Tavernier were involved in the design of the trial and critically reviewed the study protocol and the manuscript. F. Machuron performed all the statistical analyses supervised by J. Labreuche and A. Duhamel. A. Sailliol was involved in the design of the trial and critically reviewed the manuscript. A. Godier and S. Susen designed the trial. S. Susen supervised the trial, obtained funding, and critically reviewed the manuscript.

### **Disclosure of Conflict of Interests**

E. Kipnis reports non-financial support from Laboratoire Français du Biomédicament (LFB), outside the submitted work. S. Susen reports research grants from Laboratoire Français du Biomédicament (LFB) and from Stago, outside the submitted work. The other authors state that they have no conflict of interest.

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